thereunder. Failure to abide by this provision through making such an application will subject the alien to termination of parole status and institution of proceedings under sections 235 and 236 of the Act without the written notice of termination required by § 212.5(d)(2)(i) of this chapter.

* * * * *

PART 234—PHYSICAL AND MENTAL EXAMINATION OF ARRIVING ALIENS

16. The authority citation for Part 234 is revised to read as follows:

Authority: Secs. 103, 234 of the INA as amended; 8 U.S.C. 1103, 1224; Pub. L. 99–603.

§ 234.2 (Amended)

17. In § 234.2, paragraph (b) is amended by inserting the phrase "and local, county and state health departments" immediately after the word "clinic".

PART 242—PROCEEDINGS TO DETERMINE DEPORTABILITY OF ALIENS IN THE UNITED STATES: APPREHENSION, CUSTODY, HEARING, AND APPEAL

18. The authority citation for Part 242 is revised to read:

Authority: Secs. 103, 242, 244, 292 of the INA, as amended; 8 U.S.C. 1101, 1103, 1182, 1252, 1254, 1362; EO 12356; Title 1 of Pub. L. 95–145; Pub. L. 99–603.

19. Section 242.21 is amended by redesignating existing text as paragraph (a) and adding the following new paragraph (b):

§ 242.21 Appeals.

* * * * *

(b) Prohibited appeals; legalization or special agricultural worker applications. An alien respondent defined in § 210.2(f) (3) or (4), 242.13, 243.4, or 245a.2(c) (5), (6), or (7) of this chapter who fails to file an application for adjustment of status to that of a temporary resident within the prescribed thirty-day period, and who is thereafter found to be deportable by decision of an immigration judge, shall not be permitted to appeal the finding of deportability based solely on refusal by the immigration judge to entertain such an application in deportation proceedings.

PART 264—REGISTRATION AND FINGERPRINTING OF ALIENS IN THE UNITED STATES

20. The authority citation for Part 264 is revised to read:

Authority: Secs. 101, 103, 262, 264 of the INA, as amended; 8 U.S.C. 1101, 1103, 1302, 1304; Pub. L. 99–603.

§ 264.1 [Amended]

21. In § 264.1 paragraph (a) is amended by adding at the end of existing text; the following:

I–687 Application for Status as a Temporary Resident—Applicants under section 245A of the Immigration and Nationality Act, as amended.
I–691 Notice of Approval for Status as a Temporary Resident—Aliens adjusted to lawful temporary residence under 8 CFR 210.2 and 245A.2.
I–698 Application to Adjust Status from Temporary to Permanent Resident—Applicants under section 245A of the Immigration and Nationality Act, as amended.
I–700 Application for Status as a Temporary Resident—Applicants under section 210 of the Immigration and Nationality Act, as amended.

22. In 8 CFR 264.1 paragraph (b) is amended by adding at the end of the existing text the following:

I–688 Temporary Resident Card—Lawful temporary residents of the United States.
I–688A Employment Authorization Card.
I–695 Application for Replacement of Form I–688 Temporary Resident Card—While application is pending, aliens whose evidence of registration has been lost, stolen, mutilated, or destroyed; aliens whose original Form I–688 were incorrect when issued.

23. In § 264.1, paragraph (c) is amended by adding the following sentences at the end of the existing text:

(c) * * * Application by an alien lawfully admitted for temporary residence for Form I–688, Temporary Resident Card, in lieu of one lost, stolen, mutilated, or destroyed, shall be made on Form I–695 accompanied by the fee required by § 103.7(b) of this chapter, two color photographs, regardless of the applicant's age, unless the requirement for such photographs has been waived by the director of the legalization office in his or her discretion because of hardship to an applicant who is confined due to age or physical infirmity, and when issuance of Form I–688 is desired in a changed name, by appropriate documentary evidence of such change. Any Form I–688 in the applicant's possession must also be submitted with the application. An application by an alien within the United States for replacement of evidence of registration shall be submitted to the legalization office having jurisdiction over the applicant's place of residence in the United States. Prior to the issuance of Form I–688, all applicants, regardless of age, shall appear at the appropriate legalization office for interview; placement of fingerprint and signature on I–688 unless these requirements are waived at the discretion of the district director because of infirmity, illiteracy, or other compelling reasons. An alien who files application Form I–695 may be required to appear in person before an immigration officer prior to the adjudication of the application and be interrogated under oath concerning his or her eligibility for issuance of I–688 as evidence of his or her registration. In addition, the applicant may also be required to present a completed fingerprint card (Form FD–258). The decision on an application for replacement of evidence of registration shall be made by the regional processing facility director having jurisdiction over the alien's place of residence in the United States. No appeal shall lie from the decision of the regional processing facility director denying the application.

PART 299—IMMIGRATION FORMS

24. The authority citation for Part 299 is revised to read as follows:

Authority: Sec. 103 of the INA, as amended; 8 U.S.C. 1103; Pub. L. 99–603.

§ 299.1 [Amended]

25. Section 299.1 is amended by adding the following immediately before the entry "ICAO" in numerical sequence:

I–687 (____) Application for Status as a Temporary Resident (sectin 245A INA)
I–688 (____) Temporary Resident Card
I–688A (____) Employment Authorization Card
I–690 (____) Application for Waiver of Grounds of Excludability
I–691 (____) Notice of Approval of Status as a Temporary Resident
I–692 (____) Notice of Denial for Status as a Temporary Resident
I–693 (____) Medical Examination for Status as a Temporary Resident Under Pub. L. 99–603
I–694 (____) Notice of Appeal
I–695 (____) Application for Replacement of Form I–688 Temporary Resident Card (Under Pub. L. 99–603)
I–697 (____) Change of Address
I–698 (____) Application to Adjust Status from Temporary to Permanent Resident (Under the Immigration Reform and Control Act of 1986)
I–700 (____) Application for Status as a Temporary Resident (section 210 INA)
I–705 (____) Affidavit to corroborate employment claimed by an applicant for status as a temporary resident (section 210 INA)

Dated: March 5, 1987.

Alan C. Nelson,

Commissioner.

[FR Doc. 87–5840 Filed 3–17–87; 10:09 am]

BILLING CODE 4410–10–M

8 CFR Part 210

Adjustment of Status for Special Agricultural Workers

AGENCY: Immigration and Naturalization Service, Justice.

ACTION: Proposed rule.

SUMMARY: This rule would create Part 210 of 8 CFR, a new part added to conform with the new section 210 of the Immigration and Nationality Act established by Pub. L. 99–603, the Immigration Reform and Control Act of 1986 (IRCA). This rule sets the criteria and procedures to be used to adjust the status of special agricultural workers to that of temporary residents; sets standards for maintenance of that status and outlines the benefits accruing to temporary residents and the distinctions between temporary and permanent resident status; sets criteria and procedures for termination of temporary resident status; and establishes procedures for adjustment of the status of temporary resident special agricultural workers to that of permanent residents.

DATE: Comments must be received on or before April 20, 1987.

ADDRESS: Send original and two copies of comments to Assistant Commissioner for Legalization, Office of Legalization, Room LL100, 425 I Street, NW., Washington, DC 20536.

FOR FURTHER INFORMATION CONTACT: William S. Slattery, Assistant Commissioner, Legalization, 425 I Street, NW., Washington, DC 20536, (202) 786–3658.

SUPPLEMENTARY INFORMATION: This proposed rule was drafted in consideration of comments received on a preliminary working draft made available to the public by notice in the Federal Register on January 20, 1987. About 6,800 copies of the draft were requested and responses were received from 164 organizations and individuals. The Service appreciates the thoughtfulness and constructive tone of these comments and has adopted many of the suggestions in drafting this proposal.

The IRCA was enacted on November 6, 1986. One of its principal components is a provision for the adjustment of the status of seasonal agricultural workers to that of temporary, and subsequently permanent residents. This provision is designed both to legalize the status of undocumented farmworkers and to ensure that the seasonal labor needs of American growers are met. Therefore any alien who, during the twelve-month period ending on May 1, 1986 performed agricultural field labor in perishable commodities in the United States for at least 90 man-days, and who is otherwise admissible to the United States, is eligible for adjustment of status as a special agricultural worker.

Although no specific residence requirement for special agricultural worker eligibility is established by the IRCA, both the House-Senate Conference Managers' Report and colloquies on the report in the House and Senate state Congress' clear intent concerning the requirements to be imposed. Based on those sources, Group 2 Special Agricultural Workers are aliens who have both performed 90 man-days of qualifying agricultural employment and resided in the United States for three months in the one-year period ending on May 1, 1986. Group 1 Special Agricultural Workers are aliens who have both engaged in qualifying agricultural employment and resided in the United States for an aggregate period of six months in each of the one-year periods ending on May 1, 1984, 1985, and 1986. Although the Conference Managers' Report refers to a six-month residence requirement for Group 2 workers, both the House and Senate colloquies on the report indicate that this is an error and that a three-month residence requirement was intended; CONG. REC. H10591 (daily ed. October 15, 1986) (remarks of Rep. Panetta, Rep. Rodino, and Rep. Lungren); CONG. REC. S16910 (daily ed. October 17, 1986) (remarks of Sen. Wilson and Sen. Simpson). Satisfaction of the 90 man-day employment requirement constitutes evidence that an applicant has met the three-month residence requirement.

The definition of qualifying employment in this rule is based on the language of section 210(h) of the Immigration and Nationality Act in which "seasonal agricultural services" are defined. The types of employment which are ruled not to be qualifying are inferred from those which are expressly designated as qualifying employment. The definition of the term "man-days" as not less than one hour per day of qualifying agricultural employment conforms to the Fair Labor Standards Act definition and appears consistent with the references in the legislative history to these criteria. Although an application premising eligibility on 90 hours of work over a 90-day period would be highly suspect, the practice of crediting a day on which at least one hour of work was performed as a work day for the purpose of qualification for workers' benefits is based on FLSA precedent and appears applicable here. Defining any day on which piece work was performed as a "man-day" is based on the Conference Managers' Report.

Although, according to the Conference Managers' Report, an applicant for adjustment of status under this part may meet his or her burden of proof by demonstrating the performance of requisite qualifying employment as a matter of "just and reasonable inference", a mere personal attestation unsupported by corroborating evidence that the applicant performed such employment will not suffice to create such an inference. In the cases cited in the Conference Managers' Report as guidelines for the "just and reasonable inference" standard, the fact of the plaintiffs' employment was clearly demonstrated by evidence of record. The points to be resolved in those cases were the actual or estimated amount of work performed and, consequently, the amount of unpaid compensation owing to the plaintiffs. Based on these cases, in the context of this rule, the "just and reasonable inference" standard can be applied to questions relative to the amount of employment performed but not to the more fundamental question of whether qualifying employment was in fact performed. If an applicant claims to have performed the requisite amount of qualifying employment, but can prove only that he or she performed part of that employment, the "just and reasonable inference" standard is then to be applied to analysis of the evidence actually submitted. This rule also applies this standard to work performed by minors and spouses but credited to a principal family member. An applicant's burden of proof in relation to the required period(s) of residence also is based on these standards.

This rule also provides that all affidavits submitted in evidence must be made under oath and must be accompanied by certified copies of corroborating evidence or contain the affiants' agreement to corroborate their statements if required. These standards are established to conform to the provisions of the IRCA governing the burden of proof of applicants and the prevention and detection of fraud. Provisions for Service verification of other forms of evidence are also established for this reason.

This rule provides that the Service may solicit lists from agricultural producers, farm labor contractors, collective bargaining organizations, and other groups or organizations which maintain records of employment to provide a partial database against which applicants' claims of qualifying employment can be checked. In that the special agricultural worker provisions of

the IRCA are intended to ensure the availability of needed labor for agricultural employers, the Service believes that such employers would be willing to facilitate the process of verifying claimed qualifying employment by providing rosters of former employees.

This rule provides that all documents entered in evidence except certain classes of records must be submitted in the original. It is projected that the special agricultural worker program will encounter a significant fraudulent documents problem. Original documents are required so that they may be subjected to forensic or intelligence analysis if a need for such analysis is indicated.

This rule provides that fees for applications must be submitted in the form of a money order, cashier's check, or bank check and that currency or personal checks will not be accepted.

This rule provides that aliens who have assisted in the persecution of others and those who are nonimmigrant exchange visitors subject to the foreign residence requirement of section 212(e) of the Act who have not satified that requirement or received a waiver of it are ineligible for special agricultural worker classification. Though there are no express provisions to this effect in section 210 of the Act, the establishment of these criteria is consistent with the overall scheme of the Immigration and Nationality Act relating to those classes of persons.

This rule contains provisions which interpret the confidentiality and fraud provisions of sections 210(b) (6) and (7) of the Act to permit issuance of an order to show cause and initiation of deportation proceedings against aliens determined as a result of a Service investigation to have engaged in fraud or willful misrepresentation of material facts in applying for status as special agricultural workers. Section 210(b)(6) of the Act permits the use of information furnished in connection with special agricultural worker applications for the purpose of enforcement of the anti-fraud provisions of section 210(b)(7) of the Act. As evidenced by the inclusion of this provision and section 210(b)(7) itself in the IRCA, Congress was concerned with the problem of fraud in special agricultural worker applications and with projections of extensive use of fraudulent or false documents in such applications given the high benefit-risk ratio. Congress intended that vigorous efforts be made to deter, detect, and eliminate such practices. Criminal prosecution alone would be of limited effectiveness in realizing this goal given the procedures and limited resources of the criminal justice system. Because a significant number of fraudulent attempts are anticipated, it is likely that prosecution will be declined in many cases not due to lack of sufficient evidence or similar deficiencies, but due to the inability of the criminal justice system to process the number of cases generated. The Service interprets section 210(b)(6)(A) of the Act to require enforcement of section 210(b)(7) through deportation proceedings as well as through criminal prosecution.

Temporary residents found to be deportable based on information not protected by the confidentiality provisions can be brought directly into deportation proceedings, just as an alien whose status has been adjusted under section 245 of the Act can be brought into proceedings without his or her status having been rescinded under section 246 of the Act.

Special Agricultural Workers will be temporarily disqualified from certain programs of public assistance to be specified at a later date.

Consular officers at offices designated by the Secretary of State will process and adjudicate applications from aliens abroad under this Part, using the standards established in this Part and following procedures substantially identical with those set forth by INS for processing applications in the United States. Conforming regulations will be promulgated by the Secretary of State in consultation with the Attorney General.

In accordance with 5 U.S.C 605(b), the Commissioner certifies that this rule if promulgated will not have a significant economic impact on a substantial number of small entities.

This is not a major rule as defined within the meaning of section 1(b) of EO 12291.

The information collection requirements contained in this regulation will be submitted to OMB for review under the Paperwork Reduction Act.

List of Subjects in 8 CFR Part 210

Aliens, Permanent resident status, Reporting and record keeping requirements, Temporary resident status.

Accordingly, it is proposed to amend Chapter I of Title 8 of the Code of Federal Regulations by adding a new Part 210 to read as follows:

PART 210—SPECIAL AGRICULTURAL WORKERS

Sec.

Authority: Pub. L. 99–603, 100 Stat. 3359; 8 U.S.C. 1101 note.

§ 210.1 Definition of terms used in this part.

(a) *Act.* The Immigration and Nationality Act, as amended by the Immigration Reform and Control Act of 1986.

(b) *Application period.* The 18 month period during which an application for adjustment of status to that of a temporary resident may be accepted, beginning on June 1, 1987 and ending on November 30, 1988.

(c) *Complete application.* A complete application consists of an executed Form I–700, Application for Temporary Resident Status as a Special Agricultural Worker, evidence of qualifying agricultural employment and residence, a report of medical examination, the applicant's fingerprints on Form FD–258, and the prescribed number of photographs. An application is not complete until the required fee has been paid and recorded.

(d) *Determination Process.* Determination process as used in this part means reviewing and evaluating all information provided pursuant to an application for the benefit sought and making a determination thereon. If fraud, willful misrepresentation of a material fact, a false writing or document, or any other activity prohibited by section 210(b)(7) of the Act is discovered during the determination process the Service shall refer the case to a U.S. Attorney for possible prosecution and/or issue an Order to Show Cause and Warrant of Arrest.

(e) *Group 1.* Special agricultural workers who have performed qualifying agricultural employment in the United States for at least 90 man-days in the aggregate in each of the twelve-month periods ending on May 1, 1984, 1985, and 1986, and who have resided in the United States for six months in the aggregate in each of those twelve-month periods. The status of a Group 1 temporary resident will be adjusted to that of an alien lawfully admitted for permanent residence as of December 1, 1989.

(f) *Group 2.* Special agricultural workers who during the twelve-month period ending on May 1, 1986 have performed at least 90 man-days in the aggregate of qualifying agricultural employment in the United States. The status of a Group 2 temporary resident

will be adjusted to that of an alien lawfully admitted for permanent residence as of December 1, 1990.

(g) *Legalization Office.* Legalization offices are local offices of the Immigration and Naturalization Service which accept and process applications for legalization or special agricultural workers status, under the authority of the district directors in whose districts such offices are located.

(h) *Man-day.* The term "man-day" means the performance during any day of not less than one hour of qualifying agricultural employment for wages paid. If employment records relating to an alien applicant show only piece rate units completed, then any day in which piece rate work was performed shall be counted as a man-day.

(i) *Nonfrivolous application.* A complete applicaiton will be determined to be nonfrivolous at the time the applicant appears for an interview at a legalization office if it contains: (1) evidence or information which shows on its face that the applicant is admissible to the United States or, if inadmissible, that the applicable grounds of excludability may be waived under the provisions of section 210(c)(2)(i) of the Act, and (2) evidence or information which shows on its face that the applicant performed at least 90 man-days of employment in seasonal agricultural services during the twelve-month period from May 1, 1985 through May 1, 1986, and (3) documentation which establishes a reasonable inference of the performance of the seasonal agricultural services claimed by the applicant.

(j) *Other perishable commodities.* [Reserved]

Note.—Regulatory definition will be provided by Department of Agriculture and published by the Immigration and Naturalization Service as an amendment to this regulation.

(k) *Overseas processing office.* Overseas processing offices are offices outside the United States in which, under the authority of the Secretary of State, applications for adjustment to temporary resident status as a special agricultural worker are received, processed, adjudicated, granted or denied, pursuant to regulations or procedures specified by the Secretary of State.

(l) *Public cash assistance.* Public cash assistance means income or needs-based monetary assistance. This includes but is not limited to supplemental security income received by the alien or his immediate family members through federal, state, or local programs designed to meet subsistence levels. It does not include assistance in kind, such as food stamps, public housing, or other non-cash benefits, nor does it include work-related compensation or certain types of medical assistance (Medicare, emergency treatment, services to pregnant women or children under 18 years of age, or treatment in the interest of public health).

(m) *Qualified designated entity.* A qualified designated entity is any state, local, church, community, or voluntary agency, farm labor organization, association of agricultural employers or individual determined by the Service to be qualified to assist aliens in the preparation of applications for Legalization and/or Special Agricultural Worker status.

(n) *Qualifying agricultural employment.* Qualifying agricultural employment is seasonal field work related to planting, cultural practices, cultivating, growing and harvesting of fruits, vegetables, and other perishable commodities as defined by the Secretary of Agriculture by regulation. Agricultural employment which is not field work (e.g. the sorting or packing of agricultural products at other than a field site, the processing or distribution of agricultural products, equipment maintenance, or administrative duties) is not qualifying employment for the purpose of eligibility for adjustment of status under section 210 of the Act. Field work related to products other than fruits, vegetables, or other perishable commodities is not qualifying employment for the purpose of such eligibility. The requisite period of qualifying agricultural employment depends on whether the alien is applying for Group 1 or Group 2 status.

(o) *Regional processing facility.* Regional Processing Facilities are Service offices established in each of the four Service regions to adjudicate, under the authority of the Directors of the Regional Processing Facilities, applications for adjustment of status under sections 210 and 245a of the Act.

(p) *Service.* The Immigration and Naturalization Service (INS).

(q) *Special agricultural worker.* Any individual granted temporary resident status in the Group 1 or Group 2 classification or permanent resident status under section 210(a) of the Act.

(r) *Subject to an Order to Show Cause.* Subject to an Order to Show Cause means actual service of the Order to Show Cause upon the alien through the mail or by personal service.

§ 210.2 Application for temporary resident status.

(a)(1) *Application for temporary resident status.* An alien agricultural worker who believes that he or she is eligible for adjustment of status under the provisions of § 210.3 of this part may file an application for such adjustment at a qualified designated entity, at a legalization office, or at an overseas processing office outside the United States. Such application must be filed within the application period except that an alien described in paragraph (b)(2) of this section must file such application during the period(s) specified therein.

(2) *Application for Group 1 status.* An alien who believes that he or she qualifies for Group 1 status as defined in § 210.1(d) of this part and who desires to apply for that classification must so endorse his or her application at the time of filing. Applications not so endorsed will be regarded as applications for Group 2 status as defined in § 210.1(e) of this part.

(3) *Numerical limitations.* The numerical limitations of sections 201 and 202 of the Act do not apply to the adjustment of aliens to lawful temporary or permanent resident status under section 210 of the Act. No more than 350,000 aliens may be granted temporary resident status in the Group 1 classification. If more than 350,000 aliens are determined to be eligible for Group 1 classification, the first 350,000 aliens who file applications for that classification shall be accorded that classification upon approval of their applications. Applicants who may be eligible for Group 1 classification who file after the first 350,000 applications have been received shall be classified as Group 2 aliens. There is no limitation on the number of aliens whose resident status may be adjusted from temporary to permanent in Group 2 classification.

(b) *Filing date of application*—(1) *General.* The date the alien submits an application to a qualified designated entity, legalization office or overseas processing office shall be considered the filing date of the application, provided that in the case of an application filed at a qualified designated entity the alien has consented to have the entity forward the application to a legalization office. Qualified designated entities are required to forward completed applications to the appropriate legalization office within 60 days after receipt. Except as provided in paragraph (a)(2) of this section, applications must be filed no later than November 30, 1988.

(2) *Filing date for eligible aliens apprehended prior to the application period.* An alien who was apprehended by the Service on or after November 6, 1986 and prior to June 1, 1987 and who has established a nonfrivolous claim to eligibility for adjustment of status under

section 210 of the Act must file an application for adjustment of status during the period beginning on June 1, 1987 and ending on June 30, 1987.

(c) *Filing of application*—(1) *General.* The application must be filed on Form I–700 at a qualified designated entity, at a legalization office, or at an overseas processing office. Only aliens who entered before November 6, 1986 and remained in the United States, other than during a period of travel authorized by the Service, may file applications in the United States. All other aliens seeking adjustment of status under this part must file applications for that benefit outside the United States. If the applicant is 14 years or older, the application must be accompanied by a completed Form FD–258 (Fingerprint Card).

(2) *Applications in the United States.* (i) In the case of applications filed at a Service legalization office, the district director, at his or her discretion, may require filing either by mail or in person, or may permit filing in either manner. The applicant must appear for a personal interview at the legalization office when scheduled.

(ii) All fees for applications filed in the United States must be submitted in the exact amount in the form of a money order, cashier's check, or bank check made payable to the Immigration and Naturalization Service. No personal checks or currency will be accepted. Fees will not be waived or refunded under any circumstances.

(3) *Applications outside the United States.* An application for temporary residence under this part filed by an alien outside the United States must be filed with the required fee at an overseas processing office. Consular officers at overseas processing offices are authorized to approve or deny such applications.

(d) *Interview.* Each applicant, regardless of age, must appear at the appropriate Service legalization office or overseas processing office and must be fingerprinted for the purpose of issuance of Form I–688. Each applicant shall be interviewed by an immigration or consular officer, except that the interview may be waived when it is impractical because of the health of the applicant.

(e) *Medical examination.* An applicant under this part shall be required to be examined by a selected civil surgeon or, in the case of an applicant abroad, by a physician or clinic designated to perform medical examinations of immigrant visa applicants, whose report setting forth the findings concerning the mental and physical condition of the applicant shall be incorporated into the record. Any applicant certified as excludable under paragraphs (1), (2), (3), (4), or (5) of section 212(a) of the Act may appeal to a Board of Medical Officers of the U.S. Public Health Service as provided in section 234 of the Act and Part 235 of this chapter.

(f) *Limitation on access to information and confidentiality.* (1) Except for consular officials engaged in the processing of applications overseas and employees of a qualified designated entity where an application is filed with that entity, no person other than a sworn officer or employee of the Department of Justice or bureau or agency thereof, will be permitted to examine individual applications.

(2) Files and records prepared by qualified designated entities under this section are confidential. The Attorney General and the Service shall not have access to these files and records without the consent of the alien.

(3) Information furnished pursuant to an application for temporary resident status under this section shall only be used in the determination process or to enforce the provisions of section 210(b)(7) of the Act, relating to fraud and false statements in applications as provided in paragraph (f)(4) of this section.

(4) If a determination is made by the Service that the alien has, in connection with his or her application, engaged in fraud or willful misrepresentation of a material fact, provided a false writing or document in making his or her application, or engaged in any other activity prohibited by section 210(b)(7) of the Act, the Service shall refer the matter to the U.S. Attorney for possible prosecution of the alien or any person who created or supplied a false writing or document for use in an application for adjustment of status under this part. If prosecution is declined, the Service may issue an order to show cause and warrant of arrest, unless the United States Attorney has notified the Service that the matter submitted is without merit.

(g) *Decision.* The applicant shall be notified of the decision and, if the application is denied, of the reason therefor. Appeal from an adverse decision under this part may be taken by the applicant on Form I–694, in accordance with the provisions of § 103.3(a)(2) of this chapter. An applicant for Group 1 status as defined in § 210.1(e) of this part who is determined to be ineligible for that status may be classified as a temporary resident eligible for permanent residence under Group 2 as defined in § 210.1(f) of this part if otherwise eligible for Group 2 status. In such a case the applicant shall be notified of the decision to accord him or her Group 2 status and to deny Group 1 status. He or she is entitled to file an appeal in accordance with the provisions of § 103.3(a)(2) of this chapter from that portion of the decision denying Group 1 status.

(h) *Motions.* The regional processing facility director may *sua sponte* reopen and reconsider any adverse decision. When an appeal to the Associate Commissioner, Examinations (Administrative Appeals Unit) has been filed, the INS director of the Regional Processing Facility may issue a new decision that will grant the benefit which has been requested. The director's decision must be served on the appealing party within forty-five (45) days of receipt of any briefs and/or new evidence, or upon expiration of the time allowed for the submission of any briefs.

(i) *Certifications.* The regional processing facility director may, in accordance with § 103.4 of this chapter, certify a decision to the Associate Commissioner, Examinations (Administrative Appeals Unit) when the case involves an unusually complex or novel question of law or fact.

§ 210.3 Eligibility.

(a) *General.* An alien who, during the twelve-month period ending on May 1, 1986, has both engaged in qualifying agricultural employment in the United States for at least 90 man-days is eligible for status as an alien lawfully admitted for temporary residence if otherwise admissible under the provisions of section 210(c) of the Act and if he or she is not ineligible under the provisions of paragraph (d) of this section.

(b) *Proof of eligibility*—(1) *Burden of proof.* An alien applying for adjustment of status under this part has the burden of proving by a preponderance of the evidence that he or she has worked the requisite number of man-days, and in the case of a Group 1 applicant, has resided in the United States for the requisite periods, is admissible to the United States under the provisions of section 210(c) of the Act, and is otherwise eligible for adjustment of status under this section. If the applicant cannot provide documentation which shows qualifying employment for each of the requisite man-days, or in the case of a Group 1 applicant, which meets the residence requirement, the applicant may meet his or her burden of proof by providing documentation sufficient to establish the requisite employment or residence as a matter of just and

reasonable inference. The inference to be drawn from the documentation provided shall depend on the extent of the documentation, its credibility and amenability to verification as set forth in paragraphs (d) (2) and (3) of this section.

(2) *Evidence.* The sufficiency of all evidence produced by the applicant will be judged according to its probative value and credibility. Original documents will be given greater weight than copies. To meet his or her burden or proof, an applicant must provide evidence of eligibility apart from his or her own testimony. Analysis of evidence submitted will include consideration of the fact that work performed by minors and spouses is sometimes credited to a principal member of a family.

(3) *Verification.* Affidavits and other personal testimony by an applicant which are not corroborated, in whole or in part, by other credible evidence (including testimony of persons other than the applicant) will not serve to meet an applicant's burden of proof. All evidence of identity, qualifying employment, admissibility, and eligibility submitted by an applicant for adjustment of status under this part will be subject to verification by the Service. Failure by an applicant to release information protected by the Privacy Act or related laws when such information is essential to the proper adjudication of an application may result in denial of the benefit sought. The Service may solicit from agricultural producers, farm labor contractors, collective bargaining organizations and other groups or organizations which maintain records of employment, lists of workers against which evidence of qualifying employment can be checked. If such corroborating evidence is not available and the evidence provided is deemed insufficient, the application may be denied.

(c) *Documents.* A complete application for adjustment of status filed under this part must be accompanied by proof of identity, evidence of qualifying employment, evidence of residence and such evidence of admissibility or eligibility as is required hereunder and as may be requested by the examining immigration officer in accordance with such requirement. Wherever possible documents must be submitted in the original except the following: Official government records, employment or employment related records maintained by employers, unions, or collective bargaining organizations; school records maintained by a school or school board; or other records maintained by a party other than the applicant. Copies of records maintained by parties other than the applicant which are submitted in evidence must be certified as true and correct by such parties and must bear their seal or signature or the signature and title of persons authorized to act in their behalf. If the return of original documents is desired by the applicant, they must be accompanied by notarized copies or copies certified true and correct by a qualified designated entity or by the alien's representative in the format prescribed in § 204.2(j)(1) or (2) of this chapter. Such certified copies unaccompanied by original documents are unacceptable for the purposes of an application under this part. At the discretion of the district director or consular officer, original documents, even if accompanied by certified copies, may be temporarily retained for forensic examination.

(1) *Proof of identity.* Evidence to establish identity is listed below in descending order of preference:

(i) Passport;

(ii) Birth certificate;

(iii) Any national identity document from a foreign country bearing a photo and/or fingerprint (e.g., "cedula", "cartilla", "carte d'identite," etc.);

(iv) Driver's license or similar document issued by a state if it contains a photo;

(v) Baptismal record or marriage certificate; or

(vi) Affidavits.

(2) *Assumed names*—(i) *General.* In cases where an applicant claims to have met any of the eligibility criteria under an assumed name, the applicant has the burden of proving that the applicant was in fact the person who used that name.

(ii) *Proof of common identity.* The most persuasive evidence is a document issued in the assumed name which identifies the applicant by photograph, fingerprint or detailed physical description. Other evidence which will be considered are affidavit(s) by a person or persons other than the applicant, made under oath, which identify the affiant by name and address, state the affiant's relationship to the applicant and the basis of the affiant's knowledge of the applicant's use of the assumed name. Affidavits accompanied by a photograph which has been identified by the affiant as the individual known to the affiant under the assumed name in question will carry greater weight. Other documents using the assumed name which are in the possession of the applicant may serve to establish the common identity when substantiated by corroborating detail.

(3) *Proof of employment.* The applicant may establish qualifying employment by primary evidence, or where such primary evidence is not reasonably available, by secondary evidence, or by a combination of the two.

(i) *Primary evidence.* An applicant may establish the performance of qualifying employment through government employment records or records maintained by agricultural producers, farm labor contractors, collective bargaining organizations and other groups or organizations which maintain records of employment.

(ii) *Secondary evidence.* If primary evidence of qualifying employment is not reasonably available to the applicant, or if the primary evidence does not provide complete information with respect to employment, the applicant may submit any other evidence which may tend to corroborate performance of qualifying employment. Such secondary evidence includes but is not limited to worker identification issued by employers or collective bargaining organizations, union membership cards or other union records such as dues receipts or records of the applicant's involvement or that of his or her immediate family with organizations providing services to farmworkers. Also included are work records such as pay stubs, piece work receipts, W–2 Forms or copies of income tax returns certified by the IRS. Affidavits may be submitted under oath, by agricultural producers, foremen, farm labor contractors, fellow employees, or other persons with specific knowledge of the applicant's employment. The affiant must be identified by name and address; the name of the applicant and the relationship of the affiant to the applicant must be stated; and the source of the information in the affidavit (e.g. personal knowledge, reliance on information provided by others, etc.) must be indicated. The affidavit must also provide information regarding the crop and the type of work performed by the applicant and the period during which such work was performed. The affiant must provide a certified copy of corroborating records or state the affiant's willingness to personally verify the information provided. The weight and probative value of any affidavit accepted will be determined on the basis of the substance of the affidavit and any documents which may be affixed thereto which may corroborate the information provided.

(4) *Proof of residence.* Evidence to establish residence in the United States during the requisite period(s) includes: Employment records as described in paragraph (c)(3) of this section; utility

bills (gas, electric, phone, etc.), receipts, or letters from companies showing the dates during which the applicant received service; school records (letters, report cards, etc.) from the schools that the applicant or his or her children have attended in the United States showing the name of school, name and, if available, address of student, and periods of attendance, and hospital or medical records showing similar information; attestations by churches, unions, or other organizations to the applicant's residence by letter which: identify applicant by name, are signed by an official (whose title is shown), show inclusive dates of membership, state the address where applicant resided during the membership period, include the seal of the organization impressed on the letter, establish how the author knows the applicant, and the origin of the information; and additional documents that could show that the applicant was in the United States at a specific time, such as: money order receipts for money sent out of the country; passport entries; birth certificates of children born in the United States; bank books with dated transactions; letters of correspondence between the applicant and another person or organization; Social Security card; Selective Service card; automobile license receipts, title, vehicle registration, etc.; deeds, mortgages, contracts to which applicant has been a party; tax receipts; insurance policies, receipts, or letters; and any other document that will show that applicant was in the United States at a specific time. For Group 2 eligibility, evidence of performance of the required 90 man-days of seasonal agricultural services shall constitute evidence of qualifying residence.

(5) *Proof of financial responsibility.* Generally, the evidence of employment submitted under paragraph (c)(3) of this section will serve to demonstrate the alien's financial responsibility. If it appears that the applicant may be inadmissible under section 212(a)(15) of the Act, he or she may be required to submit documentation showing a history of employment without reliance on public cash assistance for all periods of residence in the United States.

(d) *Ineligible classes.* The following classes of aliens are ineligible for temporary residence under this part:

(1) An alien who has assisted in the persecution of any person or persons on account of race, religion, nationality, membership in a particular social group, or political opinion;

(2) An alien who at any time was a nonimmigrant exchange visitor under section 101(a)(15)(J) of the Act who is subject to the two-year foreign residence requirement unless the alien has complied with that requirement or the requirement has been waived pursuant to the provisions of section 212(e) of the Act.;

(3) An alien who was in the custody of the Service or was apprehended as a deportable alien after November 6, 1986 and prior to June 1, 1987 who was determined to have a nonfrivolous claim to eligibility for adjustment of status under the provisions of section 210(d)(1) of the Act and who does not file an application for adjustment of status to that of temporary resident under this part prior to July 1, 1987;

(4) An alien who was apprehended as a deportable alien subsequent to the beginning of the application period on June 1, 1987 who does not file an application for adjustment of status to that of temporary resident under this part prior to the thirty-first day after his or her release from Service custody or December 1, 1988, whichever is earlier.

(5) An alien excludable under the provisions of section 212(a) of the Act whose grounds of excludability may not be waived, pursuant to section 210(c)(2)(B)(ii) of the Act.

(e) *Exclusion grounds*—(1) *Grounds of exclusion not to be applied.* Sections (14), (20), (21), (25), and (32) of section 212(a) of the Act shall not apply to applicants applying for temporary resident status.

(2) *Waiver of grounds for exclusion.* Except as provided in paragraph (c)(3) of this section, the Attorney General or the Secretary of State, if the application is filed overseas, may waive any other provision of section 212(a) of the Act only in the case of individual aliens for humanitarian purposes, to assure family unity, or when the granting of such a waiver is in the public interest. If an alien is excludable on grounds which may be waived as set forth in this paragraph, he or she shall be advised of the procedures for applying for a waiver of grounds of excludability on Form I-690. When an application for waiver of grounds of excludability is filed jointly with an application for temporary residence under this section, it shall be accepted for processing at the legalization office or overseas processing office. If an application for waiver of grounds of excludability is submitted after the alien's preliminary interview at the legalization office it shall be forwarded to the appropriate regional processing facility. All applications for waivers of grounds of excludability must be accompanied by the correct fee in the exact amount. All fees for applications filed in the United States must be in the form of a money order, cashier's check, or bank check. No personal checks or curreny will be accepted. Fees will not be waived or refunded under any circumstances. An application for waiver of grounds of excludability under this part submitted at a legalization office shall be approved or denied by the director of the regional processing facility in whose jurisdiction the applicant's application for adjustment of status was filed, except that in cases involving clear statutory ineligibility or admitted fraud, such application may be denied by the district director in whose jurisdiction the application is filed, and in cases returned to a legalization office for reinterview, such application may be approved at the discretion of the district director. The applicant shall be notified of the decision and, if the application is denied, of the reason therefor. The applicant may appeal the decision within 30 days after the service of the notice pursuant to the provisions of § 103.3(a) of this chapter.

(3) *Grounds of exclusion that may not be waived.* The following provisions of section 212(a) of the Act may not be waived:

(i) Paragraphs (9) and (10) (criminals);

(ii) Paragraph (15) (public charge) except as provided in paragraph (c)(4) of this section.

(iii) Paragraph (23) (narcotics) except for a single offense of simple possession of thirty grams or less of marijuana.

(iv) Paragraphs (27), (prejudicial to the public interest), (28), (communists), and (29) (subversive);

(v) Paragraph (33) (nazi persecution).

(4) *Special rule for determination of public charge.* An alien is not excludable under paragraph (c)(3)(ii) of the section if the alien demonstrates a history of employment in the United States evidencing self-support without reliance on public cash assistance as defined in § 210.1(l) of this part.

§ 210.4 Status and benefits.

(a) *Date of adjustment.* The status of an alien whose application for temporary resident status is approved shall be adjusted to that of a lawful temporary resident as of the date on which the fee was paid at a legalization office, except that the status of an alien who applied for such status at an overseas processing office shall be adjusted as of the date of his or her entry into the United States after approval of his or her application.

(b) *Employment and travel authorization*—(1) *General.* Authorization for employment and travel abroad for temporary resident status applicants under section 210 of

the Act may only be granted by a Service legalization office. In the case of an application which has been filed with a qualified designated entity, employment authorization may only be granted after a nonfrivolous application has been received at a legalization office, and receipt of the fee has been recorded.

(2) *Employment authorization prior to the granting of temporary resident status.* Permission to travel abroad and to accept employment will be granted to the applicant, after an interview has been conducted in connection with a nonfrivolous application at a legalization office. If an interview appointment cannot be scheduled within 30 days from the date an application is filed at a legalization office, authorization to accept employment will be granted valid to the scheduled appointment date. The appointment letter will be endorsed with the temporary employment authorization. Employment authorization subsequent to an interview will be granted on Service Form I–688A, and will be restricted to six months duration, pending final determination on the application for temporary resident status. If a final determination has not been made on the application prior to the expiration date of the I–688A, that date may be extended upon return of the I–688A by the applicant to the legalization office where it was obtained.

(3) *Employment and travel authorization upon grant of temporary resident status.* Upon grant of an application for adjustment to temporary resident status by a regional processing facility, the processing facility will forward a notice of approval to the applicant at his or her last known address and to his or her qualified designated entity or representative. The applicant will be required to return to the legalization office where the application was initially received, surrender the I–688A previously issued, and will be issued Form I–688, Temporary Resident Card, authorizing employment and travel abroad. An alien whose status is adjusted to that of a lawful temporary resident under section 210 of the Act has the right to reside in the United States, to travel abroad (including commuting from a residence abroad), and to accept employment in the United States in the same manner as aliens lawfully admitted for permanent residence.

(c) *Ineligibility for immigration benefits.* An alien whose status is adjusted to that of a lawful temporary resident under section 210 of the Act is not entitled to submit a petition pursuant to section 203(a)(2) or to any other benefit or consideration accorded under the Act to aliens lawfully admitted for permanent residence, except as provided in paragraph (b)(3) of this section.

(d) *Termination of temporary resident status*—(1) *General.* The Director of the regional processing facility may terminate the temporary residence status of a special agricultural worker at any time in accordance with section 210(a)(3) of the Act if the alien is determined to be deportable under section 241 of the Act. An alien who is excludable under section 210(c) of the Act, who is not deportable under section 241 of the Act, is not subject to termination of temporary resident status if the ground of excludability arose subsequent to the adjustment of the alien's status to that of a temporary resident. The termination of an alien's temporary residence status may be based on a finding by a district director that the alien is deportable. It is not necessary that a final order of deportation have been entered in order to terminate temporary resident status.

(2) *Procedure.* The termination of an alien's status under paragraph (d)(1) of this section will be made only on notice to the alien, who shall be afforded an opportunity to offer evidence in opposition to the grounds alleged for termination of his or her status. If the alien is deportable under section 241(a)(10) of the Act because he or she was excludable at the time of his or her adjustment of status to that of lawful temporary resident, he or she shall be advised of the procedures for applying for a waiver of grounds of excludability on Form I–690 if a waiver is available under section 210(c) of the Act. If the alien is granted such a waiver, the Service proceeding to terminate the alien's lawful temporary resident status will be concluded, and the alien will be so advised.

If the alien's status is terminated, the director of the Regional Processing Facility shall notify the alien of the decision and of the reasons for the termination. The alien may appeal the decision within 30 days after the service of the notice, pursuant to the provisions of § 103.3(a)(2) of this part.

(3) *Surrender of Form I–688.* An alien whose status as a temporary resident has been terminated under this section shall, upon demand, promptly surrender to the district director having jurisdiction over the alien's place of residence or, in the case of a commuter, employment, the Form I–688, Temporary Resident Card, issued to him or her at the time of the grant of temporary resident status.

§ 210.5 Adjustment to permanent resident status.

(a) *Eligibility and date of adjustment to permanent resident status.* The status of an alien lawfully admitted to the United States for temporary residence under section 210(a)(1) of the Act, if the alien has otherwise maintained such status as required by the Act, shall be adjusted to that of an alien lawfully admitted to the United States for permanent residence as of the following dates:

(1) *Group 1.* The status of an alien determined to be eligible for Group 1 classification shall be adjusted to that of an alien lawfully admitted for permanent residence as of December 1, 1989.

(2) *Group 2.* The status of an alien determined to be eligible for Group 2 classification shall be adjusted to that of an alien lawfully admitted for permanent residence as of December 1, 1990.

(b) *Maintenance of temporary resident status; ADIT processing*—(1) *General.* Before the status of an alien lawfully admitted for temporary residence under section 210(a)(1) of the Act can be adjusted to that of an alien lawfully admitted for permanent residence, the alien must appear at a legalization office or such other Service office as is designated for this purpose for a determination that he or she has maintained temporary resident status, and for completion of processing for issuance of Form I–551, Alien Registration Receipt Card.

(2) *Maintenance of status.* Information provided by the alien concerning his or her maintenance of status will be subject to Service verification. The status of an alien described in paragraph (b)(1) of this section who has maintained temporary resident status will be adjusted to that of an alien lawfully admitted for permanent residence effective on the date appropriate for his or her group as provided in paragraph (a) of this section. The alien must execute an affidavit stating that he or she has maintained status as a temporary resident. An alien who is deportable under section 241 of the Act has failed to maintain status as a temporary resident and is subject to termination of temporary resident status as provided in § 210.4(d) of this part. An alien who is excludable under section 210(c) of the Act who is not deportable under section 241 of the Act is not subject to termination of temporary resident status if the ground of

excludability arose subsequent to the adjustment of the alien's status to that of a temporary resident. If the alien is deportable under section 241(a) of the Act because he or she was excludable at the time his or her status was adjusted to that of a lawful temporary resident, he or she shall be advised of the procedures for applying for a waiver of grounds of excludability if a waiver is available under section 210(c) of the Act. If the alien applies for such a waiver, and the waiver is granted after the dates of adjustment set in paragraph (a) of this section, the adjustment of the alien's status to that of an alien lawfully admitted for permanent residence shall be recorded as of the date of adjustment appropriate for his or her group.

(3) *ADIT processing.* An alien described in paragraph (b)(1) of this section must provide suitable ADIT photographs, and a fingerprint and signature must be obtained from the alien on Form I–89.

Dated: March 5, 1987.

Alan C. Nelson,

Commissioner, Immigration and Naturalization Service.

[FR Doc. 87–5837 Filed 3–17–87; 10:10 am]

BILLING CODE 4410–10–M

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8 CFR Part 245a

Adjustment of Status for Certain Aliens

AGENCY: Immigration and Naturalization Service, Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: This rule would implement section 245A of the Immigration and Nationality Act as amended by section 201 of the Immigration Reform and Control Act of 1986 ("IRCA"). Section 201 of IRCA directs the Attorney General to adjust the status of certain aliens to that of aliens lawfully admitted for temporary residence if they meet certain requirements. This section also directs the Attorney General to adjust the status of a temporary resident alien to that of an alien lawfully admitted for permanent residence if the alien meets certain requirements.

DATE: Comments must be received on or before April 20, 1987.

ADDRESS: Send original and two copies of comments to Assistant Commissioner for Legalization, Office of Legalization, Room LL–100, INS, 425 "I" Street NW., Washington, DC 20536.

FOR FURTHER INFORMATION CONTACT: William S. Slattery, Assistant Commissioner, Legalization, 425 "I" Street NW., Washington, DC 20536, (202) 786–3658.

SUPPLEMENTARY INFORMATION:

Background of Proposed Rule

On November 6, 1986, the President signed into law the Immigration Reform and Control Act of 1986, Pub. L. 99–603 ("IRCA"). This legislation is the most comprehensive reform of our immigration laws since the enactment of the Immigration and Nationality Act ("INA") in 1952. This legislation reflects a resolve to strengthen law enforcement to control illegal immigration. It also reflects the Nation's humanitarian concerns for certain aliens who have been residing illegally in the United States. The theme of this legislation is that the key to maintaining the immigration tradition of the United States is the firm, fair enforcement of laws, which are designed to encourage the continued flow of legal immigrants, and to close the back door to illegal entry.

Section 201 of IRCA, the subject of this proposed rule, reflects the traditional humanitarian concerns of this Nation by providing for the legalization of status of certain aliens who have been residing illegally in the United States since January 1, 1982. At the same time, as reflected under certain provisions of section 201 of IRCA, Congress intended that aliens eligible for the legalization program be admissible as immigrants, therefore requiring the aliens to meet certain standards of eligibility.

Since November 6, 1986, the Immigration and Naturalization Service has taken a number of steps to insure that the new legislation will be implemented effectively, fairly, and in an orderly manner. Service officials have engaged in a continuing dialogue with members of the public and representatives of interested organizations on how to implement this legislation. On January 20, 1987, the Service took the unprecedented step of publishing in the **Federal Register** a notice making available to the public the preliminary working draft regulations. More than 6,800 persons requested and received a copy of these preliminary draft regulations. As a result, 164 individuals and interested organizations submitted written comments. All comments were seriously considered by the Service. A number of the suggestions received by the Service are reflected in this proposed rule.

These rules implementing section 201 of IRCA are proposed against this background of openness and a good-faith on the part of the Service to maintain an ongoing dialogue.

Summary of the Proposed Rule

The proposed rule would amend 8 CFR Part 245 by creating a new Part 245a. The proposed rule would permit certain aliens, who are otherwise eligible, to adjust their status to that of aliens lawfully admitted for temporary residence.

Aliens who are eligible to apply include: Aliens who entered the United States before January 1, 1982 and who have continued to reside in the United States in an unlawful status since such date and through the date the alien files an application under this rule; aliens who entered the United States prior to January 1, 1982 as nonimmigrants and whose period of authorized stay expired before January 1, 1982 or whose unlawful status was known to INS as of such date; aliens whose status is that of Cuban-Haitian Entrants; and, aliens who prior to January 1, 1982 were either granted extended voluntary departure (EVD) or were in a deferred action status.

All applicants for legalization, with certain exceptions for those applicants who have a Cuban-Haitian Entrant status, must meet certain requirements. In general, an applicant must establish, (1) continuous residence in the United States since January 1, 1982; (2) continuous physical presence in the United States since November 6, 1986; and (3) admissibility as an immigrant. Additionally, applicants must file a timely application as prescribed under this rule, submit the result of a prescribed medical examination and provide proof that they either have registered or are registering under the Military Selective Service Act, if required to be so registered under that Act.

This rule establishes a single level of appellate review to permit the applicant to challenge a denial of his application for temporary resident status. This rule also provides that that status shall be terminated by the Service upon the occurrence of certain events.

This rule also sets forth procedures and the substantive requirements for the adjustment of status of temporary residents to that of permanent residents.

Finally, the rule provides that aliens who submit false documentation or make false representations in support of their application for legalization will be subject to criminal prosecution and eventual expulsion from the United States.

Key Provisions of the Proposed Rule

Application Period: An alien must file an application for legalization between

May 5, 1987 and May 4, 1988. However, aliens who have been served with an Order to Show Cause subsequent to November 6, 1986, must apply within thirty days of the beginning of the application period. Aliens who are served with an Order to Show Cause during the application period must apply within thirty days but not later than May 4, 1988. Failure to apply within the application period, as fully set forth in this rule, will render the alien statutorily ineligible for legalization.

Where to File the Application: Form I-687 ( ) and supporting documentation may be filed either at a Service Legalization Office or with a Qualified Designated Entity ("ODE").

What Documentation Should be Submitted to INS: In addition to the completed Form I-687, the applicant must submit the result of a medical examination, an application for waivers of grounds of excludability, if applicable, and sufficient documentary information as fully set forth in this rule, to prove the applicant's identity, his or her continuous residence in the United States since January 1, 1982, and proof of financial responsibility. The Service advises eligible aliens to start gathering this documentation as soon as possible.

Eligibility Requirements

(1) Continuous Residence Since January 1, 1982

An applicant otherwise eligible for legalization must prove that he or she "resided continuously" in the United States since January 1, 1982. However, certain absences will not be considered to have interrupted this continuous residence requirement. The Service initially considered that a single absence of more than 30 days or aggregate absences totaling more than 150 days would break the continuous residence requirement. However, in light of the public comments received on this subject, the Service has reconsidered its position and under the proposed rule a single absence of 45 days or more and aggregate absences of 180 days or more would break the continuous residence requirement.

(2) Continuous Physical Presence Since November 6, 1986

In addition to the continuous residence requirement since January 1, 1982, the applicant must prove that he has been continuously physically present in the United States since November 6, 1986. Under the proposed rule, absences that were brief, casual, and innocent will not break the physical presence requirement. Only an absence authorized by the Service for not more than thirty (30) days will be considered brief, casual, and innocent. An alien who entered the United States without inspection subsequent to November 6, 1986, will not be considered to have made an "innocent" absence. The INA imposes criminal penalties on aliens who enter the United States without inspection. Section 201 of IRCA was enacted to forgive certain past illegalities and not subsequent violations of our laws.

(3) Definition of the Term "Known to the Government"

An alien who entered the United States as a nonimmigrant before January 1, 1982, may be eligible for legalization if the alien's "unlawful status was known to the Government" as of January 1, 1982. The Service, in this proposed rule, is interpreting the term "known to the Government" to mean "INS." This interpretation as previously set forth in the preliminary draft regulations, was challenged by many commentators. The Service initially proposed that an alien's unlawful status would have been known by the Service, if the Service had made an affirmative determination that the alien was subject to deportation proceedings. In light of the public comments, the Service has reconsidered its initial proposal. Under this proposed rule, if the Service received information as of January 1, 1982 from a federal agency reflecting the fact that the alien clearly expressed to the federal agency that he or she was in violation of his or her lawful status, and that information is contained in the alien's A File, the alien's unlawful status would be known to INS regardless of whether or not the Service made a determination that the alien was subject to deportation proceedings.

Pursuant to section 103 of the INA, only the Attorney General is charged with the administration and enforcement of the immigration laws. Correspondingly, only the Attorney General can make a determination that an alien's status is "unlawful." To interpret the word "Government" to include Federal, State, and local agencies would make the administration of section 201 difficult, if not impossible, and would implicity vest government agencies with an authority that Congress specifically granted only to the Attorney General.

(4) Admissible as an Immigrant

An alien who meets the residence requirements must be admissible as an immigrant. This rule implements the statutory requirements that certain grounds of admissibility are not applicable, that other grounds may be waived, and that other grounds cannot be waived. This rule also defines the terms "felony" and "misdemeanor." The term "felony" is defined as including a felony committed outside the United States. This rule also sets forth procedures for obtaining waivers of those grounds of admissibility which may be waived. In determining a waiver based on "family unity" the proposed rule defines family unity as limited to spouses, unmarried minor children and parents.

Administrative Appellate Review

This proposed rule establishes a single level of administrative appellate review to adjudicate appeals from legalization decisions. The proposed appellate authority is the Associate Commissioner for Examinations.

Termination of Temporary Resident Status

Consistent with section 245A(b)(2) of IRCA, this proposed rule sets forth the procedural and substantive grounds for terminating the status of a temporary resident alien. The rule proposes that a decision to terminate status may be appealed to the Associate Commissioner for Examinations.

Adjustment of Temporary Resident Status to Permanent Resident Status

This rule sets forth the proposed procedural and substantive requirements that a temporary resident alien must comply with in order to change his or her status to that of an alien lawfully admitted for permanent residence. This rule proposes to eliminate the requirement of a second medical examination to the extent that all applicants for temporary residents must submit to a medical examination.

Temporary Disqualification of Newly Legalized Aliens From Receiving Certain Public Welfare Assistance

The Attorney General will publish a separate list of programs identified as programs of financial assistance furnished under Federal law (whether through grant, loan, guarantee, or otherwise) on the basis of financial need which newly legalized aliens (with limited exceptions) may not receive for five (5) years.

In accordance with 5 U.S.C. 605(b), the Commissioner of Immigration and Naturalization Service certifies that this rule, if promulgated, will not have a significant economic impact on a substantial number of small entities.

This is not a major rule as defined within the meaning of section 1(b) of EO 12291.

The information collection requirements contained in this regulation will be submitted to OMB for review under the Paperwork Reduction Act.

List of Subjects in 8 CFR Part 245a

Aliens, Temporary resident status and permanent resident status.

Proposed Rule

Accordingly, pursuant to the Immigration Reform and Control Act of 1986, and section 103 of the Immigration and Nationality Act, as amended, the Immigration and Naturalization Service proposes to add a new Part 245a in Title 8, Code of the Federal Regulations to be known as 8 CFR Part 245a. Part 245a is proposed to read as follows:

PART 245a—ADJUSTMENT OF STATUS TO THAT OF PERSONS ADMITTED FOR LAWFUL TEMPORARY OR PERMANENT RESIDENT STATUS UNDER SECTION 245A OF THE IMMIGRATION AND NATIONALITY ACT, AS AMENDED BY PUB. L. 99-603, THE IMMIGRATION REFORM AND CONTROL ACT OF 1986

Sec.

Authority: Pub. L. 99-603, 100 Stat. 3359; 8 U.S.C. 1101 note.

§ 245a.1 Definitions.

As used in this chapter:

(a) The term "Act" means the Immigration and Nationality Act, as amended by The Immigration Reform and Control Act of 1986.

(b) The term "Service" means the Immigration and Naturalization Service (INS).

(c)(1) The term "resided continuously" as used in section 245A(a)(2) of the Act, means that the alien shall be regarded as having resided continuously in the United States if, at the time of filing of the application for temporary resident status: (i) No single absences from the United States has exceeded forty-five (45) days, unless the alien can establish that due to emergent reasons, his or her return to the United States could not be accomplished within the time period allowed; (ii) the aggregate of all absence has not exceeded one hundred and eighty (180) days between January 1, 1982 through the date the application for temporary resident status is filed; (iii) the alien was maintaining residence in the United States; and (iv) the alien's departure from the United States was not based on an order of deportation. An alien who has been absent from the United States in accordance with the Service's advance parole procedures shall not be considered as having interrupted his or her continuous residence as required at the time of filing an application.

(2) The term "continuous residence," as used in section 245A(b)(1)(B) of the Act, means that the alien shall be regarded as having resided continuously in the United States if, at the time of applying for adjustment from temporary residence to permanent resident status: No single absence from the United States has exceeded thirty (30) days, and the aggregate of all absences has not exceeded ninety (90) days between the date of granting of lawful temporary resident status and of applying for permanent resident status, unless the alien can establish that due to emergent reasons the return to the United States could not be accomplished within the time period(s) allowed.

(d) In the term "alien's unlawful status was known to the government," the term "government" means the Immigration and Naturalization Service. An alien's unlawful status was "known to the government" only if:

(1) The Service received factual information constituting a violation of the alien's nonimmigrant status from any agency, bureau or department, or subdivision thereof, of the Federal government, which information was stored or otherwise recorded in the official Service alien file, whether or not the Service took follow-up action on the information received. In order to meet the standard of "information constituting a violation of the alien's nonimmigrant status," the alien must have made a clear statement or declaration to the other federal agency, bureau or department that he or she was in violation of nonimmigrant status; or

(2) An affirmative determination was made by the Service prior to January 1, 1982 that the alien was subject to deportation proceedings. Evidence that may be presented by an alien to support an assertion that such a determination was made may include, but is not limited to, official Service documents issued prior to January 1, 1982, i.e., Forms I-94, Arrival-Departure Records granting a period of required departure; Forms I-210, Voluntary Departure Notice letter; Forms I-221, Order to Show Cause and Notice of Hearing, and Forms I-543, Order of Denial of Application for Change of Nonimmigrant Status granting a period of required departure. Evidence from Service records that may be used to support a finding that such a determination was made may include, but is not limited to, record copies of the aforementioned forms and other documents contained in alien files, i.e., Forms I-213, Record of Deportable Alien; Unexecuted Forms I-205, Warrant of Deportation; Forms I-265, Application for Order to Show Cause and Processing Sheet; Forms I-541, Order of Denial of Application for Extension of Stay granting a period of required departure, or any other Service record reflecting that the alien's nonimmigrant status was considered by the Service to have terminated or the alien was otherwise determined to be subject to deportation proceedings prior to January 1, 1982, whether or not deportation proceedings were instituted.

(e) The term "to make a determination" as used in § 245a.2(t)(3) of this part means obtaining and reviewing all information required to adjudicate an application for the benefit sought and making a decision thereon. If fraud, willful misrepresentation of a material fact, providing of a false writing or document, or any other activity prohibited by section 245A(c)(6) of the Act is established during the process of making the determination on the application, the Service shall refer the United States Attorney for possible prosecution of the alien or of any person who created or supplied a false writing or document for use in an application for adjustment of status under this part. If prosecution is declined by the United States Attorney, the Service may issue an Order to Show Cause and Warrent of Arrest, unless the United States Attorney has notified the Service that the matter submitted is without merit.

(f) The term "physical presence" as used in section 245A(a)(3)(A) of the Act means actual continuous presence in the United States since date of enactment (11/6/86) until filing of any application for adjustment of status unless a departure is specifically authorized by the Service pursuant to the advance parole procedures set forth in § 212.5(e) of this chapter, or an alien unknowingly (without knowledge of such departure) departed the United States on or after November 6, 1986.

(g) The term "brief, casual, and innocent" means a departure authorized by the Service (advance parole) of not more than thirty (30) days for legitimate emergency or humanitarian purposes unless a further period of authorized departure has been granted in the discretion of the district director. Aliens who reenter or attempt to reenter the U.S. without inspection will not be considered as having made a brief, casual and innocent departure.

(h) The term "brief and casual" as used in section 245A(b)(3)(A) of the Act, means temporary trips abroad as long as

the alien establishes a continuing intention to adjust to lawful permanent resident status. However, such absences must not exceed the specific periods of time required in order to maintain continuous residence.

(i) The term "public cash assistance" means income or needs-based monetary assistance, to include but not limited to supplemental security income, received by the alien or his or her immediate family members through federal, state, or local programs designed to meet subsistence levels. It does not include assistance in kind, such as food stamps, public housing, or other non-cash benefits, nor does it include work-related compensation or certain types of medical assistance (Medicare, emergency treatment, services to pregnant women or children under 18 years of age, or treatment in the interest of public health).

(j) The term "Legalization Office" means local offices of the Immigration and Naturalization Service which accept and process applications for Legalization or Special Agricultural Worker status, under the authority of the INS district directors in whose districts such offices are located.

(k) The term "Regional Processing Facility" means Service offices established in each of the four Service regions to adjudicate, under the authority of the INS Directors of the Regional Processing Facilities, applications for adjustment of status under section 245A(a) or 245A(b)(1) of the Act.

(l) The term "designated entity" means any state, local, church, community, farm labor organization, voluntary organization, association of agricultural employers or individual determined by the Service to be qualified to assist aliens in the preparation of applications for Legalization status.

(m) The term "family unity" as used in section 245A(d)(2)(B)(i) of the Act means maintaining the family group without deviation or change. The family group shall include the spouse, unmarried minor children who are not members of some other household, and parents who reside regularly in the household of the family group.

(n) The term "prima facie" as used in section 245A(e)(1) and (2) of the Act means eligibility is established if the applicant presents a completed I–687 and specific factual information which in the absence of rebuttal proves a claim of eligibility under this part.

(o) The term "misdemeanor" means a crime punishable by imprisonment for a term of one year or less but more than five days, regardless of the term such alien actually served, if any.

(p) The term "felony" means a crime, including a crime committed outside the United States, punishable by imprisonment for a term of more than one year regardless of the term such alien actually served, if any.

(q) The term "subject to an Order to Show Cause" means actual service of the Order to Show Cause upon the alien through the mail or by personal service.

§ 245a.2 Application for temporary residence.

(a) *Application period for temporary residence.* (1) An alien who has resided unlawfully in the United States since January 1, 1982, who believes that he or she meets the eligibility requirements of section 245A of the Act must make application within the twelve month period beginning on May 5, 1987 and ending on May 4, 1988.

(2)(i) An alien who was apprehended by the Service on or after November 6, 1986 and prior to May 5, 1987 and who has established prima facie eligibility for adjustment of status under section 245A(a) of the Act must file an application for adjustment during the period beginning on May 5, 1987 and ending on June 3, 1987.

(ii) An alien who is the subject of an Order to Show Cause issued under section 242 of the Act during the period beginning on May 5, 1987 and ending on April 4, 1988 must file an application for adjustment of status to that of a temporary resident prior to the thirty-first day after the issuance of the Order to Show Cause.

(iii) An alien who is the subject of an Order to Show Cause issued under section 242 of the Act during the period beginning on April 5, 1988 and ending on May 4, 1988 must file an application for adjustment of status to that of a temporary resident not later than May 4, 1988.

(iv) Failure of any alien described in paragraphs (a)(2)(i) through (iii) of this section to file an application for adjustment of status to that of a temporary resident under section 245A(a) of the Act during the respective time period(s) stipulated will render the alien statutorily ineligible for such adjustment of status.

(b) *Eligibility.* (1) The following categories of aliens who are otherwise admissible under section 212(a) of the Act are eligible to apply for status to that of a person admitted for temporary residence:

(i) An alien (other than an alien who entered as a nonimmigrant) who establishes that he or she entered the United States in an unlawful status prior to January 1, 1982 and who has thereafter resided continuously in the United States and who has been physically present in the United States from November 6, 1986 until the date of filing the application.

(ii) An alien who establishes that he or she entered the United States as a nonimmigrant prior to January 1, 1982 and whose period of authorized admission expired through the passage of time prior to January 1, 1982 and who has thereafter resided continuously in the United States and who has been physically present in the United States from November 6, 1986 until the date of filing the application.

(iii) An alien who establishes that he or she entered the United States as a nonimmigrant prior to January 1, 1982 and whose unlawful status was known to the Government as of January 1, 1982 and who has thereafter resided continuously in the United States and who has been physically present in the United States from November 6, 1986 until the date of filing the application.

(iv) An alien described in paragraphs (b)(1)(i) through (iii) of this section was at any time a nonimmigrant exchange visitor (as defined in section 101(a)(15)(J) of the Act), must establish that he or she was not subject to the two-year foreign residence requirements of section 212(e) or has fulfilled that requirement or has received a waiver of such requirements and has resided continuously in the United States in unlawful status since January 1, 1982.

(v) An alien who establishes that he or she was granted voluntary departure, voluntary return, extended voluntary departure or placed in deferred action catgory by the Service prior to January 1, 1982 and who has thereafter resided continuously in the United States and who has been physically present in the United States from November 6, 1986 until the date of filing the application.

(vi) An alien who establishes that he or she was paroled into the United States prior to January 1, 1982, and whose parole status terminated prior to January 1, 1982 and who has thereafter resided continously in the United States and who has been physically present in the United States from November 6, 1986 until the date of filing the application.

(vii) An alien who establishes that he or she is a national of Cuba or Haiti who entered the United States prior to January 1, 1982 and who has thereafter resided continuously in the United States and who has been physically present in the United States from November 6, 1986 until the date of filing the application, without regard to whether such alien

has applied for adjustment of status pursuant to section 202 of the Act.

(viii) An alien's eligibility under the categories described in §§ 245.2a(b)(1)(i) through (vii) shall not be affected by entries to the United States subsequent to January 1, 1982 that were not documented on Service Form I–94, Arrival-Departure Record.

(c) *Ineligible aliens.* (1) An alien who has been convicted of a felony (including crimes commited outside of the United States), or three or more misdemeanors (committed in the United States).

(2) An alien who has assisted in the persecution of any person or persons on account of race, religion, nationality, membership in a particular social group or political opinion.

(3) An alien excludable under the provisions of section 212(a) of the Act whose grounds of excludability may not be waived, pursuant to section 245A(d)(2)(B)(ii) of this Act.

(4) An alien who at any time was a nonimmigrant exchange visitor who is subject to the two-year foreign residence requirement unless the requirement has been satisfied or waived pursuant to the provisions of section 212(e) of the Act who has resided continuously in the United States in an unlawful status since January 1, 1982.

(5) An alien who was in the custody of or apprehended by the Service on or after November 6, 1986 and prior to May 5, 1987 and has established prima facie eligibility for adjustment of status, who does not file an application for adjustment of status to that of a temporary resident under section 245A(a) of the Act, prior to June 4, 1987.

(6) An alien who is the subject of an Order to Show Cause issued under section 242 of the Act during the period beginning on May 5, 1987 and ending on April 4, 1988 who does not file an application for adjustment of status to that of temporary resident under section 245A(a) of the Act prior to the thirty-first day after issuance of the order.

(7) An alien who is the subject of an Order to Show Cause issued under section 242 of the Act during the period beginning on April 5, 1988 and ending on May 4, 1988 who does not file an application for adjustment of status to that of a temporary resident under section 245A(a) of the Act prior to May 5, 1988.

(8) An alien who was paroled into the United States prior to January 1, 1982 and whose parole status terminated subsequent to January 1, 1982.

(d) *Documentation.* Evidence to support an alien's eligibility for the legalization program shall include documents establishing proof of identity, proof of residence, and proof of financial responsibility, as well as photographs, a completed fingerprint card (Form FD–258), and a completed medical report of examination (Form I–693). All documentation submitted will be subject to Service verification as to facts or authenticity. Applicants submitted with unverifiable documentation may be denied. Failure by an applicant to authorize release to INS of information protected by the Privacy Act and/or related laws in order for INS to adjudicate a claim may result in denial of the benefit sought. Acceptable supporting documents for these three categories are discussed below.

(1) *Proof of identity.* Evidence to establish identity is listed below in descending order of preference:

(i) Passport; (ii) Birth Certificate; (iii) Any national identity document from the alien's country of origin bearing photo and fingerprint (e.g., a "cedula" or "cartilla"); (iv) Driver's license or similar document issued by a state if it contains a photo; (v) Baptismal Record/Marriage Certificate; or (vi) Affidavits.

(A) *Assumed names.*

(1) *General.* In cases where an applicant claims to have met any of the eligibility criteria under an assumed name, the applicant has the burden of proving that the applicant was in fact the person who used that name. The applicant's true identity is established pursuant to the requirements of paragraph (d)(1) of this section. The assumed name must appear in the documentation provided by the applicant to establish eligibility. To meet the requirements of this paragraph documentation must be submitted to prove the common identity, i.e., that the assumed name was in fact used by the applicant.

(2) *Proof of common identity.* The most persuasive evidence is a document issued in the assumed name which identifies the applicant by photograph, fingerprint or detailed physical description. Other evidence which will be considered are affidavit(s) by a person or persons other than the applicant, made under oath, which identify the affiant by name and address, state the affiant's relationship to the applicant and the basis of the affiant's knowledge of the applicant's use of the assumed name. Affidavits accompanied by a photograph which has been identified by the affiant as the individual known to affiant under the assumed name in question will carry greater weight.

(2) *Proof of residence.* Evidence to establish proof of continuous residence in the United States during the requisite period of time may consist of any combination of the following:

(i) Past employment records, which may consist of pay stubs, W–2 Forms, certified copies of income tax returns which were filed, letters from employer(s) or, if the applicant has been in business for himself or herself, letters from banks and other firms with whom he or she has done business. In all of the above, the name of the alien and the name of the employer or other interested organization must appear on the form or letter, as well as relevant dates. Letters from employers should be on employer letterhead stationary, if the employer has such stationary, and must include: (A) Alien's address at the time of employment; (B) exact period of employment; (C) periods of layoff; (D) duties with the company; (E) whether or not the information was taken from official company records; and (F) where records are located and whether the Service may have access to such records. If such records are unavailable, an affidavit form-letter stating that the alien's employment records are unavailable and why such records are unavailable may be accepted in lieu of paragraphs (d)(2)(i) (E) and (F) of this section stated in this paragraph. This affidavit form-letter shall be signed, attested to by the employer under penalty of perjury, and shall state the employer's willingness to come forward and give testimony if requested.

(ii) Utility bills (gas, electric, phone, etc.), receipts, or letters from companies showing the dates during which the applicant received service are acceptable documentation.

(iii) School records (letters, report cards, etc.) from the schools that the applicant or their children have attended in the United States must show name of school and periods of school attendance.

(iv) Hospital or medical records showing treatment or hospitalization of the applicant or his or her children must show the name of the medical facility or physician and the date(s) of the treatment or hospitalization.

(v) Attestations by churches, unions, or other organizations to the applicant's residence by letter which: (A) Identifies applicant by name; (B) is signed by an official (whose title is shown); (C) shows inclusive dates of membership; (D) states the address where applicant resided during membership period; (E) includes the seal of the organization impressed on the letter or the letterhead of the organization, if the organization has letterhead stationary; (F) establishes how the author knows the applicant;

and (G) establishes the origin of the information being attested to.

(vi) Additional documents to support the applicant's claim may include:

(A) Money order receipts for money sent in or out of the country;

(B) Passport entries;

(C) Birth certificates of children born in the United States;

(D) Bank books with dated transactions;

(E) Letters or correspondence between applicant and another person or organization;

(F) Social Security card;

(G) Selective Service card;

(H) Automobile license receipts, title, vehicle registration, etc.;

(I) Deeds, mortgages, contracts to which applicant has been a party;

(J) Tax receipts;

(K) Insurance policies, receipts, or letters; and

(L) Any other relevant document.

(3) *Proof of financial responsibility.* An applicant for adjustment of status under this part is subject to the provisions of section 212(a)(15) of the Act relating to excludability of aliens likely to become public charges unless the applicant demonstrates a history of employment in the United States evidencing self-support without receipt of public cash assistance. Generally, the evidence of employment submitted under paragraph (d)(2)(i) of this section will serve to demonstrate the alien's financial responsibility during the document period(s) of employment. If the alien's period(s) of residence in the United States include significant gaps in employment or if there is reason to believe that the alien may have received public assistance while employed, the alien may be required to provide proof that he or she has not received public cash assistance. An applicant for residence who is likely to become a public charge will be denied adjustment. The burden of proof to demonstrate the inapplicability of this provision of law lies with the applicant who may provide:

(i) Evidence of a history of employment (i.e., employment letter, W–2 Forms, income tax returns, etc.);

(ii) Evidence that he/she is self-supporting (i.e., bank statements, stocks, other assets, etc.); or

(iii) Form I–134, Affidavit of Support, completed by a spouse in behalf of the applicant and/or children which guarantees complete or partial financial support of the applicant.

(4) *Burden of proof.* An alien applying for adjustment of status under this part has the burden of proving by a preponderance of the evidence that he or she resided in the United States for the requisite periods, is admissible to the United States under the provisions of section 245a of the Act, and is otherwise eligible for adjustment of status under this section. The inference to be drawn from the documentation provided shall depend on the extent of the documentation, its credibility and amenability to verification as set forth in paragraph (d) of this section.

(5) *Evidence.* The sufficiency of all evidence produced by the applicant will be judged according to its probative value and credibility. To meet his or her burden of proof, an applicant must provide evidence of eligibility apart from his or her own testimony. In judging the probative value and credibility of the evidence submitted greater weight will be given to the submission or original documentation.

(e) *Filing of application:* (1) The application must be filed on Form I–687 at an office of a designated entity or at a Service Legalization Office within the jurisdiction of the District wherein the applicant resides. If the application is filed with a designated entity, the alien must have consented to having the designated entity forward the application to the legalization office. In the case of applications filed at a legalization office, the district director may, at his or her discretion: (i) Require the applicant to file the application in person; or (ii) require the applicant to file the application by mail; or (iii) permit the filing of applications either by mail or in person. The applicant must appear for a personal interview at the legalization office when scheduled. If the applicant is 14 years of age or older, the application must be accompanied by a completed Form FD–258 (Applicant Card).

(2) Wherever possible documents must be submitted in the original except the following: Official government records; employment or employment-related records maintained by employers, unions, or collective bargaining organizations; school records maintained by a school or school board; or other records maintained by a party other than the applicant. Copies of records maintained by parties other than the applicant which are submitted in evidence must be certified as true and correct by such parties and must bear their seal or signature or the signature and title of persons authorized to act in their behalf. If the return of original documents is desired by the applicant, they must be accompanied by notarized copies or copies certified true and correct by a designated entity or by the alien's representative in the format prescribed in § 204.2(j)(1) or (2) of this chapter. Such certified copies unaccompanied by original documents are unacceptable for the purpose of an application under this part. At the discretion of the district director, original documents, even if accompanied by certified copies, may be temporarily retained for forensic examination by the Document Analysis Unit at the Regional Processing Facility having jurisdiction over the legalization office to which the documents were submitted.

(3) A separate application (I–687) must be filed by each eligible applicant. All fees required by § 103.7(b)(1) of this chapter must be submitted in the exact amount in the form of a money order, cashier's check, or certified bank check, made payable to the Immigration and Naturalization Service. No personal checks or cash will be accepted. Fees will not be waived or refunded under any circumstances.

(f) *Filing date of application.* The date the alien submits a completed application to a Service Legalization Office or designated entity shall be considered the filing date of the application, provided that the case of an application filed at a designated entity the alien has consented to having the designated entity forward the application to the Service Legalization Office having jurisdiction over the location of the alien's residence. The designated entities are required to forward completed applications to the appropriate Service Legalization Office within sixty days of receipt.

(g) *Selective Service Registration:* At the time of filing an application under this section, male applicants between the ages of 18 and 26 are required to be registered under the Military Selective Service Act. An applicant shall present evidence that he has previously registered under that Act, in the form of a letter of acknowledgement from the Selective Service System, or such alien shall present a completed and signed Form SSS–1 at the time of filing Form I–687 with the Immigration and Naturalization Service or a designated entity. Form SSS–1 will be forwarded to the Selective Service System by the Service.

(h) *Continuous residence.* (1) For the purpose of this Act, an applicant for *temporary resident status* shall be regarded as having resided continuously in the United States if, at the time of filing of the application: (i) No single absence from the United States has exceeded forty-five (45) days, unless the alien can establish that due to emergent reasons, his or her return to the United States could not be accomplished within the time period allowed; (ii) the aggregate of all absences has not

exceeded one hundred and eighty (180) days between January 1, 1982 through the date the application for temporary resident status if filed; (iii) the alien was maintaining a residence in the United States; and (iv) the alien's depature from the United States was not based on an order of deportation.

(2) An alien who has been absent from the United States in accordance with the Service's advance parole procedures shall not be considered as having interrupted his or her continuous residence as required at the time of filing an application under this section.

(i) *Medical examination.* An applicant under this part shall be required to submit to an examination by a selected civil surgeon. The selected civil surgeon shall report the findings of the mental and physical condition of the applicant and the determination of the alien's immunization status. Results of the medical examination must be presented to the Service at the time of interview and shall be incorporated into the record. Any applicant certified under paragraphs (1), (2), (3), (4), or (5) of section 212(a) of the Act may appeal to a Board of Medical Officers of the U.S. Public Health Service as provided in section 234 of the Act and Part 235 of this chapter.

(j) *Interview.* Each applicant, regardless of age, must appear at the appropriate Service Legalization Office and must be fingerprinted for the purpose of issuance of Form I–688. Each applicant shall be interviewed by an immigration officer, except that the interview may be waived for a child under 14, or when it is impractical because of the health or advanced age of the applicant.

(k)(1) *Grounds of exclusion not to be applied.* The following paragraphs of section 212(a) of the Act shall not apply to applicants for temporary resident status: (14) Workers entering without Labor Certification; (20) immigrants not in possession of valid entry document; (21) visas issued without compliance with section 203; (25) illiterates; and (32) graduates of non-accredited medical schools.

(2) *Waiver of grounds of exclusion.* Except as provided in paragraph (k)(3) of this section, the Attorney General may waive any other provision of section 212(a) of the Act only in the case of individual aliens for humanitarian purposes, to assure family unity, or when the granting of such a waiver is in the public interest. If an alien is excludable on grounds which may be waived as set forth in this paragraph, he or she shall be advised of the procedures for applying for a waiver of grounds of excludability on Form I–690. When an application for waiver of grounds of excludability is filed jointly with an application for temporary residence under this section, it shall be accepted for processing at the legalization office. If an application for waiver of grounds of excludability is submitted after the alien's preliminary interview at the legalization office, it shall be forwarded to the appropriate Regional Processing Facility. All applications for waivers of grounds of excludability must be accompanied by the correct fee in the exact amount. All fees for applications filed in the United States must be in the form of a money order, cashier's check, or bank check. No personal checks or cash will be accepted. Fees will not be waived or refunded under any circumstances. An application for waiver of grounds of excludability under this part shall be approved or denied by the director of the Regional Processing Facility in whose jurisdiction the applicant's application for adjustment of status was filed, except that in cases involving clear statutory ineligibility or admitted fraud, such application may be denied by the district director in whose jurisdiction the application is filed, and in cases returned to a Service Legalization Office for re-interview, such application may be approved at the discretion of the district director. The applicant shall be notified of the decision and, if the application is denied, of the reason therefor. A party affected under this part by an adverse decision may appeal the decision within 30 days after the service of the notice only to the Service's Administrative Appeals Unit pursuant to the provisions of § 103.3(a) of this chapter.

(3) *Grounds of exclusion that may not be waived.* Notwithstanding any other provision of the Act, the following provisions of section 212(a) may not be waived by the Attorney General under paragraph (k)(2) of this section: (i) Paragraphs (9) and (10) (criminals); (ii) Paragraph (15) (public charge); (iii) Paragraph (23) (narcotics) except for a single offense of simple possession of thirty grams or less of marijuana; (iv) Paragraphs (27) (prejudicial to the public interest), (28) (communist), and (29) (subversive); (v) Paragraph (33) (Nazi persecution).

(4) *Special rule for determination of public charge.* An alien who has a consistent employment history which shows the ability to support himself and his or her family even though his income may be below the poverty level is not excludable under paragraph (k)(3)(ii) of this section. The alien's employment history need not be continuous in that it is uninterrupted. It should be continuous in the sense that the alien shall be regularly attached to the workforce, has an income over a substantial period of the applicable time, and has demonstrated the capacity to exist on his or her income and maintain his or her family without recourse to public cash assistance. This regulation is prospective in that the Service shall determine, based on the alien's history, whether he or she is likely to become a public charge. Past acceptance of public cash assistance within a history of consistent employment will enter into this decision. The weight given in considering applicability of the public charge provisions will depend on many factors, but the length of time an applicant has received public cash assistance will constitute a significant factor.

(5) *Public Assistance and Criminal History Verification.* Declarations by an applicant that he or she has not been the recipient of public cash assistance and/or has not had a criminal record are subject to a verification of facts by the Service. The applicant must agree to fully cooperate in the verification process. Failure to assist the Service in verifying information necessary for proper adjudication may result in a denial of the application.

(l) *Continuous physical presence since November 6, 1986.* (1) An alien applying for adjustment to temporary resident status must establish that he or she has been continuously physically present in the United States since November 6, 1986.

(2) Brief, casual and innocent absences from the United States shall not be considered to interrupt the continuous physical presence required in paragraph (l)(1) of this section. A brief, casual and innocent absence is defined as a departure authorized by the Service of not more than thirty (30) days for legitimate emergency or humanitarian purposes unless a further period of authorized departure has been granted at the discretion of the district director.

(m) *Departure.* (1) During the time period from the date that an alien's application establishing prima facie eligibility for temporary resident status is reviewed at a Service Legalization Office and the date status as a temporary resident is granted, the alien applicant can only be readmitted to the United States provided his or her departure was authorized under the Service's advance parole provisions contained in § 212.5(e) of this chapter.

(2) An alien whose application for temporary resident status has been approved may be admitted to the United

States upon return as a returning temporary resident provided he or she:

(i) Is not under deportation proceedings;

(ii) Has not been absent from the United States more than thirty (30) days on the date application for admission is made;

(iii) Has not been absent from the United States for an aggregate period of more than 90 days since the date the alien was granted lawful temporary resident status;

(iv) Presents Form I–688; and

(v) Presents himself or herself for inspection.

(3) the period of time in paragraph (m)(2)(ii) of this section may be waived at the discretion of the Attorney General in cases where the absence from the United States was due merely to a brief temporary trip abroad required due to emergent or extenuating circumstances beyond the alien's control.

(n)(1) *Employment and travel authorization; general.* Authorization for employment and travel abroad for temporary resident status applicants under section 245A(a) of the Act may only be granted by a Service Legalization Office. In the case an application which has been filed with a designated entity, employment authorization may only be granted by the Service after the application has been properly received at the Service Legalization Office.

(2) *Employment authorization prior to the granting of temporary resident status.* Permission to accept employment will be granted to the applicant upon review of an application establishing prima facie eligibility for temporary resident status. Applications may be presented in person, through designated entities, or through the mail to a legalization office. Applicants who walk-in or mail-in their applications to offices that schedule appointments will receive a form letter fee receipt and scheduled appointment. If an appointment cannot be scheduled within thirty (30) days, authorization to accept employment wil be given valid to the scheduled appointment date. Form I–688A, Employment Authorization, will be given to the applicant after an interview has been completed by an immigration officer. This temporary employment authorization will be restricted to six months duration, pending final determination on the application for temporary resident status.

(3) *Employment and travel authorization upon grant of temporary resident status.* Upon grant of an application for adjustment to temporary resident status by a Regional Processing facility, the processing facility will forward a notice of approval to the alien at his or her last known address and to his or her designated entity or representative. The alien will be required to return to the Service Legalization Office where the application was initially received, surrender the I–688A previously issued, and will be issued Form I–688, Temporary Resident Card, authorizing employment and travel abroad.

(4) *Revocation of employment authorization upon denial of temporary resident status.* Upon denial of an application for adjustment to temporary resident status by a Regional Processing Facility, Notice of Revocation of employment authorization will be forwarded to the alien at his or her last known address. Employment authorization will not be granted solely on the basis of an appeal having been filed.

(o) *Decision.* The applicant shall be notified in writing of the decision, and, if the application is denied, of the reason therefor. A party affected under this part by an adverse decision is entitled to file an appeal on Form I–694.

(p) *Appeal process.* An adverse decision under this part may be appealed to the Associate Commissioner, Examinations (Administrative Appeals Unit). Any appeal with the required fee shall be filed with the Regional Processing Facility within thirty (30) days after service of the notice of denial in accordance with the procedures of section 103.3(a) of this chapter. An appeal received after the thirty (30) day period has tolled will not be accepted. The thirty (30) day period includes any time required for service or receipt by mail.

(q) *Motions.* The Regional Processing Facility director may *sua sponte* reopen and reconsider any adverse decision. When an appeal to the Associate Commissioner, Examinations (Administrative Appeals Unit) has been filed, and the INS director of the Regional Processing Facility may issue a new decision that will grant the benefit which has been requested. The director's new decision must be served on the appealing party within 45 days of receipt of any briefs and/or new evidence, or upon expiration of the time allowed for the submission of any briefs.

(r) *Certifications.* The Regional Processing Facility director may, in accordance with § 103.4 of this chapter, certify a decision to the Associate Commissioner, Examinations (Administrative Appeals Unit) when the case involves an unusually complex or novel question of law or fact.

(s) *Date of adjustment to temporary residence.* The status of an alien whose application for temporary resident status is approved shall be adjusted to that of a lawful temporary resident as of the date on which the application was fee receipted at a Service Legalization Office.

(t) *Limitation on access to information and confidentiality.* (1) No person other than a sworn officer or employee of the Justice Department of bureau or agency thereof, will be permitted to examine individual applications, except employees of designated entities where applications are filed with the same designated entity. For purposes of this part, any contract personnel employed by the Service to work in connection with the legalization program shall be considered an "employee of the Justice Department or bureau or agency thereof."

(2) Files and records prepared by designated entities under this section are confidential. The Attorney General and the Service shall not have access to these files and records without the consent of the alien.

(3) No information furnished pursuant to an application for legalization under this section shall be used for any purpose except: (i) To make a determination on the application; or, (ii) for the enforcement of the provisions encompassed in section 245A(c)(6) of the Act, except as provided in paragraph (t)(4) of this section.

(4) If a determination is made by the Service that the alien has, in connection with his or her application, engaged in fraud or willful misrepresentation of a material fact, provided a false writing or document in making his or her application, or engaged in any other activity prohibited by section 245A(c)(6) of the Act, the Service shall refer the matter to the United States Attorney for possible prosecution of the alien or of any person who created or supplied a false writing or document for use in an application for adjustment of status under this part. If prosecution is declined by the United States Attorney, the Service may issue an order to show cause and warrant of arrest, unless the United States Attorney has notified the Service that the matter submitted is without merit.

(5) If the investigation conducted by the Service results in the conviction of an applicant for a violation of section 245A(c)(6) of the Act, the applicant shall be considered to be inadmissible to the United States on the ground described in section 212(a)(19) of the Act.

(6) Information obtained in a granted legalization application and contained

in the applicant's file in subject to subsequent review in reference to future benefits applied for (including petitions for naturalization and permanent resident status for relatives).

(u) *Termination of temporary resident status.* (1) Termination of temporary resident status; General. The status of an alien lawfully admitted for temporary residence under section 245A(a)(1) of the Act may be terminated at any time in accordance with section 245A(b)(2) of the Act. It is not necessary that a final order of deportation be entered in order to terminate temporary resident status. The temporary resident status may be terminated upon the occurrence of any of the following:

(i) It is determined that the alien was ineligible for temporary residence under 245A of this Act;

(ii) The alien commits an act which renders him or her inadmissible as an immigrant, except as provided under § 245a.2(k) (2) or (3) of this part;

(iii) The alien is convicted of any felony (including crimes committed outside of the United States), or three or more misdemeanors (committed in the United States);

(iv) The alien fails to file for adjustment of status from temporary resident to permanent resident on Form I–698 within thirty-one (31) months of the date he/she was granted status as a temporary resident under § 245a.1 of this part.

(2) *Procedure.* Termination of an alien's status under paragraph (u)(1) of this section will be made only on notice to the alien sent by certified mail directed to his or her last known address. The alien must be given an opportunity to offer evidence in opposition to the grounds alleged for termination of his or her status. Evidence in opposition must be submitted within thirty (30) days after the service of the Notice of Intent to Terminate. If the alien's status is terminated, the director of the regional processing facility shall notify the alien of the decision and the reasons for the termination, and further notify the alien that any Service Form I–94, Arrival-Departure Record or other official Service document issued to the alien authorizing employment and/or travel abroad, or any Form I–688, Temporary Resident Card previously issued to the alien will be declared void by the director of the regional processing facility within thirty (30) days if no appeal of the termination decision is filed within that period. The alien may appeal the decision to the Associate Commissioner, Examinations (Administrative Appeals Unit). Any appeal with the required fee shall be filed with the regional processing facility within thirty (30) days after the service of the notice of termination. If no appeal is filed within that period, the I–94, I–688 or other official Service document shall be deemed void, and must be surrendered without delay to an immigration officer or to the issuing office of the Service.

(3) *Termination not construed as rescission under section 246.* For the purposes of this part the phrase "termination of status" of an alien granted lawful temporary residence under section 245A(a) of the Act shall not be construed to necessitate a rescission of status as described in section 246 of the Act, and the proceedings required by the regulations issued thereunder shall not apply.

(4) *Return to unlawful status after termination.* Termination of the status of any alien previously adjusted to lawful temporary residence under section 245A(a) of the Act shall act to return such alien to the unlawful status held prior to the adjustment, and render him or her amendable to exclusion or deportation proceedings under section 236 or 242 of the Act, as appropriate.

§ 245a.3 Application for adjustment of status from temporary to permanent resident

(a) *Application period for permanent residence.* An alien who has resided in the United States for a period of eighteen (18) months after the granting of temporary resident status may make application for permanent resident status during the twelve month period beginning on the day after the requisite eighteen months temporary residence has been completed. Applications for lawful permanent residence under section 245A(b)(1) of the Act will be accepted at legalization offices beginning on November 7, 1988.

(b) *Eligibility.* Any alien physically present in the United States who has been lawfully admitted for temporary resident status under section 245A(a) of the Act, may apply for adjustment of status to that of an alien lawfully admitted for permanent residence if the alien:

(i) Applies for such adjustment during the one-year period beginning with the nineteenth month that begins after the date the alien was granted such temporary resident status;

(2) Establishes continuous residence in the United States since the date the alien was granted such temporary residence status. An alien shall be regarded as having resided continuously in the United States for the purposes of this part if, at the time of applying for adjustment from temporary to permanent resident status, no single absence from the United States has exceeded thirty (30) days, or the aggregate of all absences has not exceeded ninety (90) days between the date of granting of lawful temporary resident status and applying for permanent resident status unless the alien can establish that due to emergent reasons, the return to the United States could not be accomplished within the time period(s) allowed.

(3) Is admissible to the United States as an immigrant, except as otherwise provided in paragraph (f) of this section; and has not been convicted of any felony (including crimes committed outside of the United States), or three or more misdemeanors committed in the United States); and

(4)(i)(A) can demonstrate that the alien either; (1) Meets the requirements of section 312 of the Immigration and Nationality Act, as amended, (relating to minimal understanding of ordinary English and a knowledge and understanding of the history and government of the United States), or; (2) is satisfactorily pursuing a course of study recognized by the Attorney General to achieve such an understanding of English and such a knowledge and understanding of the history and government of the United States, or; (B) has demonstrated that the alien met the requirements of paragraph (b)(4)(i)(A)(1) of this section at the time of interview for adjustment of status to that of lawful temporary resident under section 245A(a); or (C) the requirements of paragraph (b)(4)(i)(A)(1) of this section may be waived at the discretion of the Attorney General if the alien is 65 years or older.

(ii) A course of study in the English language and in the history and government of the United States shall satisfy the requirement or paragraph (b)(4)(i)(A)(2) of this section; if (A) It is sponsored or conducted by an established public or private institution of learning recognized as such by a qualified state certifying agency, or by an institution of learning approved to issue Forms I–20 in accordance with § 214.3 of this chapter, or by a qualified designated entity within the meaning of section 245A(c)(2) of the Act; and (B) the course materials for such instruction include textbooks published under the authority of section 346 of the Act.

(c) *Ineligible aliens.* (1) An alien who has been convicted of a felony (including crimes committed outside of the United States), or three or more misdemeanors (committed in the United States).

(2) An alien who has assisted in the persecution of any person or persons on account of race, religion, nationality, membership in a particular social group or political opinion.

(3) An alien excludable under the provisions of section 212(e) of the Act whose grounds of excludability may not be waived, pursuant to section 245(d)(2)(B)(ii) of the Act.

(4) An alien who was previously granted temporary resident status pursuant to section 245A(a) of the Act who has not filed an application for permanent resident status under section 245A(b)(1) of the Act during the one year period which began with the nineteenth month that begins after the date the alien was granted such temporary resident status.

(5) An alien who was not previously granted temporary resident status under section 245A(a) of the Act.

(d) *Filing of application.* (1) The application must be filed on Form I–698 in person at a designated Legalization Office within the jurisdiction of the District wherein the applicant resides. Form I–698 must be accompanied by the documents specified in the instructions. If the alien is 14 years or older, the application must be accompanied by a completed Form FD–258 (Fingerprint Card).

(2) All documents must be submitted in the original except the following: Official government records; employment or employment-related records maintained by employers, unions, or collective bargaining organizations; school records maintained by a school or school board; or other records maintained by a party other than the applicant. Copies of records maintained by parties other than the applicant which are submitted in evidence must be certified as true and correct by such parties and must bear their seal or signature or the signature and title of persons authorized to act in their behalf. If the return of original documents is desired by the applicant, they must be accompanied by notarized copies or copies certified true and correct by a designated entity or by the alien's representative in the format prescribed in § 204.2(j) (1) or (2) of this chapter. Such certified copies unaccompanied by original documents are unacceptable for the purpose of an application under this part. At the discretion of the district director, original documents, even if accompanied by certified copies, may be temporarily retained for forensic examination by the Document Analysis Unit at the Regional Processing Facility having jurisdiction over the legalization office to which the documents were submitted.

(3) A separate application (I–698) must be filed by each eligible applicant. All fees required by § 103.7(b)(1) of this chapter must be submitted in the exact amount in the form of a money order, cashier's check or certified bank check. No personal checks or currency will be accepted. Fees will not be waived or refunded under any circumstances.

(e) *Interview.* Each applicant, regardless of age, must appear at the appropriate Service legalization office and must be fingerprinted for the purpose of issuance of Form I–551. Each applicant shall be interviewed by an immigration officer, except that the interview may be waived for a child under 14, or when it is impractical because of the health or advanced age of the applicant.

(f) *Numerical limitations.* The numerical limitations of sections 201 and 202 of the Act do not apply to the adjustment of aliens to lawful permanent resident status under section 245A(b) of the Act.

(g)(1) *Grounds of exclusion not to be applied.* The following paragraphs of section 212(a) of the Act shall not apply to applicants for adjustment of status from temporary resident to permanent resident status; (14) workers entering without Labor Certification; (20) immigrants not in possession of valid entry document; (21) visas issued without compliance of section 203; (25) illiterates; and (32) graduates of non-accredited medical schools.

(2) *Waiver of grounds of excludability.* Except as provided in paragraph (g)(4) of this section, the Service may waive any provision of section 212(a) of the Act only in the case of individual aliens for humanitarian purposes, to assure family unity, or when the granting of such a waiver is otherwise in the public interest. In any case where a provision of section 212(a) of the Act has been waived in connection with an alien's application for lawful temporary resident status under section 245A(a) of the Act, no additional waiver of the same ground of excludability will be required when the alien applies for permanent resident status under 245A(b)(1) of the Act. In the event that the alien becomes excludable under any other provision of section 212(a) of the Act subsequent to the date temporary residence was granted, a waiver of the additional ground of excludability will be required before permanent resident status may be granted.

(3) *Grounds of exclusion that may not be waived.* Notwithstanding any other provision of the Act the following provisions of section 212(a) of the Act *may not* be waived by the Attorney General under paragraph (g)(2) of this section:

(i) Paragraphs (9) and (10) (criminals);

(ii) Paragraph (15) (public charge) insofar as it relates to an application for adjustment to permanent residence by an alien other than an alien who is eligible for benefits under Title XVI of the Social Security Act or section 212 of Pub. L. 93–66 for the month in which such alien is granted lawful temporary residence status under subsection (a);

(iii) Paragraph (23) (narcotics), except for a single offense of simple possession of thirty grams or less of marijuana;

(iv) Paragraphs (27) (prejudicial to the public interest), (28) (communists), and (29) (subversive);

(v) Paragraph (33) (Nazi persecution).

(4) *Special rule for determination of public charge.* An alien who has a consistent employment history which shows the ability to support himself or herself and his or her family even though his or her income may be below the poverty level is not excludable under paragraph (g)(3)(ii) of this section. The alien's employment history need not be continuous in that it is uninterrupted. It should be continuous in the sense that the alien shall be regularly attached to the workforce, has an income over a substantial period of the applicable time, and has demonstrated the capacity to exist on his or her income and maintain his or her family without recourse to public cash assistance. This regulation is prospective in that the Service shall determine, based on the alien's history, whether he or she is likely to become a public charge. Past acceptance of public cash assistance within a history of consistent employment will enter into this decision. The weight given in considering applicability of the public charge provisions will depend on many factors, but the length of time an applicant has received public cash assistance will constitute a significant factor.

(5) *Public cash assistance and criminal history verification.* Declarations by an applicant that he or she has not been the recipient of public cash assistance and/or has not had a criminal record are subject to a verification of facts by the Service. The applicant must agree to fully cooperate in the verification process. Failure to assist the Service in verifying information necessary for proper adjudication may result in a denial of the application.

(h) *Departure.* An applicant for adjustment to lawful permanent resident status under section 245A(b)(1) of the

Act who was granted lawful temporary resident status under section 245A(a) of the Act, shall be permitted to return to the United States after such brief and casual trips abroad, as long as the alien reflects a continuing intention to adjust to lawful permanent resident status. However, such absences from the United States must not exceed the periods of time specified in § 245a.3(b)(2) of this chapter in order for the alien to maintain continuous residence as specified in the Act.

(i) *Decision.* The applicant shall be notified in writing of the decision, and, if the application is denied, of the reason therefor. A party affected under this part by an adverse decision is entitled to file an appeal on Form I–694.

(j) *Appeal Process.* An adverse decision under this part may be appealed to the Associate Commissioner, Examinations (Administrative Appeals Unit). Any appeal with the required fee shall be filed with the Regional Processing Facility within thirty (30) days after service of the Notice of Denial in accordance with the procedures of § 103.3(a) of this chapter. An appeal received after the thirty (30) day period has tolled will not be accepted. The thirty (30) day period includes any time required for service or receipt by mail.

(k) *Motions.* The Regional Processing Facility director may *sua sponte* reopen and reconsider any adverse decision. When an appeal to the Associate Commissioner, Examinations (Administrative Appeals Unit) has been filed, the INS director of the Regional Processing Facility may issue a new decision that will grant the benefit which has been requested. The director's new decision must be served on the appealing party within forty-five (45) days of receipt of any briefs and/or new evidence, or upon expiration of the time allowed for the submission of any briefs.

(l) *Certifications.* The regional processing facility director may, in accordance with § 103.4 of this chapter, certify a decision to the Associate Commissioner, Examinations (Administrative Appeals Unit) when the case involves an unusually complex or novel question of law or fact.

(m) *Date of Adjustment to Permanent Residence.* The status of an alien whose application for permanent resident status is approved shall be adjusted to that of a lawful permanent resident as of the date on which the application is approved by the director of the regional processing facility.

Dated: March 5, 1987.

Alan C. Nelson,

Commissioner.

[FR Doc. 87–5838 Filed 3–7–87; 10:07 am]

BILLING CODE 4410–10–M

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8 CFR Parts 109 and 274a

Control of Employment of Aliens

AGENCY: Immigration and Naturalization Service, Justice.

ACTION: Proposal rule.

SUMMARY: The proposed changes would add Part 274a and redesignate Part 109 with minor changes as Subpart B, by: (1) The addition of definitions to clarify the regulations; (2) addition of new sections to establish procedures for the verification of employment eligibility for workers in the United States; (3) addition of new sections to establish enforcement and process procedures for violations; (4) redesignating Part 109 (Employment Authorization) as Subpart B of Part 274a to consolidate what would otherwise be dispersed regulations under one part for clarity and uniformity. These additions are necessitated by the provisions of the recently passed Immigration Reform and Control Act of 1986, Pub. L. 99–603, which amended the Immigration and Nationality Act (Act) by adding provisions relating to the control of illegal immigration. These provisions make it unlawful to hire, recruit or refer for a fee, unauthorized aliens for employment in the United States. The statute also requires the establishment of an employment eligibility verification system designed to prevent the employment of unauthorized aliens. Prompt establishment of the procedures contained in these proposed regulations is necessary in order to ensure that Service operations are conducted in a manner consistent with the public interest and Congressional intent of the Act. For these reasons, this rule is proposed for solicitation of comments, which will be considered in formulating the final regulations.

DATE: Comments must be submitted on or before April 20, 1987.

ADDRESS: Please submit written comments in triplicate to: Office of Investigations, Immigration and Naturalization Service, 425 I Street, NW., Room 7240, Washington, DC 20536.

FOR FURTHER INFORMATION CONTACT: Walter D. Cadman, Senior Special Agent, Immigration and Naturalization Service, 425 I Street, NW., Washington, DC 20536, Telephone: (202) 633–2997.

SUPPLEMENTARY INFORMATION:

Background

Since 1972 numerous attempts have been made by Congress and recent Administrations to pass immigration reform legislation. The imposition of sanctions on employers has been a cornerstone of nearly all such attempts with the view that curbing illegal immigration would not be effective without such sanctions. The Select Commission on Immigration and Refugee Policy was established by Congress in October 1978. It was created to review immigration policy issues, assess the impact of legal and illegal immigrants on the nation, and recommend changes in policy and practice. The Commission made a series of over seventy recommendations concerning these issues in its final report in May 1981. Those recommendations included the imposition of employer sanctions to control illegal immigration. Thereafter a Cabinet level task force reviewed the Select Commission Report and other recommendations on immigration reform. In 1981 and 1982 alone some twenty-eight hearings were conducted by House and Senate immigration subcommittees on proposed immigration reform.

On November 6, 1986, after fourteen years of immigration reform legislation history the President signed into law the Immigration Reform and Control Act of 1986, Pub. L. 99–603, (IRCA). This legislation is the most comprehensive reform of our immigration laws in thirty-five years. The employer sanctions provisions of IRCA are one of three cornerstone on which immigration reform is based. The other two are increased enforcement measures and legalization. Legalization is being addressed separately from these proposed rules.

Statutory authority

Section 101 of IRCA is designed to control the unlawful employment of aliens in the United States by imposing civil and criminal penalties on those persons and entities that hire, recruit or refer for a fee unauthorized aliens. Section 101 of IRCA amends the Act by adding section 274A which closes a large gap in the enforcement of our immigration laws by: (1) Making it unlawful to hire, recruit or refer for a fee unauthorized aliens; (2) requiring those who hire, recruit or refer for a fee individuals for employment, to verify both the identity and employment eligibility of such individuals and (3) making it unlawful to continue to employ unauthorized aliens hired after

November 6, 1986. While section 112 of the IRCA amends section 274(a) of the Act (which sets forth criminal penalties for individuals who harbor illegal aliens), employment of illegal aliens in and of itself does not constitute harboring under section 274(a) of the Act as amended.

While the changes to Part 109 are minor, INS recognizes that further changes are necessary and invites comments on this part.

Drafting Information and Enforcement Strategy

Since 1975 INS has vigorously worked in the spirit of cooperation with employers on an ad hoc basis to encourage a policy of employing only U.S. citizens and aliens lawfully authorized to work in the United States. The success of this effort, called Operation Cooperation, has been encouraging, but with the limits of INS resources and lack of statutory backing such programs have been of limited effectiveness. Mandatory compliance is the only effective mechanism that reduces "pull" factors that encourage rather then discourage illegal immigration.

Since enactment of IRCA on November 6, 1986, INS has been working to develop these rules along with a balanced enforcement policy. On January 20, 1987, INS took the unprecedented step of publishing a notice in the **Federal Register** to solicit comments from the public and other interested parties concerning draft rules implementing the employer provisions of IRCA. Interested parties were provided with preliminary working drafts for review and comments. Comments were received from over 100 individuals or groups, including Congressional sources, law firms, interest groups, business and labor organizations, and educational institutions. These comments were reviewed and elevated in the development of this proposed rule. Many of the comments and suggestions were incorporated in this text including but not limited to: simplification of Employment Eligibility Verification (Form I–9); restructuring the text to minimize the amount of information required to be referenced by those affected; simplification and clarification of the text language; and clarification of several provisions to minimize the impact on those affected, such as the compliance period and rehire issues. The proposed rule specifies that the point at which the employment eligibility verification must take place is at the time of hire or referral to an employer. The Service invites comment on issues concerning the nature of verification, the mandatory and universal aspect of the requirements for employers to complete and maintain the designated form, and the application of penalties to procedural as well as substantive violations of the Act.

While this proposed rule will not satisfy the concerns of all those who commented, INS feels that most issues have been addressed in the spirit of mutual dialogue with the intent of minimizing the impact of this far reaching legislation on the affected parties, to the extent permitted by the statute, Congressional intent and the public interest.

INS will continue to encourage voluntary cooperation and compliance along with traditional enforcement in achieving the goal of this legislation. In an effort to achieve this objective, INS has established a new office for Employer and Labor Relations at the assistant commissioner level to administer a staff dedicated to education and cooperation with the employers and other interested parties. Many public appearances have been made by INS officials in the last few months to inform and solicit comments from interested parties. INS envisions a balanced approach between education/cooperation and strict enforcement of penalties for egregious violators. INS intends to continue a process of dialogue during the comment period.

Other Information

A statement concerning the proposed Employment Eligibility Verification, Form I–9, is being submitted concurrently with this notice, to OMB for review in accordance with the Paperwork Reduction Act, 44 U.S.C. Chapter 35.

This proposed rule is a major rule within the context of E.O. 12291 in terms of the effect it will have on the national economy. A Preliminary Regulatory Impact Analysis in conjunction with a Regulatory Flexibility Analysis as required by 5 U.S.C. 603 and 604, is being prepared, and will be available for review by the public upon request.

List of Subjects in 8 CFR Parts 109, 274a

Administrative practice and procedure, aliens, employment.

For the reasons set out in the preamble, INS proposes to amend Chapter I of Title 8 of the Code of Federal Regulations as follows:

PART 109—EMPLOYMENT AUTHORIZATION—[REMOVED AND RESERVED]

1. Part 109 would be revised and redesignated as Subpart B of a new Part 274a to read as set forth below.

2. A new Part 274a would be added to read as follows:

PART 274a—CONTROL OF EMPLOYMENT OF ALIENS

Subpart A—Employer Requirements

Secs.

Subpart B—Employment Authorization

Authority: Secs. 101, 1103, 274A of the Immigration and Nationality Act, 8 U.S.C. 1101, 1103, 1324A.

Subpart A—Employer Requirements

§ 274a.1 Definitions.

For the purpose of this chapter—

(a) The term "unauthorized alien" means, with respect to employment of an alien at a particular time, that the alien is not at that time either (1) an alien lawfully admitted for permanent residence, or (2) authorized by the Immigration and Naturalization Service to be employed;

(b) The term "entity" means any legal entity, including but not limited to, a corporation, partnership, joint venture, governmental body, agency, proprietorship, or association;

(c) The term "hire" means the actual commencement of employment of an employee for wages or other remuneration;

(d) The term "refer for a fee" means the act of sending or directing a person or transmitting documentation or information to another, directly or indirectly, with the intent to obtain employment for such person, for remuneration whether on a retainer or contingency basis;

(3) The term"recruit for a fee" means the act of soliciting a person, directly or

indirectly, with the intent of referring that person to another, for remuneration whether on a retainer or contingency basis;

(f) The term "employee" means an individual who provides services or labor for an employer for wages or other remuneration but shall not include independent contractors or those engaged in casual employment as stated in paragraph (h) of this section;

(g) The term "employer" means a person or entity, including anyone acting directly or indirectly in the interest thereof, who engages the services or labor of an employee to be performed in the United States for wages or other remuneration;

(h) The term "employment" means any service or labor performed by an employee for an employer within the United States, including service or labor performed on a U.S. vessel or aircraft which touches at a port in the United States, not including casual employment by individuals who provide domestic service in a private home that is sporadic, irregular or incidental.

(i) The term "State employment agency" means any State government unit designated to cooperate with the United States Employment Service in the operation of the public employment service system;

(j) The term "pattern or practice" means regular, repeated and intentional activities, but does not include isolated, sporadic or accidental acts.

§ 274a.2 Verification of employment eligibility.

(a) *General.* This section states the requirements and procedures persons or entities must comply with when hiring, recruiting or referring for a fee, individuals in the United States, or continuing to employ aliens knowing that the aliens are (or have become) unauthorized aliens. The Form I–9, Employment Eligibility Verification Form, has been designated by the Service as the form to be used in complying with the requirements of this section. Form I–9 need only be completed for individuals who are hired, recruited or referred for a fee for employment, after November 6, 1986. In conjunction with completing the Form I–9, an employer, recruiter or referrer for a fee, must examine documents that evidence both individual's identity and employment eligibility. The employer, recruiter or referrer for a fee and the individual must complete an attestation on the Form I–9 under penalty of perjury. However, if an individual attests to an employer, recruiter or referrer for a fee, that he/she is an alien who intends to apply or has applied for benefits under the provisions of section 245A or 210A of the Act, then the individual is authorized to work in the United States until September 1, 1987 without providing the employer, recruiter or referrer for a fee, with documentary evidence of work authorization. In this case, the employer, recruiter or referrer for fee, shall indicate on the Form I–9, that the individual intends to apply or has applied for such benefits under section 245A or 210A of the Act. Employers, recruiters and referrers for a fee who fail to comply with the employment verification requirements set forth in § 274a.2(b) of this part shall be subject to penalties as stated in § 274a.10 of this part.

(b) *Employment verification requirements.*—(1) *Examination of documents and completion of Form I–9.* (i) An individual who is hired, recruited or referred for a fee for employment must: (A) complete the attestation and the other appropriate sections of the Form I–9 at the time of hiring, recruitment or referral for a fee for employment; and

(B) present to the employer documentation as set forth in paragraph (b)(1)(v) of this section establishing his/her identity and employment eligibility within the time limits set forth in paragraphs (b)(1)(ii) through (v) of this section. However, pursuant to the "Special Rule" set forth in § 274a.13 of this part, legalization, special agricultural worker and Cuban/Haitian entrant adjustment applicants are not required to present documentation establishing work authorization until after September 1, 1987.

(ii) An employer must within three business days of the hire: (A) Physically examine the documentation presented by the individual establishing identity and employment eligibility as set forth in (b)(1)(v) of this section; and

(B) complete the attestation and the other appropriate sections of the Form I–9.

(iii) An employer, who hires an individual for employment for a duration of less than three business days, must comply with paragraphs (b)(1)(ii)(A) through (B) of this section before the end of the employee's first working day.

(iv) A recruiter or referrer for a fee for employment must comply with paragraphs (b)(1)(ii)(A) through (B) of this section at the time of the recruitment or referral.

(v) The individual may present either an original document which establishes both employment authorization and identity, or an original document which establishes employment authorization and a separate original document which establishes identify.

(A) The following documents are acceptable to evidence both identity and employment eligibility:

(*1*) United States passport.

(*2*) Certificate of United States Citizenship, INS Form N–560.

(*3*) Certificate of Naturalization, INS Form N–550.

(*4*) An unexpired foreign passpoart which:

(*i*) Contains an unexpired stamp therein which reads, "processed for I–551 . . ." or

(*ii*) Has attached thereto a Form I–94 bearing the same name as the employment authorization stamp, so long as the period of endorsement has not yet expired and the proposed employment is not in conflict with any restrictions or limitations identified on the Form I–94.

(*5*) Alien Registration Receipt Card, INS Form I–15, or Resident Alien, INS Form I–551, provided that it contains a photograph of the bearer.

(*6*) Temporary Resident Card, INS Form I–688, or Employment Authorization Card, INS Form I–688A, provided that it contains a photograph of the bearer.

(B) The following documents are acceptable to establish identity only:

(*1*) A State issued driver's license or identification card containing a photograph, or if the document does not contain a photograph, identifying information should be included such as: name, date of birth, sex, height, color of eyes and address;

(*2*) It will be necessary to designate other documents of identification which may be used in the case of a minor, or in a State which does not issue an identification card other than a driver's license. The Service desires to provide for the use of a wide range of documents to establish identity, and requests suggestions and comments from the public and particularly from federal, State, or local agencies which issue documents which could serve that purpose.

(C) The following are acceptable documents to establish employment authorization only:

(*1*) A social security card other than one not valid for employment purposes.

(*2*) An unexpired reentry permit, INS Form I–327.

(*3*) An unexpired Refugee Travel document, INS Form I–571.

(*4*) A Certification of Birth issued by the Department of State, Form FS–545.

(*5*) A Certification of Birth Abroad issued by the Department of State, Form DS–1350.

(6) An original or certified copy of a birth certificate issued by a State or recognized subdivision thereof establishing birth in a State.

(2) *Retention and Inspection of Form I-9.* (i) Form I-9 must be retained by an employer, recruiter or referrer for a fee for the following time periods: (A) In the case of recruiting or referring (without hiring) an individual for a fee, three years after the date of the recruitment or referral; or

(B) In the case of hiring of an individual, three years after the date of the hire or one year after the date the individual's employment is terminated, whichever is later.

(ii) Any person or entity required to retain Form I-9 in accordance with this section shall make such forms available for inspection upon oral request and presentation of credentials by an authorized officer of the Service or the Department of Labor. No subpoena, warrant, or advance notice shall be required for such inspection; however, a person or entity shall have three business days to comply with such a request. Any refusal or delay in presentation of the Form I-9 for inspection after three business days have elapsed is a violation of the retention requirements as set forth in § 274A(b)(3) of the Act.

(3) *Copying of documentation.* An employer, recruiter or referrer for a fee, may copy a document presented by an individual for purposes of complying with the verification requirements of paragraph (b) of this section only if the copy is retained with the Form I-9.

(4) *Limitation on use of Form I-9.* Form I-9 and any information contained in or appended to such Form I-9, may only be used by the Service for enforcement of: Sections 274A and 274B of the Act and 18 U.S.C. 1001, 1028, 1546, and 1621.

(c) *Employment verification requirements in the case of hiring an individual who was previously employed.* (1) When an employer hires an individual whom he/she has previously employed, and where the employer has completed the Form I-9 and complied with the verification requirements set forth in paragraph (b) of this section with regard to the individual, the employer shall inspect the Form I-9 which was previously completed and:

(i) If upon inspection of the Form I-9 relating to the individual, the employer determines that the individual is authorized to work, no additional verification or new Form I-9 need be completed where the individual is hired within one year of the initial execution of the Form I-9; or

(ii) If upon inspection of the Form I-9, the employer determines that the individual is no longer authorized to work in the United States, the employer shall not rehire the individual unless all the employment verification requirements set forth in paragraph (b) of this section are met.

(2) For purposes of retention of the Form I-9 by an employer for a previously employed individual hired pursuant to paragraph (c)(1) of this section, the employer shall retain the Form I-9 for a period of three years commencing from the date of the hire or one year after the date the individual's employment is terminated, whichever is later.

§ 274a.3 Continuing employment of unauthorized alien.

An employer who continues the employment of an employee hired after November 6, 1986 knowing that the employee is or has become an unauthorized alien with respect to such employment is in violation of section 274A(a)(2) of the Act.

§ 274a.4 Good faith defense.

An employer, recruiter or referrer for a fee for employment who shows good faith compliance with the employment verification requirements of paragraph (b) of this section shall have established a rebuttable affirmative defense that the person or entity has not violated section 274A(a)(1)(A) of the Act with respect to such hiring, recruiting or referral.

§ 274a.5 Use of labor through contract.

An employer who knowingly uses a contract, subcontract, or exchange entered into, renegotiated or extended after the date of enactment, to obtain labor or services of an unauthorized alien shall be considered to have hired the alien for employment in the United States in violation of section 274A(a)(1)(A) of the Act.

§ 274a.6 State employment agencies.

The Service desires to develop guidelines relating to role of state employment agencies in the issuance of certificates pursuant to section 274A(a)(5) of the Act, and requests the suggestions and comments of the public on this matter. A prime concern of the Service is the prevention of counterfeiting or misuse of such certificates while limiting the burden on state agencies in their issuance.

§ 274a.7 "Grandfather" provisions for employees hired prior to November 7, 1986.

(a) The verification of employment eligibility requirements and penalties provisions as set forth in §§ 274a.2(b) and 274a.10 of this part shall not apply to:

(1) The hiring, recruiting or referring for a fee for employment of an individual for employment which occurred prior to November 7, 1986; or

(2) The continuing employment of an alien who was hired prior to November 7, 1986. An alien who falls within paragraph (a)(2) of this section shall be considered a "grandfather" employee.

(b) For purposes of this section, an alien who was hired prior to November 7, 1986 shall not lose his/her "grandfather" status if the alien:

(1) Is absent and returns to work after leave for study, illness or pregnancy; or (2) transfers from one location to another with the same employer.

(c) For purposes of this section, an alien who was hired prior to November 7, 1986 shall lose his/her "grandfather" status if the alien is:

(1) Terminated by the employer unless the "grandfather" employee is reinstated due to wrongful termination; or (2) excluded or deported from the United States or departs the United States under an order of voluntary departure.

(d) When an employer claims that he/she is not subject to the employment verification requirements of § 274a.2(b) of this part, with respect to an employee because the alien is a "grandfather" employee, the burden of proof shall be upon the employer to establish that the alien was hired prior to November 7, 1986, and that such alien did not lose such "grandfather" employee status under paragraph (c) of this section.

§ 274a.8 Prohibition of idemnity bonds.

(a) *General.* It is unlawful for a person or other entity, in hiring, recruiting or referring for a fee for employment of any individual, to require the individual to post a bond or security, to pay or agree to pay an amount, or otherwise to provide a financial guarantee or indemnity, against any potential liability arising under this part relating to such hiring, recruiting, or referring of the individual.

(b) *Penalty.* Any person or other entity who requires any individual to post a bond or security as stated in this section shall, after notice and opportunity for an administrative hearing in accordance with section 274A(e)(3)(B) of the Act, be subject to a civil fine of $1,000 for each violation and to an administrative order requiring the return to the individual of any amounts received in violation of this section or, if the individual cannot be located, to the general fund of the Treasury.

§ 274a.9 Enforcement procedures.

(a) *Procedures for the filing of complaints.* Any person or entity having knowledge of a violation or potential violation of section 274A of the Act may submit a signed, written complaint in person or by mail to the Service office in the jurisdiction the business or residence of the potential violator is located. The signed, written complaint must contain sufficient information to identify both the complainant and the potential violator, including their names and addresses, and any other relevant information. Written complaints may be delivered either by certified mail to the appropriate Service office or by personally appearing before any immigration officer at a Service office.

(b) *Investigation.* The Service shall investigate only those written complaints which have a substantial probability of validity. The Service may investigate violations on its own initiative. An immigration officer conducting the investigation shall have reasonable access to examine evidence of the person or entity being investigated.

(c) *Determination.* If it is determined after investigation that the person or entity has violated section 274A of the Act, the Service shall issue and serve upon the alleged violator a Notice of Intent to Fine. Service of this Notice may be accomplished pursuant to section 103 of this chapter.

(d) *Notice of intent to fine.* Every determination or proceeding to assess administrative penalties under section 274A of the Act is commenced by the issuance of a Notice of Intent to Fine by the Service on Form I–762. The person or entity identified in the Notice of Intent to Fine shall be known as the respondent. The Notice of Intent to Fine may be issued by an officer defined in § 242.1 of this chapter.

(1) *Contents.* (i) The Notice of Intent to Fine will contain a concise statement of factual allegations informing the respondent of the act or conduct alleged to be in violation of law, a designation of the charge(s) against the respondent, the statutory provisions alleged to have been violated, and the penalty that will be imposed.

(ii) The Notice of Intent to Fine will provide the following advisals to the respondent:

(A) That the person or entity has the right to representation by counsel of his or her own choice at no expense to the government; (B) That any statement given may be used against the person or entity; (C) That the person or entity has the right to request a hearing before an Administrative Law Judge pursuant to 5 U.S.C. 554–557, and such request must be made within 30 days from the service of the Notice of Intent To Fine; (D) That the Service will issue a final order in 45 days if a request for hearing is not received and there will be no appeal of the final order.

§ 274a.10 Penalties.

(a) *General.* Except as provided herein, this section states the civil penalties that may be imposed for violations under section 274A of the Act. In determining the level of the penalties that should be imposed, a determination of more than one violation in the course of a single proceeding or determination will be counted as a single violation.

(1) A respondent determined by the Service (if the respondent fails to request a hearing), or an Administrative Law Judge, to have knowingly hired, recruited or referred for a fee an unauthorized alien for employment in the United States or to have knowingly continued to employ such an alien shall be subject to the following order:

(i) To cease and desist from such behavior, and

(ii) To pay a civil fine according to the following schedule:

(A) First violation—not less than $250 and not more than $2,000 for each unauthorized alien; or

(B) Second violation—not less than $2,000 and not more than $5,000 for each unauthorized alien; or

(C) More than two violations—not less than $3,000 and not more than $10,000 for each unauthorized alien.

(iii) To comply with the requirements of § 274a.2(b) of this part, and such other remedial action as is appropriate.

(2) A respondent determined by the Service (if the respondent fails to request a hearing) or by an Administrative Law Judge, to have failed to comply with the employment verification requirements as set forth in § 274a.2(b) of this part, shall be subject to a civil penalty in an amount of not less than $100 and not more than $1,000 for each individual with respect to whom such violation occurred. In determining the amount of the penalty, consideration shall be given to:

(i) The size of the business of the employer being charged,

(ii) The good faith of the employer,

(iii) The seriousness of the violation,

(iv) Whether or not the individual was an unauthorized alien, and

(v) The history of previous violations of the employer.

(3) Orders issued with respect to a respondent composed of distinct, physically separate subdivisions which do their own hiring, recruiting or referring for a fee for employment (without reference to the practices of, or under the control of, or common control with another subdivision) such subdivisions shall be considered separate persons or entities.

§ 274a.11 Special rule for legalization, special agricultural worker and Cuban/Haitian entrant adjustment applicants.

An individual who claims to be eligible, and who intends to apply, or has applied, for benefits pursuant to section 245A or 210A of the Act, is not required to present an employer with documentary evidence of work authorization until after September 1, 1987. When an individual indicates to an employer that he/she claims to qualify for such benefits and that he/she intends to apply, or has applied, for temporary resident status, he or she shall provide a statement to that effect under oath or attestation on Form I–9 in lieu of documentation. The employer shall follow all of the employment verification procedures set forth in § 274a.2(b) of this part *except* that the employer shall note on the Form I–9 that the individual has stated his/her intention to seek such temporary resident status, instead of completing "List C—Employment Eligibility" on the employer portion of the I–9. After September 1, 1987, such individuals and employers will be required to fully comply with all provisions of § 274a.2(b) of this part. Nothing in this section shall be construed as constituting a grant of employment authorization by the Service to any unauthorized alien within the meaning of § 274a.12 of this part.

Subpart B—Employment Authorization

§ 274a.12 Classes of aliens eligible.

(a) *Aliens authorized employment incident to status.* The employment authorization is limited solely to the extent and conditions described for the corresponding classifications in section 101(a)(15) of the Act, 8 CFR Part 214, 22 CFR Part 41 and 22 CFR 514.24. The following classes of aliens are authorized to be employed in the United States as a condition of their admission or subsequent change to one of the indicated classes, and specific authorization need not be requested:

(1) A lawful permanent resident alien.

(2) An alien admitted to the United States as a refugee under section 207 of the Act for the period of time in that status.

(3) An alien paroled into the United States as a refugee for the period of time in that status.

(4) An alien granted asylum under section 208 of the Act for the period of time in that status.

(5) An alien admitted to the United States as a nonimmigrant fiance or fiancee for the period of admission to the United States

(6) An alien admitted in one of the following classifications, or whose status has been changed to such classification under section 247 or 248 of the Act:

(i) A foreign government official (A–1) or (A–2).

(ii) An employee of a foreign government official (A–3).

(iii) A nonimmigrant visitor for business (B–1).

(iv) A nonimmigrant crewman (D–1).

(v) A nonimmigrant treaty trader or investor (E–1) or (E–2).

(vi) A representative of an international organization (G–1), (G–2), (G–3), or (G–4).

(vii) A personal servant of an employee or representative of an international organization (G–5).

(viii) A temporary worker or trainee (H–1), (H–2), (H–2A), or (H–3).

(ix) An information media representative (I).

(x) An exchange visitor (J–1).

(xi) An intra-company transferee (L–1).

(7) An alien who is a member of a nationality group who has been granted blanket extended voluntary departure.

(8) Applicants for benefits pusuant to sections 245A and 210 of the Act until September 1, 1987.

(b) *Aliens who must apply for work authorization.* Any alien within a class of aliens described in this paragraph must apply for work authorization to the district director in whose district the alien resides:

(1) Any alien maintaining a lawful nonimmigrant status in one or more of the following classes may be granted permission to be employed:

(i) Alien spouse or unmarried dependent son or daughter of a foreign government official (A–1) or (A–2) as provided in § 214.2(a)(2) of this title, or the dependent of an employee as provided by § 214.2(a)(3) of this title.

(ii) Alien nonimmigrant student (F–1) as provided in § 214.2(f) of this chapter.

(iii) Alien spouse or an unmarried dependent son or daughter of an officer or employee of an international organization (G–4) as provided in § 214.2(g) of this chapter.

(iv) Alien spouse or minor child or an exchange visitor (J–2) as provided in § 214.2(j) of this title.

(2) Any alien who has filed a non-frivolous application for asylum pursuant to Part 208 of this chapter may be granted permission to be employed for the period of time necessary to decide the case.

(3) Any alien who has properly filed an application for adjustment of status to permanent resident alien may be granted permission to be employed for the period of time necessary to decide the case.

(4) Any alien paroled into the United States temporarily for emergent reasons or for reasons deemed strictly in the public interest: provided, the alien establishes an economic need to work.

(5) Any alien who has applied to an Immigration Judge under § 242.17 of this chapter for suspension of deportation pursuant to section 244(a) of the Act may be granted permission to be employed for the period of time necessary to decide the case: provided, the alien establishes an economic need to work.

(6) Any deportable alien granted voluntary departure, either prior to hearing or after hearing, for reasons set forth in § 242.5(a)(2)(v), (vi), or (viii) of this chapter may be granted permission to be employed for that period of time prior to the date set for voluntary departure including any extension granted beyond such date. Factors which may be considered in granting employment authorization to an alien who has been granted voluntary departure:

(i) Length of voluntary departure granted;

(ii) Dependent spouse and/or children in the United States who rely on the alien for support;

(iii) Reasonable chance that legal status may ensue in the near future; and

(iv) Reasonable basis for consideration of discretionary relief.

(7) Any alien in whose case the district director recommends consideration of deferred action, an act of administrative convenience to the government which gives some cases lower priority: Provided, the alien establishes to the satisfaction of the district director that he/she is financially unable to maintain himself/herself and family without employment.

(8) Any excludable or deportable alien who has posted an appearance and delivery bond may be granted temporary employment authorization if the district director determines that employment is appropriate under § 103.6(a)(2)(iii) of this chapter.

(c) *Basic criteria to establish economic necessity.* Title 45—Public Welfare, Poverty Income Guidelines, 45 CFR 1060.2 shall be used as the basic criteria to establish economic necessity for employment authorization requests where the alien's need to work is a factor. The applicant shall submit a signed statement listing his/her assets, income, and expenses as evidence of his/her economic need to work. Permission to work granted on the basis of the applicant's statement may be revoked under § 274a.13 of this part upon a showing that the information contained in the statement was not true and correct.

§ 274a.13 Revocation of employment authorization.

(a) *Basis for revocation of employment authorization.* Employment authorization granted under § 274a.2(b) of this part may be revoked by the district director when it appears that one or more of the conditions upon which it was granted no longer exist, or for good cause shown.

(b) *Notice of intent to revoke employment authorization.* When a district director determines that employment authorization should be revoked, he/she shall serve notice of the reasons and the intention to revoke on the alien. The alien will be granted a period of fifteen days from the date of service of notice in which to submit evidence why the authorization should not be revoked. The decision by the district director shall be final and no appeal shall lie from the decision to revoke the authorization.

Dated: March 6, 1987.

Alan C. Nelson,

Commissioner, Immigration and Naturalization Service.

Attachment

Although not a part of the CFR, the following Immigration and Naturalization Service forms were developed as a result of the Immigration Reform and Control Act of 1986. The reproductions are not official forms and should not be copied or used in any way and are being included for informational purposes only.

BILLING CODE 4410-10-M

U.S. Department of Justice
Immigration and Naturalization Service

APPLICATION FOR STATUS AS A TEMPORARY RESIDENT
Under Section 245A of the Immigration and Nationality Act

I-687 Instructions - Page 1
(Conditions of Application)

Please carefully read all of the instructions: The fee will not be refunded.

Failure to follow instructions may require return of your application and delay final action. If your application is returned, no further action will be taken. You must resubmit your application with the requested documentation or information to renew processing.

Applications for status as a temporary resident as 1) an alien who illegally entered the United States prior to January 1, 1982 or 2) an alien who entered the United States as a nonimmigrant prior to January 1, 1982 and whose authorized stay expired before such date or whose unlawful status was known to the Immigration and Naturalization Service as of January 1, 1982 must be submitted or resubmitted by May 4, 1988. Failure to do so will make the applicant ineligible for the benefit sought.

1. **Preparation of Application:** A separate application for each applicant must be typewritten or printed legibly in ink. Applications by family members must be submitted together in order to receive the reduced family fee structure identified in item #5 of the instructions. The application must be completed in full. If extra space is needed to answer any item, attach a continuation sheet and indicate the item number. Various organizations and individuals (Qualified Designated Entities) have been designated by the Attorney General to assist applicants in the preparation of their applications. Your application must be submitted to the Immigration Legalization Office having jurisdiction over your place of residence.

2. **Eligibility:** An application may be filed by any alien who would qualify within the following guidelines. If you are not certain that you would qualify, you may contact a Qualified Designated Entity near your place of residence or an Immigration Legalization Office in your area. ***The following aliens may be eligible for temporary resident status.***

   (a) An alien who can establish that he/she entered the United States before January 1, 1982 and that he/she has resided continuously in the United States in an unlawful status since such date.

   (b) An alien who entered the United States as a nonimmigrant prior to January 1, 1982 and whose authorized stay expired before such date or whose unlawful status was known to the Government as of January 1, 1982 and who has resided continuously in the United States in an unlawful status since such date.

   In order to be eligible for Temporary Resident status under paragraphs (a) and (b), the applicant must have been continuously physically present in the United States since the date of enactment of the Immigration Reform and Control Act of 1986 (November 6, 1986).

3. **Ineligible Classes:** The following classes of aliens are ineligible for temporary residence.

   (a) An alien who has been convicted of a felony or three or more misdemeanors committed in the United States.

   (b) An alien who has assisted in the persecution of any person or persons on account of race, religion, nationality, membership in a particular social group, or political opinion.

   (c) An alien who at any time was a nonimmigrant exchange visitor who is subject to the two-year foreign residence requirement unless the requirement has been satisfied or waived pursuant to the provisions of Section 212(e) of the Act.

4. **Penalties for False Statements in Applications:** Whoever files an application for adjustment of status under Section 245A of the Act and who knowingly and willfully falsifies, misrepresents, conceals or covers up a material fact or makes any false, fictitious, or fraudulent statements or representations, or makes or uses any false writing or document knowing the same to contain any false, fictitious, or fraudulent statement or entry will be subject to criminal prosecution and/or deportation.

Authority for Collecting this Information: The authority to prescribe this form is contained in the "Immigration Reform and Control Act of 1986." The information is necessary to determine whether a person is eligible for the immigration benefit sought. Information on race is requested in question #10 for statistical purposes only. You do not have to give this information. All other questions must be answered. Failure to do so may result in the denial of the application.

Confidentiality: The information provided in this application is confidential and may only be used to make a determination on the application or for enforcement of the penalties for false statements referred to in instruction #4. The information provided is subject to verification by the Immigration and Naturalization Service.

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5. **Fees:** A fee of one hundred eighty-five dollars ($185.00) for each application, or fifty dollars ($50.00) for each application for a minor child (under 18 years of age) is required at the time of filing with the Immigration and Naturalization Service. The maximum amount payable by a family (husband, wife, and any minor children) shall be four hundred twenty dollars ($420.00). The fee is not refundable regardless of the action taken on the application. A separate cashier's check or money order must be submitted for each application. ***All fees must be submitted in the exact amount.*** No cash or personel checks will be accepted. The cashier's check or money order must be made payable to "Immigration and Naturalization Service" unless applicant resides in the Virgin Islands or Guam. (Applicants residing in the Virgin Islands make cashier's checks or money orders payable to "Commissioner of Finance of the Virgin Islands". Applicants residing in Guam make cashier's check or money order payable to "Treasurer, Guam".)

6. **Photographs:** Submit two (2) color photographs of yourself taken within thirty (30) days of the date of this application. These photos must have a white background, be glossy, unretouched, and not mounted; dimension of facial image should be about one inch from chin to top of hair; you should be shown in 3/4 frontal view showing right side of face with right ear visible; using pencil or felt pen, lightly print your name on the back of each photograph. Failure to comply with the above instructions will result in the return of the application without further action.

7. **Fingerprints:** A completed fingerprint card (Form FD-258) must be submitted by each applicant 14 years of age or older. Fingerprint cards with instructions for their completion are available at Qualified Designated Entity offices. Applicants may be fingerprinted by law enforcement offices, Outreach Centers, charitable and voluntary agencies, or other reputable persons or organizations. The fingerprint card (FD-258) on which the prints are submitted, the ink used, and the quality and classifiability of the prints must meet standards prescribed by the Federal Bureau of Investigaton. The card must be signed by you in the presence of the person taking your fingerprints, who must then sign his/her name and enter the date in the spaces provided. It is important to furnish all the information called for on the card.

8. **Interview:** You will be required to be present for a personal interview by an officer of the Immigration and Naturalization Service. In most locations, interviews will be scheduled subsequent to receipt of the application.

9. **Documents - General:** All documents must be submitted in the original. If the return of original documents is desired, each must be accompanied by copies certified as true and correct by your representative or Qualified Designated Entity in the format prescribed in 8 CFR 204.2 (j)(1) or (2). Certified copies unaccompanied by original documents are unacceptable. All original documents submitted without certified copies become the property of the Attorney General and will be retained by the Service. Any document in a foreign language must be accompanied by a summary translation into English. A summary translation is a condensation or abstract of the document's text but includes all pertinent facts. The translator must certify that he/she is competent to translate into English and that the translation is accurate.

10. **Documents to Establish Identity:** The following list gives examples of the types of documents the Immigration and Naturalization Service will consider as evidence to establish your identity. This list is not all inclusive and other evidence may be considered if none of the following is available:

    - Birth Certificate, Baptismal Certificate, or other evidence of birth
    - Passport
    - National Identification Card from country of origin
    - Driver's License
    - School Identification Card
    - State Identification Card

11. **Documents to Establish Admissibility:**

    (a) Medical Report of Examination (Form I-693).

    (b) Evidence of Income: examples of documents which may be used as evidence of financial support or income include:

    - Letters from employers which illustrate full-time employment.
    - W-2 Tax Records or other wage records.
    - Bank statements or evidence of other assets.
    - Form I-134 (Affidavit of Support) completed by a responsible person in the United States.
    - Any other evidence to establish that the applicant is not likely to become a public charge.

    (c) An application for a Waiver of Grounds of Excludability (Form I-690) may be required if you answer any of the items 39 through 43 in the affirmative.

12. **Documents to Establish Residence:** Examples of documents which may be submitted to prove continuity of residence include:

    - Leases
    - Rent Receipts
    - Employer, union or other business records
    - Birth certificates of children born in the United States
    - Automobile license receipts
    - Vehicle registrations
    - Deeds
    - Mortages
    - Utility bill receipts
    - Installment loan records
    - Church records
    - Medical records

    Letters from landlords should include the landlord's present address and the beginning and terminating dates of the applicant's residence. Letters from employers' organizations or churches should be on official stationery and include relevant dates, the organization seal (if any) and the signer's name and title.

U.S. Department of Justice
Immigration and Naturalization Service

Application for Status as a Temporary Resident

(Under Section 245A of the Immigration and Nationality Act)

OMB #1115-0133

Please begin with item #1, after carefully reading the instructions. **The block below is for *Government Use Only.***

Name and Location (City or Town) of Qualified Designated Entity	Fee Stamp
	Fee Receipt No. (This application)
	Principal Applicant's File No. A -
Qualified Designated Entity I.D. No.	File No. (This applicant) A -

Applicant: Do not write above this line. See instructions before filling in application. If you need more space to answer fully any question on this form, use a separate sheet and identify each answer with the number of the corresponding question. ***Fill in with typewriter or print in block letters in ink.***

1. I hereby apply for status as indicated by the block checked below (check block A or B).

☐ A Temporary Residence as an alien who illegally entered the U.S. prior to January 1, 1982.

☐ B Temporary Residence as an alien who entered the U.S. as a nonimmigrant prior to January 1, 1982 and whose authorized stay expired before such date or whose unlawful status was known to the Government as of January 1, 1982.

2. Family Name (Last Name in CAPITAL Letters)	(First Name)	(Middle Name)	3. Date of Birth (Month/Day/Year)

4. Other Names Used or Known by (Including maiden name, if married)	5. Telephone Numbers (Include Area Codes) Home: Work:

6. Home Address in the U.S. (No. and Street)	(Apt. No.)	(City)	(State)	(ZIP Code)

7. Mailing Address in the U.S. (if different from #6.)	(Apt. No.)	(City)	(State)	(ZIP Code)

8. Last Address outside the U.S. (City or Town)	(County, Province or State)	(Country)

9. Sex	10. Race			
☐ Male	☐ Asian or Pacific Islander	☐ Black, not of Hispanic origin	☐ Other (specify below)	
☐ Female	☐ Hispanic	☐ White, not of Hispanic origin		

11. Marital Status			12. Country of Citizenship
☐ Never Married	☐ Divorced		
☐ Now Married	☐ Separated	☐ Widowed	

13. Place of Birth (City or Town)	(County, Province or State)	(Country)

14. Have you previously applied for temporary residence as a legalization applicant? ☐ No ☐ Yes (if "Yes" give date, place of filing, and final disposition, if known)	15. Do you have any other record with I&NS? ☐ No ☐ Yes [If "Yes" give number(s)] A - _____ Other _____

16. When did you last come to the U.S.? (Month/Day/Year)	17. Manner of Entry (Visitor, Student, Crewman, etc.) ☐ With visa (visitor, student, etc.) specify _____ ☐ Without visa
18. Place of Last Entry ☐ U.S. Port of entry (City and State) _____ ☐ Border - Not through port (State) _____	19. List all Social Security Numbers used. (1) (3) (2) (4)
20. Mother's Name (Maiden) (Last) (First) ☐ Living ☐ Deceased (year) _____	21. Father's Name (Last) (First) ☐ Living ☐ Deceased (year) _____

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If you were admitted as a nonimmigrant, complete items 22 through 30; if not, leave blank and continue on item 31.

22. Passport Number	23. Country that Issued Passport	24. Location Visa Issued (City and Country of U.S. Consul)
25. Type of Visa Issued (B-2, F-1, etc.)	26. Date Visa Issued (Month/Day/Year)	27. Authorized Stay in U.S. Expired (Month/Day/Year)
28. Visa Class (Student, visitor, etc.)	29. Did you violate your legal status? ☐ No ☐ Yes If "Yes" explain violation and date	30. Were you notified of your violation? ☐ No ☐ Yes If "Yes" explain how notified

31. I have been married _____ times.

I have (fill in *total number* now living, whether in the U.S. or not.) _____ sons and daughters, and _____ brothers and sisters.

32. Complete all columns below for your spouse, each former spouse, and each son, daughter, brother and sister. Under Name, give first name and middle initial (give last name only if it differs from your own). Under Relationship, fill in spouse, former spouse, son, daughter, brother or sister. Under Date of Birth, give month, day, and year of birth. Under Place of Birth, give city, state and country of birth. Under Location Where Now Living, give city, state and country of current residence (if living with you, write "with me" in the column). In the last column write "Yes", "No", or "Unknown" to indicate if each is applying for residence in the U.S. If more space is needed, attach an additional sheet. Indicate on the sheet that the information refers to question #32.

Full Name (Include maiden name if applicable)	Relationship	U.S. Citizen?	Date of Birth	Place of Birth	Location Where Now Living	Applying?
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				
		☐ Yes ☐ No				

33. List all of your residences in the United States since your first entry, beginning with your present address (attach an additional sheet, if necessary)

Street Name and Number (Apt. No.)	City	State and ZIP Code	From (Month/Year)	To (Month/Year)
				Present

34. To assist in establishing the required residence, please list all affiliations or associations with clubs, organizations, churches, unions, businesses, etc.

Name of Organization	Location	From (Month/Year)	To (Month/Year)

35. Absences from the United States since entry. (List most recent absence first and list absences back to January 1, 1982).

Country	Purpose of Trip	From (Month/Year)	To (Month/Year)

36. Employment in the United States since first entry. (List present or most recent first and list back to date of entry; if none since entry, write "None".)

Full Name and Address of Employer (with ZIP Code) (or Self employed and business address)	Your Occupation	Annual Wages	Wages per Hour	From (Month/Year)	To (Month/Year)

37. ☐ I have registered under the Military Selective Service Act. My Selective Service No. is _____
☐ I am a male over the age of 17 and under the age of 26 required to register under the Military Selective Service Act and have not done so. I wish to register at this time. SSS Form 1 is attached.
☐ I am a male born after 1959 and over the age of 26 and cannot now register.
☐ I am exempt from Selective Service Registration either because I am a female or I was born before 1960.

38. I ☐ have I ☐ have not assisted in the persecution of any person or persons on account of race, religion, nationality, membership in a particular social group or political opinion.

39. I ☐ have I ☐ have not been treated for a mental disorder, drug addiction or alcoholism.

40. I ☐ have I ☐ have not been arrested, convicted or confined in a prison.

41. I ☐ have I ☐ have not been the beneficiary of a pardon, amnesty, rehabilitation decree, other act of clemency or similar action.

42. I ☐ have I ☐ have not received public assistance from any source, including, but not limited to, the United States Government, any state, county, city or municipality. (If you have, explain, including the name(s) and Social Security number(s) used.)

43. **Applicants for status as Temporary Residents must establish that they are admissible to the United States. Except as otherwise provided by law, aliens within any of the following classes are not admissible to the United States and are therefore ineligible for status as Temporary Residents.**

A. Aliens who have committed or who have been convicted of a crime involving moral turpitude (does not include minor traffic violations).

B. Aliens who have been engaged in or who intend to engage in any commercialized sexual activity.

C. Aliens who are or at any time have been anarchists, or members of or affiliated with any Communist or other totalitarian party, including any subdivision or affiliate thereof.

D. Aliens who have advocated or taught, either by personal utterance, or by means of any written or printed matter, or through affiliation with an organization:
1) Opposition to organized government;
2) The overthrow of government by force or violence;
3) The assaulting or killing of government officials because of their official character;
4) The unlawful destruction of property;
5) Sabotage, or;
6) The doctrines of world communism, or the establishment of a totalitarian dictatorship in the United States.

E. Aliens who intend to engage in activities prejudicial to the national interests or unlawful activities of a subversive nature.

F. Aliens who, during the period beginning on March 23, 1933, and ending on May 8, 1945, under the direction of, or in association with:
1) The Nazi government in Germany;
2) Any government in any area occupied by the military forces of the Nazi government in Germany;
3) Any government established with the assistance or cooperation of the Nazi government of Germany;
4) Any government which was an ally of the Nazi government of Germany;

ordered, incited, assisted or otherwise participated in the persecution of any person because of race, religion, national origin, or political opinion.

G. Aliens who have been convicted of a violation of any law or regulation relating to narcotic drugs or marihuana, or who have been illicit traffickers in narcotic drugs or marihuana.

H. Aliens who have been involved in assisting any other aliens to enter the United States in violation of the law.

I. Aliens who have applied for exemption or discharge from training or service in the Armed Forces of the United States on the ground of alienage and who have been relieved or discharged from such training or service.

J. Aliens who are mentally retarded, insane, or who have suffered one or more attacks of insanity.

K. Aliens afflicted with psychopathic personality, sexual deviation, mental defect, narcotic drug addiction, chronic alcoholism or any dangerous contagious disease.

L. Aliens who have a physical defect, disease or disability affecting their ability to earn a living.

M. Aliens who are paupers, professional beggars or vagrants.

N. Aliens who are polygamists or advocate polygamy.

O. Aliens likely to become a public charge.

P. Aliens who have been excluded from the United States within the past year, or who at any time within 5 years have been deported from the United States.

Q. Aliens who have procured or have attempted to procure a visa by fraud or misrepresentation.

R. Aliens who are former exchange visitors who are subject to but have not complied with the two-year foreign residence requirement.

Do any of the above classes apply to you? ☐ No ☐ Yes (If "Yes", explain on a separate sheet of paper.)

44. If your native alphabet is in other than Roman letters, write your name in your native alphabet.	45. Language of native alphabet
46. Signature of Applicant - *I CERTIFY*, under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. I hereby consent and authorize the Service to verify the information provided, and to conduct police, welfare and other record checks pertinent to this application.	47. Date (Month/Day/Year)
48. Signature of person preparing form, *if other than applicant. I DECLARE that this document was prepared by me at the request of the applicant and is based on all information of which I have any knowledge.*	49. Date (Month/Day/Year)
50. Name and Address of person preparing form, *if other than applicant (type or print).*	51. Occupation of person preparing form

QUALIFIED DESIGNATED ENTITY USE ONLY		
52. Reviewed by (Print or Type Name)	53. Signature	54. Date

IMMIGRATION AND NATURALIZATION SERVICE USE ONLY			
55. Recommendation: Temporary Residence ☐ Approved ☐ Denied	56. Waiver of Excludability under Section 212 (a) _____ is ☐ Approved ☐ Denied		
57. Class of Admission	58. Place of Adjustment		59. Date of Adjustment
60. Recommended by (Print or type Name and Title)	61. Signature	62. ID No.	63. Date
64. Final Action: Temporary Residence ☐ Approved ☐ Denied	65. Director Regional Processing Facility	66. ID. No.	67. Date

U.S. Department of Justice
Immigration and Naturalization Service

Application for Temporary Resident Status as a Special Agricultural Worker (SAW)
(Section 210 of the Immigration and Nationality Act)

I-700 Instructions - Page 1
(Conditions of Application)

Please carefully read all of the instructions: The fee will not be refunded.

Failure to follow instructions may require return of your application and delay final action. If your application is returned, no further action will be taken. You must resubmit your application with the requested documentation or information to renew processing.

Applications for temporary resident status as a special agricultural worker must be submitted (or resubmitted) by November 30, 1988. Failure to do so will make the applicant ineligible for the benefit sought.

1. **Preparation of Application and Filing:** A separate application for each applicant must be typewritten or printed legibly in ink. Applications by family members must be submitted together in order to receive the reduced family fee structure identified in item #5 of the instructions. The application must be completed in full. If extra space is needed to answer any item, attach a continuation sheet and indicate the item number. Various organizations and individuals (Qualified Designated Entities) have been designated by the Attorney General to assist applicants in the preparation of their applications.

   Applicants who have been in the United States since November 6, 1986 may file their applications in the United States with a legalization office of the Immigration and Naturalization Service or with a Qualified Designated Entity. All others must file their applications outside the United States at a location designated by the nearest American Consulate.

2. **Penalties for False Statements in Applications:** Whoever files an application for adjustment of status under Section 210 of the Act and who knowingly and willfully falsifies, conceals or covers up a material fact or makes any false, fictitious, or fraudulent statements or representations, or makes or uses any false writing or document knowing the same to contain any false, fictitious, or fraudulent statement or entry or creates or supplies a false writing or document for use in making such an application will be subject to criminal prosecution and/or deportation.

3. **Eligibility:** Applicants may be eligible for temporary residence in either the Group I or Group II classification.

   (a) Group I
   An applicant who can establish that he/she has performed seasonal agricultural services (field work in perishable commodities) in the United States for at least 90 man days during each of the 12 month periods ending on May 1, 1984, 1985, and 1986, and resided in the United States for an aggregate of 6 months in each 12 month period.

   (b) Group II
   An applicant who can establish that he/she has resided and performed seasonal agricultural services (field work in perishable commodities) in the United States for at least 90 man days during the 12 month period ending on May 1, 1986.

4. **Ineligible Classes:** The following classes of aliens are ineligible for temporary residence as special agricultural workers:

   (a) An alien who has assisted in the persecution of any person or persons on account of race, religion, nationality, membership in a particular social group, or political opinion;

   (b) An alien who at any time was a nonimmigrant exchange visitor under Section 101(a)(15)(J) of the Act who is subject to the two year foreign residence requirement unless the alien has complied with that requirement or the requirement has been waived pursuant to the provisions of Section 212(e) of the Act.

Authority for Collecting this Information: The authority to prescribe this form is contained in the "Immigration Reform and Control Act of 1986." The information is necessary to determine whether a person is eligible for the immigration benefit sought. Information on race is requested in question #9 for statistical purposes only. You do not have to give this information. All other questions must be answered. Failure to do so may result in the denial of the application.

Confidentiality: The information provided in this application is confidential and may only be used to make a determination on the application or for enforcement of the penalties for false statements referred to in instruction #2. The information provided is subject to verification by the Immigration and Naturalization Service.

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5. Fees: A fee of one hundred eighty-five dollars ($185.00) for each application, or fifty dollars ($50.00) for each application for a minor child (under 18 years of age) is required at the time of filing with the Immigration and Naturalization Service. The maximum amount payable by a family (husband, wife, and any minor children) shall be four hundred twenty dollars ($420.00). The fee is not refundable regardless of the action taken on the application. A separate cashier's check or money order must be submitted for each application. ***All fees must be submitted in the exact amount.*** No cash or personal checks will be accepted. The cashier's check or money order must be made payable to "Immigration and Naturalization Service" unless applicant resides in the Virgin Islands or Guam. (Applicants residing in the Virgin Islands make cashier's checks or money orders payable to "Commissioner of Finance of the Virgin Islands". Applicants residing in Guam make cashier's check or money order payable to "Treasurer, Guam".)

6. Photographs: Submit two (2) color photographs of yourself taken within thirty (30) days of the date of this application. These photos must have a white background, be glossy, unretouched, and not mounted; dimension of facial image should be about one inch from chin to top of hair; you should be shown in 3/4 frontal view showing right side of face with right ear visible; using pencil or felt pen, lightly print your name on the back of each photograph. Failure to comply with the above instructions will result in the return of the application without further action.

7. Fingerprints: A completed fingerprint card (Form FD-258) must be submitted by each applicant 14 years of age or older. Fingerprint cards with instructions for their completion are available at Qualified Designated Entity offices. Applicants in the United States may be fingerprinted by law enforcement offices, Qualified Designated Entities, or other reputable persons or organizations. Applicants outside of the United States may be fingerprinted at an American Consulate. The fingerprint card (FD-258) on which the prints are submitted, the ink used, and the quality and classifiability of the prints must meet standards prescribed by the Federal Bureau of Investigaton. The card must be signed by you in the presence of the person taking your fingerprints, who must then sign his/her name and enter the date in the spaces provided. It is important to furnish all the information called for on the card.

8. Interview: You will be required to be present for a personal interview by either an officer of the Immigration and Naturalization Service or an American consul. In most locations, interviews will be scheduled subsequent to receipt of the application.

9. Documents - General: All documents must be submitted in the original. If the return of original documents is desired, each must be accompanied by copies certified as true and correct by your representative or designated Qualified Designated Entity in the format prescribed in 8 CFR 204.2 (j)(1) or (2). Certified copies unaccompanied by original documents are unacceptable. All original documents submitted without certified copies become the property of the Attorney General and will be retained by the Service. Any document in a foreign language must be accompanied by a summary translation into English. A summary translation is a condensation or abstract of the document's text but includes all pertinent facts. The translator must certify that he/she is competent to translate into English and that the translation is accurate.

10. Documents to Establish Identity: The following list gives examples of the types of documents the Immigration and Naturalization Service will consider as evidence to establish your identity. This list is not all inclusive and other evidence may be considered if none of the following is available:

- Birth Certificate, Baptismal Certificate, or other evidence of birth
- Passport
- National Identification Card from country or origin
- Driver's License
- School Identification Card
- State Identification Card

11. Documents to Establish Admissibility:

(a) Medical Report of Examination (Form I-693).

(b) Evidence of Income: During periods of residence in the United States examples of documents which may be used as evidence of financial support or income include:

- Documents listed in item #13.
- Letters from employers which illustrate full-time employment.
- W-2 Tax Records or other wage records.
- Bank statements or evidence of other assets.
- Form I-134 (Affidavit of Support) completed by a responsible person in the United States.
- Any other evidence to establish that the applicant is not likely to become a public charge.

(c) An application for a Waiver of Grounds of Excludability (Form I-690) may be required if you answer any of the items 26 through 29 in the affirmative.

12. Documents to Establish Residence: Examples of documents which may be submitted to establish residence in the United States during the requisite period(s) include:

- Employment records
- Leases
- Birth certificates of children born in the United States
- Church records
- Medical records

13. Documents to Establish Qualifying Employment: Examples of documents which may be submitted to prove employment as a Seasonal Agricultural Worker include:

- Government employment records.
- Employment records kept by growers, their foremen, farm labor contractors, unions.
- Affidavits executed under oath by persons with specific knowledge of the applicant's employment.
- Other reliable documentation as the alien may provide, such as pay stubs, work receipts and worker identification cards.

Documentation provided by Special Agricultural Workers is subject to employer corroboration.

U.S. Department of Justice
Immigration and Naturalization Service

Application for Temporary Resident Status as a Special Agricultural Worker (Section 210 of the Immigration and Nationality Act)

OMB #1115-0131

Please begin with item #1, after carefully reading the instructions. **The block below is for *Government Use Only.***

Name and Location (City or Town) of Qualified Designated Entity	Fee Stamp
	Fee Receipt No. (This application)
	Principal Applicant's File No. A -
Qualified Designated Entity I.D. No.	File No. (This applicant) A -

Applicant: Do not write above this line. See instructions before filling in application. If you need more space to answer fully any question on this form, use a separate sheet and identify each answer with the number of the corresponding question. ***Fill in with typewriter or print in block letters in ink.***

1 **I hereby apply for status as indicated by the block checked below** (check block A or B).

☐ A Group I: Temporary Residence as an alien who has performed seasonal agricultural services in the U.S. for at least 90 days during each of the 12 month periods ending on May 1, 1984, 1985, and 1986.

☐ B Group II: Temporary Residence as an alien who has performed seasonal agricultural services in the U.S. for at least 90 days during the 12 month period ending on May 1, 1986.

2 **Family Name** (Last Name in CAPITAL Letters) (First Name) (Middle Name)	3. **Date of Birth** (Month/Day/Year)
4 **Other Names Used or Known by** (Including maiden name, if married)	5. **Telephone Numbers** (Include Area Codes) Home: Work:
6 **Address** (No. and Street) (Apt. No.) (Town or City) (State/Country) (ZIP/Postal Code)	
7 **Last Address outside the U.S.** (City or Town) (County, Province or State) (Country)	
8 **Sex** ☐ Male ☐ Female	9 **Race** ☐ Asian or Pacific Islander ☐ Black, not of Hispanic origin ☐ Other (specify below) ☐ Hispanic ☐ White, not of Hispanic origin
10 **Marital Status** ☐ Never Married ☐ Divorced ☐ Now Married ☐ Separated ☐ Widowed	11. **Country of Citizenship**
12 **Place of Birth** (City or Town) (County, Province or State) (Country)	
13 **Have you previously applied for temporary residence as a Special Agricultural Worker?** ☐ No ☐ Yes (If "Yes" give date, place of filing, and final disposition, if known)	14 **Do you have any other record with I&NS?** ☐ No ☐ Yes [If "Yes" give number(s)] A - _____ Other _____
15 **When did you last come to the U.S.?** (Month/Day/Year)	16. **Manner of Entry** (Visitor, Student, Crewman, etc.) ☐ With visa (visitor, student, etc.) specify _____ ☐ Without visa
17 **Place of Last Entry** ☐ U.S. Port of entry (City and State) _____ ☐ Border - Not through port (State) _____	18. **List all Social Security Numbers used.** (1) (3) (2) (4)
19 **Mother's Name** (Maiden) (Last) (First) ☐ Living ☐ Deceased *(year)* _____	20. **Father's Name** (Last) (First) ☐ Living ☐ Deceased *(year)* _____

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21. To assist in establishing the required residence, please list all affiliations or associations with clubs, organizations, churches, unions, businesses, etc..

Name of Organization	Location	From (Month/Year)	To (Month/Year)

22. Fieldwork in perishable commodities from May 1, 1983 through May 1, 1986 (List most recent first)
Information concerning employment in the United States is subject to corroboration by the employer.

Name of Employer	Farm Name and Location (State and County)	From (Month/Year)	To (Month/Year)	Days Worked	Type of Field Work	Type of Crop	Documentation

23. List all periods of residence in the United States since May 1, 1983 and means of support. Begin with your present address (attach an additional sheet if necessary).

Street Name and Number (Apt. No.) City State and ZIP Code	Means of Support	From (Month/Year)	To (Month/Year)
			Present

24. I ☐ have I ☐ have not assisted in the persecution of any person or persons on account of race, religion, nationality, membership in a particular social group, or political opinion.

25. I ☐ have I ☐ have not received public cash assistance from any source, including, but not limited to, the United States Government, any state, county, city or municipality. (If you have, explain; including the name(s) and Social Security number(s) used.)

26. I ☐ have I ☐ have not been treated for a mental disorder, drug addiction or alcoholism.

27. I ☐ have I ☐ have not been arrested, convicted or confined in a prison.

28. I ☐ have I ☐ have not been the beneficiary of a pardon, amnesty, rehabilitation decree, other act of clemency or similar action.

29 **Applicants for status as Temporary Residents must establish that they are admissible to the United States. Except as otherwise provided by law, aliens within any of the following classes are not admissible to the United States and are therefore ineligible for status as Temporary Residents.**

A. Aliens who have committed or who have been convicted of a crime involving moral turpitude (does not include minor traffic violations).

B. Aliens who have been engaged in or who intend to engage in any commercialized sexual activity.

C. Aliens who are or at any time have been anarchists, or members of or affiliated with any Communist or other totalitarian party, including any subdivision or affiliate thereof

D. Aliens who have advocated or taught, either by personal utterance, or by means of any written or printed matter, or through affiliation with an organization:
1) Opposition to organized government;
2) The overthrow of government by force or violence;
3) The assaulting or killing of government officials because of their official character;
4) The unlawful destruction of property;
5) Sabotage, or;
6) The doctrines of world communism, or the establishment of a totalitarian dictatorship in the United States.

E. Aliens who intend to engage in activities prejudicial to the national interests or unlawful activities of a subversive nature.

F. Aliens who, during the period beginning on March 23, 1933, and ending on May 8, 1945, under the direction of, or in association with:
1) The Nazi government in Germany;
2) Any government in any area occupied by the military forces of the Nazi government in Germany;
3) Any government established with the assistance or cooperation of the Nazi government of Germany;
4) Any government which was an ally of the Nazi government of Germany;

ordered, incited, assisted or otherwise participated in the persecution of any person because of race, religion, national origin, or political opinion.

G. Aliens who have been convicted of a violation of any law or regulation relating to narcotic drugs or marihuana, or who have been illicit traffickers in narcotic drugs or marihuana.

H. Aliens who have been involved in assisting any other aliens to enter the United States in violation of the law

I. Aliens who have applied for exemption or discharge from training or service in the Armed Forces of the United States on the ground of alienage and who have been relieved or discharged from such training or service.

J. Aliens who are mentally retarded, insane, or who have suffered one or more attacks of insanity.

K. Aliens afflicted with psychopathic personality, sexual deviation, mental defect, narcotic drug addiction, chronic alcoholism or any dangerous contagious disease.

L. Aliens who have a physical defect, disease or disability affecting their ability to earn a living.

M. Aliens who are paupers, professional beggars or vagrants.

N. Aliens who are polygamists or advocate polygamy.

O. Aliens likely to become a public charge.

P. Aliens who have been excluded from the United States within the past year, or who at any time within 5 years have been deported from the United States.

Q. Aliens who have procured or have attempted to procure a visa by fraud or misrepresentation.

R. Aliens who are former exchange visitors who are subject to but have not complied with the two-year foreign residence requirement.

Do any of the above classes apply to you? ☐ **No** ☐ **Yes** (If "Yes", explain on a separate sheet of paper.)

30 If your native alphabet is in other than Roman letters, write your name in your native alphabet.	31. Language of native alphabet
32 Signature of Applicant - *I CERTIFY*, under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. I hereby consent and authorize the Service to verify the information provided, and to conduct police, welfare and other record checks pertinent to this application.	33. Date (Month/Day/Year)
34. Signature of person preparing form, *if other than applicant. I DECLARE* that this document was prepared by me at the request of the applicant and is based on all information on which I have any knowledge.	35. Date (Month/Day/Year)
36. Name and Address of person preparing form, *if other than applicant (type or print).*	37 Occupation of person preparing form

QUALIFIED DESIGNATED ENTITY USE ONLY		
38. Reviewed by (Print or Type Name)	39. Signature	40. Date

IMMIGRATION AND NATURALIZATION SERVICE USE ONLY			
41. Recommendation: Temporary Residence ☐ Approved ☐ Denied	42. Waiver of Excludability under Section 212 (a) _____ is ☐ Approved ☐ Denied		
43. Class of Admission	44. Place of Adjustment		45. Date of Adjustment
46. Recommended by (Print or type Name and Title)	47. Signature	48. ID No.	49. Date
50. Final Action: Temporary Residence ☐ Approved ☐ Denied	51. Director Regional Processing Facility	52. ID. No.	53. Date

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U.S. Department of Justice
Immigration and Naturalization Service

Medical Examination of Aliens Seeking Adjustment of Status (P.L. 99-603)

Instructions

To Alien Applying for Adjustment of Status

A medical examination is necessary as part of your application for adjustment of status. Please communicate immediately with one of the physicians on the attached list to arrange for your medical examination, which must be completed before your status can be adjusted. The purpose of the medical examination is to determine if you have certain health conditions which may need further followup. All expenses in connection with this examination must be paid by you. The examining physician may refer you to your personal physician or a local public health department and you must comply with some health followup or treatment recommendations for certain health conditions before your status will be adjusted.

This form should be presented to the examining physician. You must sign the form in the presence of the examining physician. *The law provides severe penalties for knowingly and willfully falsifying or concealing a material fact or using any false documents in connection with this medical examination.*

To Physician Performing the Examination

Please medically examine for adjustment of status the individual presenting this form. The medical examination should be performed according to the U.S. Public Health Service "Guidelines for the Medical Examination of Aliens in the United States and Supplement" which have been provided to you separately.

If the applicant is free of medical defects listed in Section 212(a) of the Immigration and Nationality Act, endorse the form in the space provided. While in your presence, the applicant must also sign the form in the space provided. You should retain one copy for your files and return all other copies in a sealed envelope to the applicant for presentation at the immigration interview.

If the applicant has a health condition which requires followup as specified in the "Guidelines for Medical Examination of Aliens in the United States and Supplement", complete the referral information on the pink copy of the medical examination form, and advise the applicant that appropriate followup must be obtained before medical clearance can be granted. Retain the blue copy of the form for your files and return all other copies to the applicant in a sealed envelope. The applicant should return to you when the necessary followup has been completed for your final verification and signature. *Do not* sign the form until the applicant has met health followup requirements. All medical documents, including chest x-ray films if a chest x-ray examination was performed, should be returned to the applicant upon final medical clearance.

To Physician Providing Health Followup

The individual presenting this form has been found to have a medical condition(s) requiring resolution before medical clearance for adjustment of status can be granted. Please evaluate the applicant for the condition(s) identified. The requirements for clearance are outlined on the reverse of this page. When the individual has completed clearance requirements, please sign the form in the space provided and return the medical examination form to the applicant.

Form I-693 (04/01/87)

Medical Examination and Health Information

A medical examination is necessary as part of your application for adjustment of status under the Immigration Reform and Control Act of 1986. You should go for your medical examination as soon as possible. The organization or person who gave you your application packet can help you arrange the medical examination. You will have to choose a doctor from a list you will be given. The list will have the names of doctors or clinics in your area that have been approved by the Immigration and Naturalization Service for this examination. You must pay for the examination. The cost may be different from place to place, but should be in the $30 - $60 range. If you become a temporary legal resident and later apply to become a permanent resident, you will need to have another medical examination at that time.

The purpose of the medical examination is to find out if you have certain health conditions which may need further followup. The doctor will examine you for certain physical and mental health conditions. You will have to take off your clothes. If you need more tests because of a condition found during your medical examination, the doctor may send you to your own doctor or to the local public health department. For some conditions, before you can become a temporary or permanent resident, you will have to show that you have followed the doctor's advice to get more tests or take treatment.

One of the conditions you will be tested for is tuberculosis. If your are 15 years of age or older, you may choose to be tested for tuberculosis with either a chest x-ray or a skin test (an injection into the skin on your arm). The skin test costs less than a chest x-ray examination. If you choose the skin test you will have to return in 2 - 3 days to have it checked. If you do not have any reaction to the skin test you will not need any more tests for tuberculosis. If you do have any reaction to the skin test, you will then need to go ahead and have a chest x-ray examination too. If the doctor thinks you are infected with tuberculosis, you may have to go to the local health department and more tests may have to be done. The doctor will explain these to you.

If you are 14 years of age or younger, you will not need to have a test for tuberculosis unless a member of your immediate family has chest x-ray findings that may be tuberculosis. If you are in this age group and you do have to be tested for tuberculosis, you too may choose either the chest x-ray or the skin test.

You must also have a blood test for syphilis if you are 15 years of age or older

If you have any records of immunizations (vaccinations), you should bring them to show to the doctor. This is especially important for pre-school and school-age children. The doctor will tell you if any more immunizations are needed, and where you can get them (usually at your local public health department). It is important for your health that you follow the doctor's advice and go to get any immunizations.

U.S. Department of Justice
Immigration and Naturalization Service

OMB #1115-0134
Medical Examination of Aliens Seeking Adjustment of Status (P. L. 99 - 603)

(Please Type or Print Clearly)
I certify that on the date shown I examined:

DATE OF EXAMINATION MO DA YR ____

FILE No. ____

NAME: LAST FIRST MI

DATE OF BIRTH: MO DA YR ____

COUNTRY OF BIRTH:

ADDRESS: STREET CITY STATE ZIP

GENERAL PHYSICAL EXAMINATION

I examined specifically for evidence of the conditions listed below. My examination revealed:

☐ No apparent defect, disease, or disability ☐ The conditions listed below were found (check boxes that apply)

CLASS A Conditions			CLASS B Conditions
☐ Chancroid	☐ Hansen's Disease, Infectious	☐ Tuberculosis, Active	☐ Tuberculosis, Not Active
☐ Gonorrhea	☐ Lymphogranuloma Venereum	☐ Other:	☐ Hansen's Disease, Not Infectious
☐ Granuloma Inguinale	☐ Syphilis, Infectious	____	☐ Other Physical Defect, Disease or Disability:
☐ Mental Retardation	☐ Previous Occurrence of One or More Attacks of Insanity	☐ Mental Defect	____
☐ Insanity		☐ Narcotic Drug Addiction	____
☐ Sexual Deviation	☐ Psychopathic Personality	☐ Chronic Alcoholism	

EXAMINATION FOR TUBERCULOSIS

TUBERCULIN SKIN TEST

FROM Doctor ____ (Please Print)

☐ REACTION ____ mm
☐ NO REACTION ☐ NOT DONE

MO DA YR ____ DATE READ

CHEST X-RAY REPORT

FROM Doctor ____ (Please Print)

☐ NORMAL
☐ ABNORMAL ☐ NOT DONE

MO DA YR ____ DATE READ

SEROLOGIC TEST FOR SYPHILIS

TEST TYPE ____

FROM Doctor ____ (Please Print)

☐ REACTIVE TITER
☐ NONREACTIVE

MO DA YR ____ DATE READ

TEST TYPE ____

FROM Doctor ____ (Please Print)

☐ REACTIVE TITER
☐ NONREACTIVE

MO DA YR ____ DATE READ

IMMUNIZATION DETERMINATION (DTP, OPV, MMR, Td - Refer to *PHS Guidelines* for recommendations.)

☐ Applicant is current for recommended age-specific immunizations

☐ Applicant is **not** current for recommended age-specific immunizations and I have encouraged that appropriate immunizations be obtained

REMARKS: ____

CIVIL SURGEON REFERRAL FOR FOLLOW-UP OF MEDICAL CONDITION

☐ The alien named above has applied for adjustment of status. A medical examination conducted by me identified the conditions above which require resolution before medical clearance is granted or for which the alien may seek medical advice. Please provide follow-up services or refer the alien to an appropriate health care provider. The actions necessary for medical clearance are detailed on the reverse of this form.

FOLLOW-UP INFORMATION
The alien named above has complied with recommended health follow-up.
SIGNATURE ____ TITLE ____ MO DA YR ____

APPLICANT CERTIFICATION
I certify that the information contained in this form refers to me.
SIGNATURE ____ MO DA YR ____

CIVIL SURGEON CERTIFICATION
My examination showed the applicant to have met the medical examination and health follow-up requirements for adjustment of status.
SIGNATURE ____ TITLE ____ MO DA YR ____

The Immigration and Naturalization Service is authorized to collect this information under the provisions of the Immigration Reform and Control Act of 1986, Public Law 99-603. The individually identified data requested is required in order for a proper evaluation to be made of your health status, and may be shared with health departments and other public health or cooperating medical authorities. The medical examination must be completed in order for us to process your application.

Form I-693 (02/14/87)

ORIGINAL: INS A-FILE

U.S. Department of Justice
Immigration and Naturalization Service

OMB #1115-0134
Medical Examination of Aliens Seeking Adjustment of Status (P. L. 99-603)

(Please Type or Print Clearly)
I certify that on the date shown I examined:

DATE OF EXAMINATION MO DA YR

FILE No.

NAME: LAST FIRST MI

DATE OF BIRTH: MO DA YR

COUNTRY OF BIRTH:

ADDRESS: STREET CITY STATE ZIP

GENERAL PHYSICAL EXAMINATION

I examined specifically for evidence of the conditions listed below. My examination revealed:

☐ No apparent defect, disease, or disability ☐ The conditions listed below were found (check boxes that apply)

CLASS A Conditions			CLASS B Conditions
☐ Chancroid	☐ Hansen's Disease, Infectious	☐ Tuberculosis, Active	☐ Tuberculosis, Not Active
☐ Gonorrhea	☐ Lymphogranuloma Venereum	☐ Other:	☐ Hansen's Disease, Not Infectious
☐ Granuloma Inguinale	☐ Syphilis, Infectious		☐ Other Physical Defect, Disease or Disability
☐ Mental Retardation	☐ Previous Occurrence of One or More Attacks of Insanity	☐ Mental Defect	
☐ Insanity		☐ Narcotic Drug Addiction	
☐ Sexual Deviation	☐ Psychopathic Personality	☐ Chronic Alcoholism	

EXAMINATION FOR TUBERCULOSIS

TUBERCULIN SKIN TEST

FROM Doctor _____ (Please Print)

☐ REACTION _____ mm
☐ NO REACTION ☐ NOT DONE

MO DA YR
DATE READ

CHEST X-RAY REPORT

FROM Doctor _____ (Please Print)

☐ NORMAL
☐ ABNORMAL ☐ NOT DONE

MO DA YR
DATE READ

SEROLOGIC TEST FOR SYPHILIS

TEST TYPE _____
FROM Doctor _____ (Please Print)

☐ REACTIVE TITER
☐ NONREACTIVE

MO DA YR
DATE READ

TEST TYPE _____
FROM Doctor _____ (Please Print)

☐ REACTIVE TITER
☐ NONREACTIVE

MO DA YR
DATE READ

IMMUNIZATION DETERMINATION (DTP, OPV, MMR, Td - Refer to *PHS Guidelines* for recommendations.)

☐ Applicant is current for recommended age-specific immunizations

☐ Applicant is **not** current for recommended age-specific immunizations and I have encouraged that appropriate immunizations be obtained

REMARKS:

CIVIL SURGEON REFERRAL FOR FOLLOW-UP OF MEDICAL CONDITION

☐ The alien named above has applied for adjustment of status. A medical examination conducted by me identified the conditions above which require resolution before medical clearance is granted or for which the alien may seek medical advice. Please provide follow-up services or refer the alien to an appropriate health care provider. The actions necessary for medical clearance are detailed on the reverse of this form.

FOLLOW-UP INFORMATION
The alien named above has complied with recommended health follow-up.
SIGNATURE _____ TITLE _____ MO DA YR

APPLICANT CERTIFICATION
I certify that the information contained in this form refers to me.
SIGNATURE _____ MO DA YR

CIVIL SURGEON CERTIFICATION
My examination showed the applicant to have met the medical examination and health follow-up requirements for adjustment of status.
SIGNATURE _____ TITLE _____ MO DA YR

The Immigration and Naturalization Service is authorized to collect this information under the provisions of the Immigration Reform and Control Act of 1986, Public Law 99-603. The individually identified data requested is required in order for a proper evaluation to be made of your health status, and may be shared with health departments and other public health or cooperating medical authorities. The medical examination must be completed in order for us to process your application.

Form I-693 (02/14/87)

CIVIL SURGEON

U.S. Department of Justice
Immigration and Naturalization Service

OMB #1115-0134
Medical Examination of Aliens Seeking Adjustment of Status (P. L. 99 - 603)

(Please Type or Print Clearly)
I certify that on the date shown I examined:

DATE OF EXAMINATION MO DA YR | FILE No.

NAME: LAST FIRST MI | DATE OF BIRTH: MO DA YR | COUNTRY OF BIRTH:

ADDRESS: STREET CITY STATE ZIP

GENERAL PHYSICAL EXAMINATION

I examined specifically for evidence of the conditions listed below. My examination revealed:

☐ No apparent defect, disease, or disability ☐ The conditions listed below were found (check boxes that apply)

CLASS A Conditions			CLASS B Conditions
☐ Chancroid	☐ Hansen's Disease, Infectious	☐ Tuberculosis, Active	☐ Tuberculosis, Not Active
☐ Gonorrhea	☐ Lymphogranuloma Venereum	☐ Other:	☐ Hansen's Disease, Not Infectious
☐ Granuloma Inguinale	☐ Syphilis, Infectious		☐ Other Physical Defect, Disease or Disability:
☐ Mental Retardation	☐ Previous Occurrence of One or More Attacks of Insanity	☐ Mental Defect	
☐ Insanity		☐ Narcotic Drug Addiction	
☐ Sexual Deviation	☐ Psychopathic Personality	☐ Chronic Alcoholism	

EXAMINATION FOR TUBERCULOSIS

TUBERCULIN SKIN TEST

FROM Doctor _____ (Please Print)

☐ REACTION _____ mm
☐ NO REACTION ☐ NOT DONE

MO DA YR DATE READ

CHEST X-RAY REPORT

FROM Doctor _____ (Please Print)

☐ NORMAL
☐ ABNORMAL ☐ NOT DONE

MO DA YR DATE READ

SEROLOGIC TEST FOR SYPHILIS

TEST TYPE _____
FROM Doctor _____ (Please Print)

☐ REACTIVE TITER
☐ NONREACTIVE

MO DA YR DATE READ

TEST TYPE _____
FROM Doctor _____ (Please Print)

☐ REACTIVE TITER
☐ NONREACTIVE

MO DA YR DATE READ

IMMUNIZATION DETERMINATION (DTP, OPV, MMR, Td - Refer to *PHS Guidelines* for recommendations.)

☐ Applicant is current for recommended age-specific immunizations

☐ Applicant is not current for recommended age-specific immunizations and I have encouraged that appropriate immunizations be obtained

REMARKS:

CIVIL SURGEON REFERRAL FOR FOLLOW-UP OF MEDICAL CONDITION

☐ The alien named above has applied for adjustment of status. A medical examination conducted by me identified the conditions above which require resolution before medical clearance is granted or for which the alien may seek medical advice. Please provide follow-up services or refer the alien to an appropriate health care provider. The actions necessary for medical clearance are detailed on the reverse of this form.

FOLLOW-UP INFORMATION
The alien named above has complied with recommended health follow-up.
SIGNATURE _____ TITLE _____ MO DA YR

APPLICANT CERTIFICATION
I certify that the information contained in this form refers to me.
SIGNATURE _____ MO DA YR

CIVIL SURGEON CERTIFICATION
My examination showed the applicant to have met the medical examination and health follow-up requirements for adjustment of status.
SIGNATURE _____ TITLE _____ MO DA YR

The Immigration and Naturalization Service is authorized to collect this information under the provisions of the Immigration Reform and Control Act of 1986, Public Law 99-603. The individually identified data requested is required in order for a proper evaluation to be made of your health status, and may be shared with health departments and other public health or cooperating medical authorities. The medical examination must be completed in order for us to process your application.

Form I-693 (02/14/87)

APPLICANT

U.S. Department of Justice
Immigration and Naturalization Service

OMB #1115-0134
Medical Examination of Aliens Seeking Adjustment of Status (P. L. 99 - 603)

(Please Type or Print Clearly)
I certify that on the date shown I examined:

DATE OF EXAMINATION MO DA YR ____

FILE No. ____

NAME: LAST FIRST MI

DATE OF BIRTH: MO DA YR ____

COUNTRY OF BIRTH: ____

ADDRESS: STREET CITY STATE ZIP

GENERAL PHYSICAL EXAMINATION

I examined specifically for evidence of the conditions listed below. My examination revealed:

☐ No apparent defect, disease, or disability ☐ The conditions listed below were found (check boxes that apply)

CLASS A Conditions			CLASS B Conditions
☐ Chancroid	☐ Hansen's Disease, Infectious	☐ Tuberculosis, Active	☐ Tuberculosis, Not Active
☐ Gonorrhea	☐ Lymphogranuloma Venereum	☐ Other:	☐ Hansen's Disease, Not Infectious
☐ Granuloma Inguinale	☐ Syphilis, Infectious	____	☐ Other Physical Defect, Disease or Disability:
		____	
☐ Mental Retardation	☐ Previous Occurrence of One or More Attacks of Insanity	☐ Mental Defect	____
☐ Insanity		☐ Narcotic Drug Addiction	____
☐ Sexual Deviation	☐ Psychopathic Personality	☐ Chronic Alcoholism	

EXAMINATION FOR TUBERCULOSIS

TUBERCULIN SKIN TEST

FROM Doctor ____ (Please Print)

☐ REACTION ____ mm
☐ NO REACTION ☐ NOT DONE

MO DA YR ____ DATE READ

CHEST X-RAY REPORT

FROM Doctor ____ (Please Print)

☐ NORMAL
☐ ABNORMAL ☐ NOT DONE

MO DA YR ____ DATE READ

SEROLOGIC TEST FOR SYPHILIS

TEST TYPE ____

FROM Doctor ____ (Please Print)

☐ REACTIVE TITER
☐ NONREACTIVE

MO DA YR ____ DATE READ

TEST TYPE ____

FROM Doctor ____ (Please Print)

☐ REACTIVE TITER
☐ NONREACTIVE

MO DA YR ____ DATE READ

IMMUNIZATION DETERMINATION (DTP, OPV, MMR, Td - Refer to *PHS Guidelines* for recommendations.)

☐ Applicant is current for recommended age-specific immunizations

☐ Applicant is not current for recommended age-specific immunizations and I have encouraged that appropriate immunizations be obtained

REMARKS: ____

CIVIL SURGEON REFERRAL FOR FOLLOW-UP OF MEDICAL CONDITION

☐ The alien named above has applied for adjustment of status. A medical examination conducted by me identified the conditions above which require resolution before medical clearance is granted or for which the alien may seek medical advice. Please provide follow-up services or refer the alien to an appropriate health care provider. The actions necessary for medical clearance are detailed on the reverse of this form.

FOLLOW-UP INFORMATION
The alien named above has complied with recommended health follow-up.
SIGNATURE ____ TITLE ____ MO DA YR ____

APPLICANT CERTIFICATION
I certify that the information contained in this form refers to me.
SIGNATURE ____ MO DA YR ____

CIVIL SURGEON CERTIFICATION
My examination showed the applicant to have met the medical examination and health follow-up requirements for adjustment of status.
SIGNATURE ____ TITLE ____ MO DA YR ____

The Immigration and Naturalization Service is authorized to collect this information under the provisions of the Immigration Reform and Control Act of 1986, Public Law 99-603. The individually identified data requested is required in order for a proper evaluation to be made of your health status, and may be shared with health departments and other public health or cooperating medical authorities. The medical examination must be completed in order for us to process your application.

Form I-693 (02/14/87)

PHYSICIAN OR HEALTH DEPARTMENT

MEDICAL CLEARANCE REQUIREMENTS FOR ALIENS SEEKING ADJUSTMENT OF STATUS

MEDICAL CONDITION	ESTIMATED TIME FOR CLEARANCE	ACTION REQUIRED
Suspected Mental* Conditions	5-30 Days	Applicant must provide to civil surgeon a psychological or psychiatric evaluation from a specialist or medical facility for final classification and clearance.
Tuberculin Skin Test Reaction and Normal Chest X-Ray	Immediate	Applicant should be encouraged to seek further medical evaluation for possible preventive treatment.
Tuberculin Skin Test Reaction and Abnormal Chest X-Ray ("Inactive/Class B")	10-30 Days	Applicant should be referred to physician or local health department for further evaluation. Medical clearance should not be granted until applicant returns to civil surgeon with documentation of medical evaluation for tuberculosis.
Tuberculin Skin Test Reaction and Abnormal Chest X-Ray ("Active or Suspected Active/Class A")	10-300 Days	Applicant should obtain appointment with physician or local health department. If treatment for active disease is started, it must be completed (usually 9 months) before medical clearance granted. At completion of treatment, applicant must present to civil surgeon documentation of completion.If treatment not started, applicant must present to civil surgeon documentation of medical evaluation for tuberculosis.
Hansen's Disease	30-210 Days	Obtain evaluation from specialist or Hansen's disease clinic. If disease is Indeterminate or Tuberculoid, applicant must present to civil surgeon documentation of medical evaluation. If disease is Lepromotous or Borderline (dimorphous) and treatment is started, applicant must complete at least 6 months and present documentation to civil surgeon showing adequate supervision, treatment, and clinical response before medical clearance granted.
Venereal Diseases**	1-30 Days	Obtain appointment with physician or local public health department. Applicants with a reactive serologic test for syphilis must provide to civil surgeon documentation of evaluation for treatment. If any of the venereal diseases are infectious, applicants must present to civil surgeon documentation of completion of treatment.
Immunizations Incomplete	Immediate	Applicant should be encouraged to go to physician or local health department for appropriate immunizations.

*Mental retardation; insanity, previous attack of insanity, psychopathic personality, sexual deviation, or mental defect, narcotic drug addiction; and chronic alcoholism.

**Chancroid; gonorrhea; granuloma inguinale; lymphogranuloma venereum; and syphilis.

Application for Waiver of Grounds of Excludability
Under Sections 245A or 210 of the Immigration and Nationality Act

I-690 Instructions

Please carefully read all of the instructions.
The fee will not be refunded.

1. *Filing the Application*
The application and supporting documentation should be taken or mailed to an American Consulate if the applicant is outside of the United States and is applying for temporary resident status as a Special Agricultural Worker.

If the applicant is in the United States, a participating Qualified Designated Entity near your place of residence, or

The Service legalization office having jurisdiction over the applicant's place of residence or employment.

2. *Fee*
A fee of thirty-five dollars ($35.00), is required at the time of filing. The fee is not refundable regardless of the action taken on the application.

A separate cashier's check or money order must be submitted for each application. ***All fees must be submitted in the exact amount.*** The fee must be in the form of a cashier's check or money order. No cash or personal checks will be accepted. The cashier's check or money order must be made payable to "Immigration and Naturalization Service" unless applicant resides in the Virgin Islands or Guam. (Applicants residing in the Virgin Islands make cashier's check or money order payable to "Commissioner of Finance of the Virgin Islands." Applicants residing in Guam make cashier's check or money order payable to "Treasurer, Guam."

A fee is not required if this application is filed for an alien who:

Is afflicted with tuberculosis;
Is mentally retarded; or
Has a history of mental illness.

3. *Applicants with Tuberculosis.*
An applicant with active tuberculosis or suspected tuberculosis must complete Statement A on page two of this form. The applicant and his or her sponsor is also responsible for having:

Statement B completed by the physician or health facility which has agreed to provide treatment or observation, and

Statement C, if required, completed by the appropriate local or state health officer.

This form should then be returned to the applicant for presentation to the consular office, or to the appropriate office of the Immigration and Naturalization Service.

Submission of the application without the required fully executed statements will result in the return of the application to the applicant without further action.

4. *Applicants with Mental Conditions.*
An alien who is mentally retarded or who has a history of mental illness shall attach a statement that arrangements have been made for the submission of a medical report, as follows, to the office where this form is filed:

The medical report shall contain:

A complete medical history of the alien, including details of any hospitalization or institutional care or treatment for any physical or mental condition;

Findings as to the current physical condition of the alien, including reports of chest X-rays and a serologic test if the alien is 15 years of age or older, and other pertinent diagnostic tests; and

Findings as to the current mental condition of the alien, with information as to prognosis and life expectancy and with a report of a psychiatric examination conducted by a psychiatrist who shall, in case of mental retardation, also provide an evaluation of intelligence.

For an alien with a past history of mental illness, the medical report shall also contain available information on which the United States Public Health Service can base a finding as to whether the alien has been free of such mental illness for a period of time sufficient in the light of such history to demonstrate recovery.

The medical report will be referred to the United States Public Health Service for review and, if found acceptable, the alien will be required to submit such additional assurances as the United States Public Health Service may deem necessary in his or her particular case.

I-690

OMB #1115-0132

U.S. Department of Justice
Immigration and Naturalization Service

Application for Waiver of Grounds of Excludability
(Sec. 245A or Sec. 210 of the Immigration and Nationality Act)

Please begin with item #1, after carefully reading the instructions.

The block below is for *Government Use Only.*

Name and Location (City or Town) of Qualified Designated Entity	Fee Stamp
	Fee Receipt No. (This application)
Qualified Designated Entity I.D. No.	File No. (This applicant) A -

Applicant: Do not write above this line. See instructions before filling in application. If you need more space to answer fully any question on this form, use a separate sheet and identify each answer with the number of the corresponding question. *Fill in with typewriter or print in block letters in ink.*

1. **Family Name** *(Last Name in CAPITAL Letters)* *(First Name)* *(Middle Name)*	2. **Date of Birth** *(Month/Day/Year)*
3. **Address** *(No. and Street)* *(Apt. No.)* *(City/Town)* *(State/Country)* *(ZIP/Postal Code)*	
4. **Place of Birth** *(City or Town and County, Province or State)* *(Country)*	5. **Social Security Number**
6. **Date of visa application** *(Month/Day/Year)*—for ☐ Permanent ☐ Temporary Residence	7. **Visa applied for at:**

8. **I am inadmissable under Section(s):** ☐ 212 (a) (1) ☐ 212 (a) (3) ☐ 212 (a) (6) ☐ 212 (a) (12) ☐ 212 (a) (19) ☐ Other 212 (a) *Specify Section (* _____ *)*

9. **List reasons of excludability; if active or suspected tuberculosis, the reverse of the page must be completed.**

10. **List all immediate relatives in the United States (parents, spouse and children):**

Name	Address	Relationship	Immigration Status

11. **I should be granted a waiver because:** *(Describe family unity considerations or humanitarian or public interest reasons for granting a waiver)* If more space is needed attach an additional sheet.

12. Applicant's Signature	13. **Date** *(Month/Day/Year)*

I&NS USE ONLY

Recommended by:

(Print or Type Name and Title) _____ *Date* _____

Signature _____ *I.D.#* _____ *Director, Regional Processing Facility* _____

I-690

Form I-690 (02/14/87)

A. APPLICANT

Instructions: Leave this side *blank* if your Application for Waiver of Grounds of Excludability is for any reason *other than* active or suspected *tuberculosis*. If your application is due to active or suspected tuberculosis, take this form to any physician or medical facility under contract with the Immigration and Naturalization Service. Have the physician complete Section B. You must sign Section A (below) *in the presence of the physician*.

If medical care will be provided by a physician who checked Box 3 or 4 in Section B, have Section C completed by the local or State Health Officer who has jurisdiction in the area where you reside. Present the form to the Health Officer after Sections A and B on this side, and *all sections on the other side* have been completed.

Statement: I have reported to the physician or health facility named in Section B; have presented all X-Rays used in the Legalization medical examination to substantiate diagnosis; will submit to such examinations, treatment, isolation, and medical regimen as may be required; and will remain under the prescribed treatment or observation whether on inpatient or outpatient basis, until discharged at the discretion of the physician named, or a physician representing the facility named in Section B. Satisfactory financial arrangements have been made. **(NOTE: This statement does not relieve you from submitting evidence to establish that you are not likely to become a public charge.)**

A. Signature of Applicant	*Date*

B. PHYSICIAN OR HEALTH FACILITY

Instructions: This section of Form I-690 may be executed by a physician in private practice (under contract with the Immigration and Naturalization Service), or a physician employed by a health department, other public health facility, or military hospital.

Complete Section B (below) of this form, and have alien sign and date Section A (above) *in your presence. Please be sure the alien's signature above, and the alien's signature on the other side of this form* **are identical.**

Statement: I agree to supply any treatment or observation necessary for the proper management of the alien's tuberculous condition. I agree to submit Form CDC 75.18 to the health officer named below (*Section C) within thirty (30) days of the alien's reporting for care, indicating presumptive diagnosis, test results, and plans for future care of the alien. Satisfactory financial arrangements have been made.

I represent *(enter X in the appropriate box and type or legibly print name and address of facility):*

1. ☐ Local Health Department
2. ☐ Military Hospital
3. ☐ Other Public Health Facility
4. ☐ Private Practice or Private Health Facility under contract with the Immigration and Naturalization Service.

B. Signature of Physician	*Date*
Print or Type Name and Address of Physician and Facility. (If military, enter name and address of receiving hospital and mail directly to Centers for Disease Control, Atlanta, GA 30333.)	

C. LOCAL OR STATE HEALTH OFFICER

Instructions: If the facility or physician who signed in Section B is not in your health jurisdiction and is not familiar to you, you may wish to contact the health officer responsible for the jurisdiction of the facility or physician prior to endorsing this document.

Statement: This endorsement signifies recognition of the physician or facility for the purpose of providing care for tuberculosis.

C. Signature of Health Officer	*Date*
Print or Type Name of Health Officer*, and Offical Name and Complete Address of Local Health Department	

Form 1-690 (02/14/87)

INSTRUCTIONS
Form I-694

1. FILING AN APPEAL:
This form must be mailed to the address given on the "Notice of Denial", and **must be received within 30 days of the date on that notice.** No extensions will be granted.

2. BRIEFS:
A brief in support of an appeal is not required, but may be desired. If a brief is to be submitted, it must be submitted with this appeal form. No extensions will be granted.

ORAL ARGUMENT:
Oral argument before the Commissioner or an officer designated by him may be requested by letter attached to this notice. The letter must set forth the reasons oral argument is desired in support of or in place of a brief. Oral argument will be denied in any case where the appeal is found to be frivolous, where oral argument will serve no useful purpose or where written material or representations will appropriately serve the interests of the appelant. If oral argument is granted, it must be held in person. The officer to whom the appeal is taken will designate in writing the time, date, and place of the oral argument. Oral argument in any one case will be limited to fifteen (15) minutes, unless justification and arrangements for additional time are made in advance.

3. COUNSEL:
In presenting and prosecuting this appeal the appellant may, if he or she desires, be represented at no expense to the Government by counsel or other duly authorized representatives.

4. FEE:
A fee of fifty dollars ($50.) must be paid for filing this appeal. It cannot be refunded regardless of the action taken on the appeal. A separate cashier's check or money order must be submitted for each application. ***All fees must be submitted in the exact amount.*** The fee must be in the form of a cashier's check or money order. No cash or personal checks will be accepted. The cashier's check or money order must be payable to "Immigration and Naturalization Service" unless the appellant resides in the Virgin Islands or Guam. (Appellants residing in the Virgin Islands make cashier's check or money order payable to "Commissioner of Finance of the Virgin Islands". Appellants residing in Guam make cashier's checks or money orders payable to "Treasurer, Guam".)

U.S. Department of Justice
Immigration and Naturalization Service

Notice of Appeal of Decision under Section 210 or 245A of the Immigration and Nationality Act.

OMB #1115-0135

In the Matter of:	FEE STAMP
Application for: ☐ Permanent Residence ☐ Temporary Residence ☐ Waiver of Grounds of Excludability	File No.: A -

I hereby appeal to the Commissioner from the decision, dated _____ in the above entitled case.

☐ My written brief or statement is attached.

☐ I waive the right to submit a written brief or statement.

Briefly, state reasons for this appeal.

APPELLANT (OR ATTORNEY OR REPRESENTATIVE) Please complete the following.

Name *(Type or Print)*

Address *(Street Name and Number)*

(City or Town) *(State)* *(ZIP Code)*

Title or Relationship to Appellant, if other than appellant.

Signature X	Date

I-694

Form I-694 (04/01/87) IMPORTANT - See instructions on Reverse Side of this Notice.

PLACE
POSTAGE
STAMP
HERE

Immigration and Naturalization Service

Change of Address Card for Legalization
and Special Agricultural Workers
This card is NOT to be used by persons other than those applying for legal status under Sec. 245A or Sec. 210 of P.L. 99-603.

Change of Address Card for Legalization and Special Agricultural Workers
This card is NOT to be used by persons other than those applying for legal status under Sec. 245A or Sec. 210 of P.L. 99-603.

OMB #1115-0130

U.S. Department of Justice
Immigration and Naturalization Service

Change of Address Card for Legalization and Special Agricultural Workers (SAW)

INSTRUCTIONS: This form is to be used ONLY by Legalization and SAW applicants (in connection with an application for status under Sec. 245A or Sec. 210 of the Immigration and Nationality Act) reporting a change of address. Mail to the Legalization Office where your application was submitted.

Name (Last in CAPS)	(First)	(Middle)
Country of Birth	Date of Birth (Month/Day/Year)	A-File No:

Present Address (Street or Rural Route)	(City or Post Office)	(State and ZIP Code)

IF ABOVE ADDRESS IS TEMPORARY I expect to remain there _____ years _____ months.

Last Address (Street or Rural Route)	(City or Post Office)	(State and ZIP Code)

SIGNATURE	DATE

Form I-697 (02-14-87)

INSTRUCTIONS
Form I-695

COMPLETE APPLICATION

Items 1–11
Type or print in block letters, in ink, all information requested in items 1 through 11.

Item 12. Explanation.
Type or print in block letters, in ink, the reason a new document is needed. If information on the original was incorrect when it was issued, or has since changed, provide that information as it appears on the original. If the original has been destroyed, lost, or stolen, explain how you believe that happened and provide the date (or approximate date) you believe the incident occured. If the space provided in block 12 is not adequate, attach an additional sheet.

Item 13.
Applicant must sign and date item 13.

Item 14.
If the person preparing this form is other than the applicant, that person must sign and date item 14.

SUBMIT ALL of the following, ***IN PERSON,*** with this application to the Immigration Legalization Office having jurisdiction over your place of residence:

DOCUMENT, if the document previously issued to you was mutilated.

CASHIER'S CHECK OR MONEY ORDER, in the amount of $15.00, made payable to the "U.S. Immigration and Naturalization Service." This fee is for filing the application and ***MAY NOT BE REFUNDED.*** (Applicants residing in the Virgin Islands make cashier's check or money order payable to "Commissioner of Finance of the Virgin Islands." Applicants residing in Guam make cashier's check or money order payable to "Treasurer, Guam.")

PHOTOGRAPHS (2), taken within 30 days of the date of this application. Photographs must have a white background, be glossy, unretouched, and not mounted; dimension of facial image should be about one inch from chin to top of hair, and should be ¾ frontal view showing right side of face with right ear visible. Use pencil or felt pen to lightly print your name on the back of ***EACH*** photograph, ***AS IT IS TO APPEAR ON THE REPLACEMENT DOCUMENT.***

PENALTIES: Severe penalties are provided by law for knowingly and willfully falsifying or concealing a material fact or using any false document in the submission of this application. Also, a false representation may result in the denial of this application and any other application you may make for any benefit under the immigration laws of the United States.

OMB #1115-0129

U.S. Department of Justice
Immigration and Naturalization Service

Application for Replacement of Form I-688A, Employment Authorization, or Form I-688, Temporary Residence Card (Under P.L. 99-603)

Please begin with item #1, after carefully reading the instructions.

The block below is for *Government Use Only.*

Name and Location (City or Town) of Qualified Designated Entity	Fee Stamp
	Fee Receipt No. (This application)
Qualified Designated Entity I.D. No.	File No. (This applicant) A -

Please read instructions on reverse.
FEE WILL NOT BE REFUNDED.

1. **I hereby apply for a replacement of**
   - ☐ Form I-688A, Employment Authorization Card
   - ☐ Form I-688, Temporary Residence Card

   A replacement is needed because:
   - ☐ Original was lost, stolen, or destroyed. (Give date and details in Block 12.)
   - *(If reason is one of the following, attach original document.)*
   - ☐ Original was incorrect when issued *(no fee required)*
   - ☐ Original was mutilated

2. **Family Name** *(Last Name in CAPITAL Letters)* *(First Name)* *(Middle Name)*

3. **Date of Birth** *(Month/Day/Year)*

4. **Home Address in the U.S.** *(No. and Street)* *(Apt. No.)* *(City)* *(State)* *(ZIP Code)*

5. **Telephone Numbers** (Include Area Code)
   Home:
   Work:

6. **Name used when admitted as temporary resident** (If different from #2):

7. **The date you were admitted or adjusted to temporary residence status:**

8. **Social Security Number:**

9. **Sex:** ☐ Male ☐ Female

10. **Place of Birth:** *(Town/City)* *(State/Country)*

11. **Country of Citizenship:**

12. **Explanation:**

13. **Signature of Applicant:** ***I CERTIFY*** **that the information above is true and correct to the best of my knowledge and belief. If original document is not attached, I agree to mail it to the Legalization office in the event it is recovered.**

Signature *Date Signed*

14. **Signature of Person Preparing Form if** ***other than applicant: I DECLARE*** **that this application was prepared by me at the request of the applicant and is based on all information of which I have any knowledge.**

Signature *Address* *Date Signed*

This section for use by IMMIGRATION OFFICER only.
Recommend Application be ☐ **Granted** ☐ **Denied** **By:** *(Immigration Officer)* *(Date)*

Director, Regional Processing Facility:	Replacement Issued by:	On *(Date):*	Replacement Receipt No.:

I-688

Form I-695 (02/24/87)

Employment Eligibility Verification

NOTICE: Authority for collecting the information on this form is in Title 8, United States Code, Section 1324A. It will be used to verify the individual's eligibility for employment in the United States. Failure to present this form for inspection to officers of the Immigration and Nationality Service or Department of Labor within the time period specified by regulation, or improper completion or retention of this form may be a violation of 8 USC §1324A and may result in a civil money penalty.

Section 1. Employee's/Preparer's instructions for completing this form.

Instructions for the employee.

All employees, upon being hired, must complete Secton 1 of this form. Any person hired after November 6, 1986 must complete this form. (For the purpose of completion of this form the term "hired" applies to those employed, recruited or referred for a fee.)

All employees must print or type their complete name, address, date of birth, and Social Security Number. The block which correctly indicates the employee's immigration status must be checked. If the second block is checked, the employee's Alien Registration Number must be provided. If the third block is checked, the employee's Alien Registration Number ***or*** Admission Number must be provided, as well as the date of expiration of that status, if it expires.

All employees must sign and date the form.

Instructions for the preparer of the form, if not the employee.

If the employee is assisted with completing this form, the person assisting must certify the form by signing it, and printing or typing their complete name and address.

Section 2. Employer's instructions for completing this form.

(For the purpose of completion of this form, the term "employer" applies to employers and those who recruit or refer for a fee.)

Employers must complete this section by examining evidence of identity and employment authorization, and:

- checking the appropriate box in List A ***or*** boxes in both Lists B and C;
- recording the document identification number and expiration date (if any);
- recording the type of form if not specifically identified in the list;
- signing the certification section.

NOTE: Employers are responsible for reverifying employment eligibility of aliens upon expiration of any employment authorization documents, should they desire to continue the alien's employment.

Copies of documentation presented by an individual for the purpose of establishing identity and employment eligibility may be copied and retained for the purpose of complying with the requirements of this form and no other purpose. Any copies of documentation made for this purpose should be maintained with this form.

Employers may photocopy or reprint this form, as necessary, for their use.

RETENTION OF RECORDS.

After completion of this form, it must be retained by the employer during the period beginning on the date of hiring and ending:

- three years after the date of such hiring, or;
- one year after the date the individual's employment is terminated, whichever is later.

EMPLOYMENT ELIGIBILITY VERIFICATION

1 EMPLOYEE INFORMATION AND VERIFICATION: (To be completed and signed by employee.)

Name: (Print or Type) Last	First	Middle	Maiden
Address: Street Name and Number	City	State	ZIP Code
Date of Birth (Month/Day/Year)		Social Security Number	

I attest, under penalty of perjury, that I am (check a box):

- ☐ A citizen or national of the United States.
- ☐ An alien lawfully admitted for permanent residence. (Alien Number A _____).
- ☐ An alien authorized by the Immigration and Naturalization Service to work in the United States. (Alien Number A _____). or Admission Number _____, expiration of employment authorization, if any _____)

I attest, under penalty of perjury, the documents that I have presented as evidence of identity and employment eligibility are genuine and relate to me. I am aware that federal law provides for imprisonment and/or fine for any false statements or use of false documents in connection with this certificate.

Signature	Date (Month/Day/Year)

PREPARER/TRANSLATOR CERTIFICATION (If prepared by other than the individual). I attest, under penalty of perjury, that the above was prepared by me at the request of the named individual and is based on all information of which I have any knowledge.

Signature	Name (Print or Type)		
Address (Street Name and Number)	City	State	Zip Code

2 EMPLOYER REVIEW AND VERIFICATION: (To be completed and signed by employer.)

Examine one document from those in List A and check the correct box, *or* examine one document from List B *and* one from List C and check the correct boxes. Provide the ***Document Identification Number*** and ***Expiration Date,*** for the document checked in that column.

List A Identity and Employment Eligibility		List B Identity	and	List C Employment Eligibility
☐ United States Passport		☐ A State issued driver's license or I.D. card with a photograph, or information, including name, sex, date of birth, height, weight, and color of eyes. (Specify State)_____)		☐ Original Social Security Number Card (other than a card stating it is not valid for employment)
☐ Certificate of United States Citizenship				☐ A birth certificate issued by State, county, or municipal authority bearing a seal or other certification
☐ Certificate of Naturalization		☐ U.S. Military Card		☐ Unexpired INS Employment Authorization Specify form # _____
☐ Unexpired foreign passport with attached Employment Authorization		☐ Other (Specify document and issuing authority) _____		
☐ Alien Registration Card with photograph				
Document Identification # _____		***Document Identification*** # _____		***Document Identification*** # _____
Expiration Date (if any) _____		***Expiration Date (if any)*** _____		***Expiration Date (if any)*** _____

CERTIFICATION: I attest, under penalty of perjury, that I have examined the documents presented by the above individual, that they appear to be genuine, relate to the individual named, and that the individual, to the best of my knowledge, is authorized to work in the United States.

Signature	Name (Print or Type)	Title
Employer Name	Address	Date

Form I-9 (03/06/87)
OMB No. 1115-0000
[FR Doc. 87-5839 Filed 3-17-87; 10:08 am]
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U.S. Department of Justice
Immigration and Naturalization Service

federal register

Thursday
March 19, 1987

Part VII

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 312, 314, 511, and 514
New Drug, Antibiotic, and Biologic, Drug Product Regulations; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 312, 314, 511, and 514

[Docket No. 82N-0394]

New Drug, Antibiotic, and Biologic Drug Product Regulations

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising its regulations governing the submission and review of investigational new drug applications (IND's). The new regulations (called the IND Rewrite) will ensure FDA's ability to monitor carefully the safety of patients participating in clinical investigations, while also facilitating the development of new beneficial drug therapies. The improvements will also help sponsors of clinical investigations prepare and submit high quality IND applications and permit FDA to review them efficiently and with minimal delay. This action is one part of a larger effort by FDA to improve the agency's drug approval process, including the earlier publication of companion regulations governing new drug applications (NDA's) for marketing approval. Elsewhere in this issue of the **Federal Register**, FDA is reproposing procedures governing: (1) Availability of investigational drugs for treatment use; and (2) sale of investigational drugs. Both of these issues had been addressed in the IND Rewrite proposal.

DATES: These final regulations are effective June 17, 1987. FDA will, however, accept applications until March 19, 1988, that are in the format required under either the current regulations or this final rule. For additional information concerning this effective date, see "Paperwork Reduction Act" appearing in the preamble of this document. Comments regarding "Outside Review Boards" by April 20, 1987.

ADDRESS: Written comments on the revised regulations to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Steven H. Unger, Center for Drugs and Biologics (HFN-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8046.

SUPPLEMENTARY INFORMATION:

I. Introduction

This final rule continues the rulemaking efforts by the Department of Health and Human Services and FDA to revise Federal regulations governing the new drug approval process. This phase of the regulations (called the IND Rewrite) makes final new procedures in 21 CFR Part 312 for FDA review of investigational new drug applications and for monitoring the progress of investigational drug use. The IND Rewrite was issued as a proposal in the **Federal Register** of June 9, 1983 (48 FR 26720). The first phase of these regulatory revision efforts (called the NDA Rewrite) covers FDA procedures in 21 CFR Part 314 for FDA review of new drug and antibiotic applications for marketing. This first phase was completed with publication of final regulations in the **Federal Register** of February 22, 1985 (50 FR 7452). Collectively, the IND and NDA Rewrites conclude an effort begun when FDA made concept papers available for public comment (44 FR 58919; October 12, 1979) and held a public meeting on November 9, 1979, to discuss them. These regulations are promulgated under the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 et seq.).

The objectives of the IND Rewrite final rule are to establish an efficient investigational drug process in order both: (a) To focus FDA's attention during the early phase of clinical research on protecting the safety of human test subjects and to give sponsors greater freedom to design, revise, and implement clinical research studies; and (b) to facilitate consultation between FDA and drug sponsors, once the preliminary human studies have been completed and a drug appears to have marketing potential, to help ensure that the design of major clinical trials is acceptable and will support marketing approval if the test results are favorable. These regulations are also intended to encourage innovation and drug development while continuing to assure the safety of test subjects. In addition, through better planning and closer consultation, FDA's later review of applications for marketing should proceed more efficiently. These changes will benefit the consumer by enhancing the prompt marketing availability of safe and effective therapies.

In preparing the final rule, FDA carefully reviewed more than 50 comments received from pharmaceutical manufacturers, trade associations, health professionals, professional societies, and consumer organizations. In addition, FDA managers met with agency employees in order to gain their views as part of the internal decisionmaking process. The agency also considered the recommendations of the Congressionally sponsored Commission on the Federal Drug Approval Process. In preparing the final rule, therefore, the agency has considered views of persons representing virtually all groups having an interest in the investigational drug process.

Like the IND and NDA Rewrite proposals and the NDA Rewrite final rule, the IND final rule has been reviewed in accordance with Executive Order 12291 (46 FR 13193; February 19, 1981) and the policy objectives outlined above.

FDA's IND Rewrite final rule complements the revised NDA regulations. For example, one of the themes of the IND/NDA Rewrites is to establish a continuing dialogue between FDA staff and drug sponsors/applicants. Accordingly, the regulations codify a sequence of four standard conferences targeted at key stages of the drug approval process. These are (in the IND regulations) the "end-of-Phase 2 conference" and the "pre-NDA conference" and (in the NDA regulations) the "ninety-day conference" and the "end-of-review conference." In addition, both the IND and NDA regulations provide for other communication between FDA staff and sponsors/applicants on an as needed basis, as well as a strong commitment to resolve any disputes in a timely manner.

In the **Federal Register** of September 27, 1977 (42 FR 49612), FDA proposed to issue rules (21 CFR Part 52) governing the obligations of sponsors and monitors of clinical investigations. In a related document, published in the **Federal Register** of August 8, 1978 (43 FR 35210), FDA proposed comprehensive rules governing the obligations of clinical investigators (21 CFR Part 54). While restating and clarifying many of the obligations of sponsors and clinical investigators previously set forth in the IND regulations (§ 312.1), these two documents also proposed to: (a) Change some existing requirements covering the conduct and review of clinical investigations; and (b) extend the requirements to persons who conduct clinical investigations of any product regulated by FDA. On the assumption that these two proposals would be made final before, or at the same time as, the IND Rewrite final rule, the agency in the IND Rewrite proposal did not systematically address issues relating to sponsor and clinical investigator responsibilities.

Because those proposals to establish Parts 52 and 54 have not been made final, FDA has retained in new Part 312 most of those existing requirements governing clinical investigator and sponsor/monitor obligations that were to have been transferred to proposed Parts 52 and 54. The responsibilities of sponsors and clinical investigators prescribed in this final rule are substantially the same as those set forth in the existing IND regulations.

In connection with issuance of the IND and NDA Rewrites, FDA has significantly expanded the use of guidelines. FDA has recently issued guidelines on how to fulfill certain technical requirements in order to provide applicants with greater guidance in these areas. These guidelines, which apply to regulatory requirements for both NDA and IND applications, should materially assist implementation of the new regulations.

Elsewhere in this issue of the **Federal Register**, FDA is reproposing new rules on: (i) The distribution of drugs for treatment use and (ii) the sale of investigational drugs. Comments received on these issues are addressed in the reproposal. Pending the adoption of new rules on the sale of investigational drugs, FDA has retained in this final rule the current provisions on sale.

Highlights of the final IND rule, the agency's economic analysis, and a discussion of related issues are contained in the following introductory sections. The remainder of this preamble is devoted to a section-by-section analysis of comments received, responses to them, and the contents of the final regulations.

II. Highlights of the Final Rule

The guiding principle in the IND Rewrite final rule is that different stages of the IND process will be regulated differently. Safety concerns will predominate at the beginning of the process to ensure that research subjects are not exposed to unreasonable risks. In the later phases of drug investigation, FDA will also evaluate the scientific merit of study protocols to ensure that planned clinical studies are capable of producing valid information on safety and effectiveness necessary to obtain marketing approval. In response to comments and further internal deliberations, the final rule has modified certain provisions of the proposal to meet these objectives better. The major provisions of the final rule are summarized as follows:

1. *Regulation of the early phase of human research.* The final rule incorporates the proposed revisions designed to give drug sponsors greater freedom during the early phase of human research (Phase 1) by permitting such research to proceed unless it presents an unreasonable and significant risk to test subjects. Thus, the final rule narrows the scope of FDA's review of Phase 1 studies to focus on the safety of human test subjects and permit clinical investigators in Phase 1 to modify protocols on the basis of experience gained during the investigation without prior notification to FDA. Moreover, the final rule emphasizes to drug sponsors that the amount of toxicology and chemistry information required in the initial IND submission depends on the nature and extent of the proposed clinical studies. These changes are intended to encourage innovation in drug development while continuing current safeguards governing the safety of test subjects.

In the proposed rule, FDA solicited comments on the merits of adopting a dual track system for Phase 1 studies in which drug firms would have the option of submitting IND's either to FDA or to nongovernmental "Outside Review Boards" (ORB's). As discussed later in this preamble, FDA has decided to solicit further comment on the feasibility of ORB's, focusing in particular on the possible establishment of a pilot program.

2. *Format for IND submission.* The final rule establishes a new format for IND submissions, similar to that in the proposal, that will result in better organized applications and thus facilitate agency review. The revised format focuses on the proposed human studies so that supporting toxicology and chemistry information can be reviewed in light of the proposed clinical investigations. The new IND will consist of a greatly simplified IND form that serves as a cover sheet, a brief overview of the investigational plan, and the protocols and supporting technical information on the drug's chemistry, pharmacology, and toxicology.

3. *IND safety reports.* The final rule specifies a drug company's obligations in reviewing and reporting adverse drug reaction information, clarifying the proposal in several respects. The rule requires that sponsors promptly review and evaluate all safety information received by the sponsor and that the sponsor report to FDA within 10 working days all adverse drug reactions that are both serious and unexpected. In addition, the final rule requires the sponsor to notify FDA by telephone of any unexpected death or life-threatening experience no later than 3 working days after the sponsor first learns of the experience. This telephone call will provide an early warning of the most serious kinds of adverse experiences and will enable FDA to discuss with the sponsor the need, if any, to modify or discontinue the study. These safety report provisions should significantly improve FDA's ability to monitor the safety of clinical studies.

4. *Amendment procedures.* Like the proposal, the final rule divides the IND amendment procedures into three distinct categories: (i) Protocal amendments, for new protocols and changes in existing protocols; (ii) information amendments, for additional data as they develop; and (iii) IND safety reports, as described above. Appropriate reporting intervals apply to each category depending upon the need for prompt agency review. The final rule also clarifies the scope of the annual reports, which are intended to provide an overview of the progress to date and future plans for the IND.

5. *Meetings between FDA and drug sponsors.* The final rule codifies FDA's proposal to extend to the sponsor of any IND an opportunity for an "end-of-Phase 2" conference with FDA to obtain concurrence on an overall plan for the conduct of Phase 3 trials and the design of specific studies. The final rule also codifies the policy that gives IND sponsors and opportunity to meet with FDA for a "pre-NDA" conference to discuss appropriate formats for data presentation in a marketing application.

6. *"Clinical hold" procedures.* The final rule adopts procedures essentially the same as those contained in the proposal pertaining to FDA's instituting a "clinical hold." A clinical hold is an order either not to begin or not to continue a clinical study. The final rule limits clinical holds in Phase 1 studies to situations where there is an unreasonable and significant risk to human subjects. In Phases 2 and 3, FDA's authority to issue a clinical hold would extent to serious defects in study design that would render the study incapable of producing valid evidence of safety and effectiveness. All clinical holds must be approved by the director of the division in FDA's Center for Drugs and Biologics with responsibility for review of the IND.

7. *Exemptions for certain studies on marketed drugs.* The final rule exempts from most IND requirements certain investigations conducted with drugs already approved for marketing. The exemption applies where safety is not an issue (because of a similarity in dose route of administration, and patient population with the approved labeling)

and where the investigation is not being conducted for the purpose of changing the drug labeling (for example, where the study is not for purposes of adding a new indication or comparative safety claim). The agency expects that this exemption will apply primarily to researchers in academic or other institutions. This exemption is intended to reduce burdens on researchers while permitting FDA resources to be devoted to monitoring clinical investigations requiring FDA oversight and to reviewing marketing applications. Although exempt from most IND requirements, the investigations would nonetheless be subject to the general prohibition against promotion of investigational drugs (§ 312.7), and to the other regulations designed to protect the rights and safety of patients, such as the institutional review board (21 CFR Part 56) and informed consent (21 CFR Part 50) regulations.

8. *Dispute resolution.* The final rule has been significantly revised to emphasize, similar to the NDA final rule, the use of informal meetings and other informal communications as the means for resolving differences between FDA and sponsors. For administrative and procedural issues, the final rule establishes an ombudsman whose function will be to facilitate timely and equitable resolutions of administrative and managerial disagreements about IND's. For scientific and medical disputes, the final rule encourages applicants to seek resolution through informal meetings with appropriate agency staff and management representatives as the need may arise. The final rule also provides for the participation of outside experts at these informal meetings when feasible. This procedure supersedes the appeals process described in the IND Rewrite proposal.

III. Economic Analysis

FDA has examined the economic consequences of the changes implemented by the final rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354). The agency concludes that these revisions will have favorable economic impacts on the health care system, drug sponsors, and the agency without compromising the safety of human subjects. Although some of these favorable impacts are quantifiable, others with greater potential for savings can only be characterized in a very generalized, nonquantitative manner at this time.

Quantifiable impacts include an estimated net annual savings of $4.9 million to sponsors, arising from a simplified IND format; reduced and/or staged submission of manufacturing and controls data; a reduction in the number of amendments that are submitted during the first year that an IND is active; savings in start-up expenses associated with studies that would no longer be placed on clinical hold under the revised criteria; and savings of sponsor-investigator resources currently used to prepare IND's that will no longer be necessary. The only projected cost increase is modest by comparison and arises from requirements to improve the quality of annual reports. These revisions will also produce some savings in agency review resources.

A potential for substantially larger savings is presented by the provisions for increased use of guidelines, meetings, and informal advice to aid commercial IND sponsors in assembling the data for those IND's that lead to the submission of a marketing application. These initiatives, taken together, could result in substantial savings from fewer deficiencies being noted in the NDA review process due to better designed clinical trials, as well as further savings from the elimination of some unnecessary or poorly designed clinical studies. For example, gaining advice on the proper protocol for a major clinical study could save a year or more in the process if it prevents the need to redo certain key research as a result of faulty study design.

As stated in the proposal, the agency concludes that these revisions are not a major rule as defined in Executive Order 12291. The agency also certifies that the changes will not have a significant impact on a substantial number of small entities. The net savings, described above, will accrue to all sponsors, regardless of size, and the preponderance of unquantifiable savings will probably accrue to the public and to sponsors of commercial IND's, most of whom are not small entities. A copy of the agency's revised assessment of economic impact is on file with the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

The revisions to the IND regulations have a significance well beyond the specific cost reductions summarized above. As noted earlier, these regulations are part of a comprehensive review of the new drug approval process designed to accelerate the development and marketing of new drug therapies without compromising the safety and effectiveness of new drugs. Collectively, FDA's new regulations, guidelines, procedures, and policies should produce considerable benefits. A quicker, more efficient drug development process means that the American public will have more safe and effective drugs sooner. A less costly drug development process means that the pharmaceutical industry will be able to develop more new drugs with the same number of research dollars, or alternatively to market less costly drugs. Either outcome will be of direct benefit to the American public. Most importantly, the prompt availability of safe and effective drug therapies has enormous potential benefit to patients and the public in terms of improving the length and quality of life and in reducing health care and hospital costs.

IV. Paperwork Reduction Act of 1980

This final rule contains information collection requirements that were submitted for review and approval to the Director of the Office of Management and Budget (OMB), as required by section 3507 of the Paperwork Reduction Act of 1980. The requirements were approved and assigned OMB control number 0910–0162.

Only § 312.33 contains changes that are different from the proposal that was submitted to OMB that may require a change in the reporting burden. Revised information collection estimates reflecting these changes will be submitted for approval to OMB. The reporting requirements of § 312.33 will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the **Federal Register** prior to June 17, 1987.

V. Comments on the Proposed Rule

Applicability of IND Requirements (§ 312.2)

1. *Changes permitted to marketed product.* Many comments asked for clarification of the proposed exemption in § 312.2. The exemption would permit a sponsor to conduct a study with a lawfully marketed drug without having to submit an IND if the study did not involve use of the drug in a way that significantly increased the risks associated with use of the product, and if certain other conditions were met. These comments in general were interested in knowing to what extent a sponsor could change the drug product or the conditions of the drug's use and remain within the terms of the exemption. Specifically, one comment asked whether it would be permissible to conduct a study with a capsule of a drug that is lawfully marketed in tablet

form. Other comments urged that the exemption permit modifications in the packaging or labeling of a marketed drug that do not affect a product's quality, safety, or effectiveness.

The exemption was not intended to require an investigator to use the drug in exactly the dosage form, dosage levels, and patient populations described in the marketed labeling for the product, but rather to permit changes to the lawfully marketed drug product that do not increase the risks (or, as explained in response to paragraph 8 below, the acceptability of the risks) over the risk presented by use of the product in conformance with its marketed labeling. Because assessing the risks involved in specific uses of a product depends on a number of variable factors, the agency cannot in advance describe precisely the degree to which particular drug products might be altered through dosage level changes, dosage form changes, or changes in the intended patient population and stay within the exemption. As guidance, the agency will, on request, provide advice on the applicability of the exemption to particular drug uses, and will provide public notice when specific situations are identified that would require an IND.

Some general examples may nonetheless be stated. The agency believes that, in general, the use in a clinical investigation of a drug in capsule form that is lawfully marketed in tablet form should not, in itself, raise safety concerns necessitating submission of an IND. Of course, there may be exceptions. For example, the agency can foresee circumstances in which reformulation to capsule form of a drug product might so affect its bioavailability as to raise safety concerns warranting submission of an IND. There might also be significant problems involved in grinding up and encapsulating enteric-coated or film-coated tablets. Apart from these exceptions, however, FDA believes that the change from tablet to capsule should rarely result in the removal of a study from the terms of the § 312.2 exemption. In contrast, FDA would presume that any change from one dosage form to an intravenous (I.V.) dosage form (including a change from an intramuscular (I.M.) dosage form to an I.V. dosage form) would significantly increase the risk so as to warrant an IND.

FDA also believes that the substitution of an investigational label for an approved label should rarely, if ever, raise safety concerns triggering the need to submit an IND. Similarly, modifications in packaging and labeling that do not impair a drug's stability or quality should not remove a product from the terms of the exemption. Indeed, because the study will be investigational, it is expected that the labeling for the drug will be changed to some extent for purposes of the investigation.

2. One comment argued that studies of over-the-counter (OTC) drugs involving dosage levels of the active ingredient lower than the marketed level should be exempted because such studies would invariably pose fewer risks for subjects than would be posed by the marketed version of the drug.

The agency does not believe it is desirable to indicate, apart from the general rule, specific situations in which an IND will not be required. Applying the general rule, however, there would appear to be few situations in which use of an OTC drug at a dosage level lower than the marketed level would raise safety concerns. However, where a drug is used to treat a life-threatening illness or to prevent irreversible damage, safety concerns might appropriately trigger the need to submit an IND.

3. The proposal defined "investigational new drug" to include "a marketed drug that is used for any purpose or in any way other than that described in its labeling * * *." Given this definition, one comment asked whether FDA intended a postapproval study of a labeled indication—an indication that, by definition, would not be deemed investigational—to be subject to IND requirements.

The agency believes that a postapproval study of an indication contained in a marketed product's labeling (whether conducted by a commercial sponsor or otherwise) is, and should be, subject to all relevant requirements governing the investigational use of drugs, including the requirements of Part 312. All studies, including those involving use of a marketed drug for a labeled indication, pose risks that patients' interests will be subordinated to the interests of the study, and therefore implicate FDA's responsibilities for the rights and safety of human subjects. To clarify the agency's view that it has jurisdiction over all clinical studies, the definition of "investigational new drug" has been revised to make clear that it includes any drug used in a clinical investigation.

It should be emphasized that even though a study of a marketed drug involving an indication contained in the product's approved labeling would be subject to all relevant requirements governing the use of investigational drugs, such a study would, like a study of a marketed drug for an unlabeled indication, be exempt from IND submission requirements if it met the conditions of § 312.2.

4. Several comments expressed concern that the proposed exemption from IND submission requirements did not extend to studies intended to support a significant change in the advertising for the drug. One comment argued that studies used to support advertising claims are rarely submitted to FDA and that it is the responsibility of the party making the claim to ensure that support for the claim is adequate. Another comment contended that the reference to advertising in the prohibition is inappropriate as current regulations provide that advertising must be based on drug's approved labeling and many studies are done for the purposes of making comparative statements within the parameters of approved labeling. This comment urged that the exemption from IND submission requirements should apply unless the purpose of the study is to make a significant change in the approved product's labeling. Finally, one comment argued that, given Federal Trade Commission jurisdiction over advertising for OTC drugs, a study to support an advertising claim for a nonprescription drug is not a study subject to the general jurisdiction of FDA.

The agency disagrees with the suggestion that it lacks authority to regulate studies of OTC drugs in human subjects that are conducted for the purpose of modifying drug advertising. Such studies, like clinical studies intended to change prescription drug advertising, involve the use of a human drug for an investigational purpose and are, therefore, appropriately subject to all rules administered by FDA governing the protection of human subjects. However, given that FDA does not routinely become involved in reviewing OTC advertising content, the case for requiring IND's for OTC advertising studies is not as compelling as it is for prescription drug advertising studies. For this reason, FDA has revised the final rule to exempt OTC advertising studies from IND submission requirements.

5. Several comments requested assurance that the results of a study conducted under the exemption in § 312.2 could later be submitted in support of a marketing application. One comment contended that a refusal to accept studies would be unnecessarily wasteful of limited resources and would expose human subjects to unnecessary clinical experimentation.

FDA advises that a study that is conducted in good faith under the terms of the exemption in § 312.2 (i.e., without the filing of an IND) will later be acceptable to the agency in support of an IND or marketing application. Therefore, where the agency finds that a study was conducted under the exemption on the reasonable belief that each of the significant elements of the exemption applied, the FDA will not subsequently raise any objections to its acceptance, assuming adequate guarantees of the ethical propriety and scientific validity of the study. On the other hand, where there is evidence that the sponsor had no reasonable basis for concluding that a study should have been exempted, FDA may take other regulatory action, as appropriate.

As FDA is willing to discuss and advise sponsors on the applicability of the exemption to planned clinical investigations, the agency believes there should be few occasions for determining after the fact that a study did not qualify for the exemption, but should have been conducted under an IND.

6. One comment recommended that the proposal be clarified to indicate that the exemption for lawfully marketed drug products was confined to drug products lawfully marketed in the United States.

Because approval requirements may differ among countries, the agency intended to limit the exemption to studies involving drugs lawfully marketed in the United States. FDA has revised the regulation accordingly.

7. One comment expressed concern that the determination of whether a drug study "increased the risks" of the drug was very judgmental, and that the degree of judgment involved would lead conscientious investigators routinely to solicit agency help in determining whether an IND is needed. On the other hand, another comment suggested that the provision is so ambiguous that its usefulness is likely to be limited by fear of transgressing. The comment claimed that without a definition of what is meant by "significantly increases the risks," the provision could well tie an investigator to the dose, route of administration, and patient population identified in the approved labeling.

The exemption is not intended necessarily to tie the investigator to the dose, route of administration, and patient population(s) described in the product's approved labeling, but rather is designed to permit deviations from the approved labeling to the extent that such changes are supported by the scientific literature and generally known clinical experiences. As noted in the preamble to the proposed rule, FDA recognizes that a considerable amount of professional judgment must be exercised in determining whether the conditions of an investigation "significantly increase" the risk associated with use of the drug. Because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption. As noted, FDA will provide advice on the question when requested.

8. One comment argued that in some cases where a drug is approved for use at a high dosage level to treat a very serious illness, it may not be appropriate to use it investigationally at that dosage level in the study of a less serious condition. The comment suggested that such uses should not be exempted from IND requirements.

The comment correctly identifies a defect in the proposed exemption scheme. Under the proposal, an IND would be required only if a change "significantly increase[d] the risks associated with use of the drug." However, in the case cited in the comment, a change in patient population arguably would not affect the risks at all ("risks" understood as the incidence or seriousness of adverse drug reactions), but would plainly affect the acceptability of those risks ("acceptability" incorporating the notion of drug benefit and understood as the willingness of a patient to run the risks associated with the drug to undertake the proposed therapy). FDA concludes that a change that significantly diminishes the acceptability of the risk raises safety concerns that necessitate submission of an IND, and has revised the regulation to incorporate this concept.

9. A comment urged that "patient population" as used in proposed § 312.2(b)(1) be defined specifically. The comment asked whether "patient population" referred solely to demographics, such as age, sex, or race, or also referred to disease groups, such as heart patients or kidney dialysis patients. The comment claimed that if disease groups were intended to be included, it could be that any use outside the labeled indications would constitute use in a different patient population, and that the inherent risk of failure for the nonlabeled use could constitute a significant risk.

"Patient population" was intended to include groups defined in terms of demographic characteristics (e.g., geriatric patients, pediatric patients) and in terms of disease processes (e.g., heart patients or kidney dialysis patients). Therefore, a significant increase in risk (or significant decrease in acceptability of risk) resulting from the clinical use of a drug in either a demographic or disease group that is not identified in the marketed labeling for the drug would necessitate submission of an IND.

The agency advises that the risk that a drug will not be effective in a patient population should not ordinarily trigger the need to submit an IND. Of course, there should be some evidence to support the reasonableness of a drug's administration for its investigational use. Also, where the consequence of therapeutic failure is irreversible injury or death, an IND would clearly be required. In other cases, because the possibility that a drug may not be effective is obviously relevant to an evaluation of its benefits and risks, the possibility of therapeutic failure should be considered in determining the acceptability of risk of an investigational use (see response to paragraph 8, above).

10. One comment contended that not all IRB's consider their involvement necessary in the circumstances described in proposed § 312.2 under which a drug study would be exempted from IND requirements.

FDA has retained a requirement for IRB review as a condition for the exemption because the agency considers review of such studies to be necessary to protect the rights and welfare of subjects. FDA believes that the generalized concern about IRB unwillingness to review studies is more theoretical than real. In the past, FDA has found little reluctance on the part of IRB's to review studies that are subject to agency regulations mandating such review. However, even if an investigator is faced with an IRB unwilling to review a planned study, the investigator may relocate the investigation to an institution whose IRB is willing to review the study or may request a waiver of IRB review (perhaps for the reasons that lead the unwilling IRB to conclude review was unnecessary). Therefore, the agency believes there should be adequate alternative means of complying with the conditions for exemption.

11. One comment objected to the statement in proposed §312.2(d) that the investigational drug regulations do not apply to the use of a lawfully marketed drug in the practice of medicine for an unlabeled indication. The comment argued that such an exemption deprived the agency of the control required to ensure the safest possible use of the drug, and also deprived the public of useful information about the drug's nonlabeled uses.

As noted in the preamble to the proposed rule, it was clearly the intent of Congress in passing the Federal Food, Drug, and Cosmetic Act that FDA not regulate the practice of medicine, which the agency has consistently viewed as including the use by physicians of marketed drugs for unlabeled indications in the "day-to-day" treatment of patients. Once a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for uses not included in the drug's approved labeling. Control of the practice of medicine in these cases is primarily exercised through State laws affecting medical licensing and practice and through products liability law.

While FDA does not regulate physicians' uses of approved drugs for unlabeled indications, the agency does continue to receive information about the drug's unlabeled uses. This information is obtained from a variety of sources, including physicians' adverse reaction reports, reports of sponsors' postmarketing surveillance activities, and reports of studies conducted by practitioners and researchers that are published in the medical literature.

12. Section 312.2 deals with exemptions from IND requirements for biological in vitro diagnostic products. As proposed, the section specified the criteria for exemption—exempting products intended to be used in a diagnostic procedure that confirmed the diagnosis made by another, medically established, diagnostic product or procedure—but did not specify the particular products that would meet these criteria and therefore be exempt from the otherwise applicable provisions of Part 312. To ensure that the scope of this exemption is not misinterpreted, FDA has revised § 312.2(b)(2) by adding new § 312.2(b)(2)(ii) to identify the specific classes of product that, in the agency's view, meet the criteria for exemption. As thus revised, the regulation lists three classes of exempted products: blood grouping serum, reagent red blood cells, and anti-human globulin. A sponsor of a study involving an investigational biological in vitro diagnostic product not on this list who nonetheless believes the product meets the criteria for exemption should discuss with FDA the appropriateness of extending the exemption to that product. If FDA agrees with the sponsor, the sponsor's product will be added to the codified list of exempted products. A sponsor of a clinical investigation involving a biological in vitro diagnostic product that is not listed in § 312.2(b)(2)(ii) must submit an IND for that investigation.

The exemption for clinical investigations involving in vitro biological diagnostic products is conditioned on compliance with the labeling and recordkeeping requirements of § 312.160. FDA has revised § 312.160 by adding labeling and record retention requirements appropriate for in vitro biological diagnostic products. Accordingly, as revised, the section requires that shipments of in vitro biological diagnostic products be labeled as follows: "CAUTION: Contains a biological product for investigational in vitro diagnostic tests only." In addition, § 312.160(a)(3) has been revised to require that records of shipments of exempted in vitro biological products be retained for the same record retention period as applies to shipments of investigational drugs subject to IND requirements.

12a. A placebo used in a clinical investigation is an "investigational new drug" as defined in this rule. As a technical matter, this means that an IND would be required for shipment and use of the placebo in a clinical study even when use of the active treatment drug in the study does not require an IND. FDA does not believe that asking for an IND in such cases serves a useful purpose. Therefore, on its own initiative, FDA has added new § 312.2(b)(5) to state that an IND is not required when a placebo is used in a clinical study that does not otherwise require submission of an IND.

Definitions and Interpretations (§ 312.3)

13. Several comments criticized the use of the term "investigational new drug application" to identify the sponsor's submission. One comment contended that the use of a term like "investigational new drug exemption" would be more consistent with the applicable statutory provisions and with FDA's decision not to adopt an affirmative approval mechanism. Another comment contended that the term "investigational new drug application" carries the connotation that the submitter of an IND is an applicant rather than a sponsor and must wait for the agency's approval prior to instituting the proposed research. This comment recommended that the term "investigational new drug notice" be adopted.

As noted in the preamble to the proposal, the phrase "investigational new drug application" was adopted because it has come to be almost universally preferred over the more cumbersome, official term—"Notice of Claimed Investigational Exemption for a New Drug." FDA believes the phrase is consistent with the pertinent provisions of the act and is also consistent with the mechanisms by which an IND goes into effect. Notwithstanding that submitters of IND's do not need to obtain approval, investigational drug studies are still subject to agency review prior to their initiation. Finally, FDA notes that to the extent that "investigational new drug application" carries a connotation for some that affirmative approval is required, the agency has revised the final regulation to define the phrase as synonymous with the former title, i.e., "Notice of Claimed Investigational Exemption for a New Drug." Therefore, FDA believes that little possibility for misunderstanding remains.

14. Although no comments were submitted on the IND Rewrite's proposed definition of "sponsor" and "sponsor-investigator," comments were received on the very similar definitions of these terms that were included in the proposed rule governing the obligations of sponsors and monitors (proposed 21 CFR Part 52). Because of the relevance of those comments to this rulemaking, the comments are summarized and discussed below.

15. One comment urged that a person who provides financial support, but who has no right to receive reports in return, be excluded specifically from the definition of "sponsor." The comment expressed concern about how the definition would affect grants to research institutions.

The agency concludes that no changes in the definition of sponsor are necessary. The definition of "sponsor" does not include the concept of financial support as a characteristic of the sponsor relationship. Someone must, however, conceive of a particular study; someone must plan the study, arrange for financing, facilities, personnel, and other necessities; someone must serve as the focal point for negotiations with other bodies such as suppliers, laboratories, and IRB's; and, if an application for the research is required under the act, someone must assume the responsibilities of a sponsor and be identified as such in the application. Clearly, not all of these tasks need to be undertaken by the same person, but generally one person accepts the principal responsibility for completing these chores. The definition of "sponsor" does not force any particular person to accept this responsibility. Rather, it is flexible enough to permit the parties involved to decide what entity will serve as the sponsor of a particular study. Thus, a person who makes a grant to support an investigational study

would not necessarily be a sponsor, unless identified as such in an application for a research permit. Instead, the recipient of the grant or some other entity may assume the responsibilities of a sponsor.

16. Another comment suggested that the word "initiates" in the definition of "sponsor" be replaced by "requests" to avoid any implication that the sponsor conducts any part of the study. One comment suggested the definition be explicit in excluding universities and medical schools in all but special circumstances.

The word "initiates" is appropriate. The definition of "sponsor" clearly states that the sponsor (other than a sponsor-investigator) does not actually conduct the investigation. The suggestion to substitute the word "requests" for the word "initiates" is rejected.

No basis exists for excluding universities and medical schools from the definition of "sponsor." Although these institutions may seldom initiate a clinical investigation, it is possible that they may do so. When they do, they should be subject to the regulations to assure protection of the rights of human subjects, the safety of all subjects, and the quality and integrity of data resulting from the investigation.

17. One comment objected to the exclusion of corporate sponsors from the definition of "sponsor-investigator" and stated that the creation of a double standard of enforcement for sponsors and sponsor-investigators is both confusing and a violation of equal protection because no need for the differential treatment had been demonstrated. The comment argued that pharmaceutical companies often conduct their own investigations, and that they, as well as independent individual investigators, should not be required to police themselves.

The definition of "sponsor-investigator" is not intended to create a double standard or to discriminate against any one. Rather, the definition reflects the practical necessity of distinguishing between the situation in which a single individual both initiates and conducts a clinical investigation and the situation in which a corporation initiates an investigation that is conducted by its employees. The definition of "sponsor" specifically states that employees of a corporate or agency sponsor are considered to be investigators. In the case of a single individual, it would not be appropriate for that individual to comply with certain sponsor obligations. It would be senseless, for example, to require that the sponsor-investigator monitor himself or herself. This need for special provisions does not exist in cases where a sponsoring corporation or other entity conducts its own investigations with full-time staff employees. In these cases, the sponsor may assign other employees, or use a contractor, to serve as monitors. Monitoring of such a study is thus possible and feasible.

Labeling (§ 312.6)

18. One comment asked whether the "investigational caution" statement required to appear on each drug label must appear on the labels of small, single-dose containers for which there may be significant space limitations.

FDA believes that the inclusion of the required cautionary statement on the investigational label alerts all persons involved in a drug's distribution and dispensing to the drug's investigational status. As the utility of this message is not a function of the size of the package bearing the label, FDA does not believe it should exempt unit dose packages or other small packages from the requirement. At the same time, FDA is aware that space limitations may occasionally make it difficult to include all required information on the smallest drug package containers, and the agency will consider requests for waivers under § 312.10 of label and labeling requirements on a case-by-case basis.

19. One comment urged that the immediate container label of an investigational drug intended for self-administration include the name and emergency telephone number of the investigator. The comment contended that this provision would facilitate treatment of serious adverse reactions associated with investigational drugs.

FDA is not aware of any problems attributable to the absence of emergency identifier information on investigational drug labels. The agency believes that human subjects have little difficulty in obtaining additional information about investigational drugs when the need arises. In addition, the agency notes that the informed consent form, a copy of which is given to each subject of an investigation, is required to identify the person to contact in the event of a research-related injury. For these reasons, while FDA would strongly encourage sponsors and investigators to develop a system to simplify the process by which subjects may obtain information and assistance in a drug-related emergency, the agency does not believe it should mandate identification of an emergency name and number.

Prohibition Against Prolonging an Investigation (§ 312.7(c))

20. Several comments objected to the prohibition in proposed § 312.7(c) against a sponsor prolonging an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application. These comments suggested that there may be good reasons to delay submission of a marketing application, including a finding that additional data are needed to support an effective marketing plan. One comment suggested that the final regulation retain the current provision of the regulations that allows the sponsor to give reasons for not submitting an NDA.

FDA believes that subjects should not be exposed unnecessarily to an investigational drug when sufficient data to support a marketing application have been obtained. This view is the basis of the proposed requirement. While sponsors will presumably submit marketing applications after deciding that the results of clinical studies support the applications, FDA concedes that there may be sound scientific or other reasons for delaying the submission of an application, and that such decisions are within the discretion of the sponsor. Therefore, the final rule, while continuing to prohibit a sponsor from unduly prolonging an investigation after finding that the results appear to support an application, will no longer require the submission of an application. FDA believes this change meets the concerns of the comments.

21. The final sentence of proposed § 312.7(c) would have required a sponsor to withdraw its IND if it determined that the data would support a marketing application. One comment suggested that there may be valid reasons for continuing a study, even though the results obtained are considered sufficient to support an NDA.

FDA has deleted this provision. FDA agrees that there may be sound reasons for a sponsor to continue an investigation even after determining that the data will support a marketing application. For example, a sponsor might conclude that further studies would be desirable to obtain additional safety data or to study new indications.

Sale of Investigational Drugs (§ 312.7(d))

21a. Elsewhere in this issue of the **Federal Register**, FDA is reproposing new rules regarding the sale of investigational drugs. Comments received on this issue are addressed in

that reproposal. Pending the adoption of a new final rule based on that reproposal, FDA has retained in this final rule the current provisions on sale.

Waivers (§ 312.10)

22. Proposed § 312.10 described the procedures under which FDA may waive any applicable requirement of the IND regulations. One comment complained that the provisions would give FDA too much discretion to dispense with otherwise applicable regulatory requirements. Other comments contended that because waivers should be relatively rarely needed, the granting of a waiver should be a matter of public notice and discussion.

FDA believes the first comment misconstrued the purpose of the waiver provision. The waiver provision was intended to give applicants flexibility to seek alternative ways of complying with the regulatory requirements governing the conduct of clinical studies. The provision does not authorize FDA to waive statutory requirements; nor will the agency waive regulatory requirements, particularly those concerning the protection of the safety and welfare of human subjects, unless sponsors comply fully with the stated condition justifying waivers.

FDA's requirements for the confidentiality of information apply to the existence of IND's and extend to waiver requests that are part of IND submissions. Moreover, FDA believes that the administrative burdens involved in routinely giving notice of requests for waivers would represent a needless encumbrance on the review process and would, given the limited nature of the waiver process, outweigh whatever benefits might flow from such disclosures.

23. One comment suggested that the waiver regulation identify the specific person or office to be contacted to obtain a waiver.

In general, waiver requests regarding IND's should be directed to the division with responsibility for review of the IND. Because this is the same for IND submissions and contacts generally, the agency does not consider it necessary to list the contact point in the rule itself.

Guidelines (§ 312.145)

24. Many comments contended that, to ensure the integrity and scientific validity of technical guidelines, the public should be provided with an opportunity to participate in the creation or modification of these guidelines.

Because FDA recognizes the significant contribution the industry, the medical community, and other members of the public can make to the development of scientifically sound guidelines, FDA has routinely solicited comment on previous scientific guidelines. With respect to the guidelines that have already been developed to implement the NDA and IND Rewrites, FDA did issue them as draft guidelines before making them final. Any future guidelines will be similary developed. FDA believes these actions should provide an appropriate degree of public input into the process.

25. A number of comments approved of the proposed policy to issue a list of guidelines applicable to the regulations administered by the Center for Drugs and Biologics. Additionally, one comment recommended that the list of guidelines be published at least once per year in the **Federal Register**. Another comment recommended the establishment of the centralized public archive of guidelines.

The Center for Drugs and Biologics has prepared a list of guidelines that apply to all regulations administered by the Center. The list may be obtained from the Legislative, Consumer, and Professional Affairs Branch, Division of Regulatory Affairs (HFN–365), Office of Compliance, Center for Drugs and Biologics, 5600 Fishers Lane, Rockville, MD 20857. Given the ready availability of this list, the agency does not believe its annual publication in the **Federal Register** is necessary.

With respect to the request for a centralized archive of guidelines, the agency advises that a public file of guidelines is now maintained by the agency's Dockets Management Branch. In accordance with § 10.80 of the agency's regulations, the file maintained by that Branch includes all public comments received in developing the guidelines.

Investigational New Drug Application

Requirement for an IND (§ 312.20)

26. One comment noted that, historically, reviewing divisions of the Center for Drugs and Biologics have required a separate IND to be filed for each dosage form of a drug substance under clinical investigation. The comment recommended revising this policy to permit a sponsor to conduct clinical investigations of several different dosage forms under a single IND.

The comment is not correct regarding current agency policy. FDA does not routinely require separate IND's for different dosage forms of a drug substance under clinical investigation. The agency may require separate IND's if separate applications will simplify agency review of the submissions—for example, if different dosage forms of an investigational drug are assigned to different reviewing divisions. A sponsor with any questions about the appropriateness of submitting a single IND in this situation should discuss the matter with the division responsible for review of the initial IND submission.

Outside Review Boards

27. In the preamble to the proposed rule, FDA discussed the issue of, and solicited comments on, establishing a "dual track" system in which drug sponsors would have the option of submitting IND's either to FDA or to third party, nongovernmental bodies—"Outside Review Boards" (ORB's). ORB's would parallel FDA in performing a "scientific review" of proposed human research studies involving pharmacology, toxicology, chemistry, and clinical issues. The IND's being considered for this dual track system were the initial IND's that cover the first introduction of a drug into humans and the early clinical pharmacology and effectiveness studies (Phase 1). FDA's preliminary view, as stated in the preamble to the proposed rule, was that the dual track system may be unnecessary in light of the many changes contained in the agency's proposed rule.

Six comments supported the ORB concept while 12 comments opposed adopting a dual track ORB system. These comments, both those in favor of and opposed to ORB's, did not raise new issues or arguments from those noted and discussed by FDA in the preamble to the proposed rule. For example, several comments in favor of ORB's stated that the concept was worth trying on a pilot basis, though acknowledging that even a pilot test would require FDA to establish standards or guidelines for their operation. One comment's endorsement of the ORB concept, however, included a recommendation for extension of ORB review to Phase 2, or at least early Phase 2, trials. Comments against the dual track system cited essentially the same arguments previously noted by FDA in the proposal: that there would be no obvious benefit to the use of ORB's in shortening the review time of IND's as FDA now reviews IND's promptly; that "permissive" ORB's might surface, thereby allowing drug sponsors to "shop around" to find favorable reviewers; and that the independence of ORB's might be questioned where the drug sponsor provides large financial grants to the institution establishing the ORB.

FDA has carefully considered three comments and concludes that it would be desirable to consider further the merits of undertaking a pilot project in this area. However, because the comments submitted represented diverse views, even within the regulated community, the agency is now soliciting comments on the following points in order to determine if a pilot test of ORB's should be undertaken and, if so, to identify the best possible candidates for such a pilot program:

(1) Which institutions, organizations, or other entities would be interested in participating in such a pilot program?

(2) Which drug categories should be involved in a pilot program? For example, should the pilot program focus on one category of drugs or should it include a broader spectrum?

(3) What should FDA's responsibilities be, if any, in monitoring the participating ORB in ensuring that there is no conflict of interest of ORB members, and in evaluating the IND's being considered.

(4) To whom would the ORB be accountable (e.g., FDA, Congress, or other oversight organizations)?

(5) What would be the legal liability, if any, of ORB members or their affiliated institutions, for the consequences of the ORB's decisions?

(6) How long should such a pilot program last, what should be the criteria for assessing its success or failure, and who, in addition to FDA, should participate in the evaluation?

(7) Who should fund the ORB participating in any pilot program?

Interested persons are invited to submit specific proposals for participating, including the make-up of its proposed ORB. Proposals should be submitted by April 20, 1987.

Phases of an Investigation (§ 312.21)

28. Several comments contended that both previous and proposed divisions of a clinical investigation into three phases created "uncertainty and ambiguity." One comment recommended adopting instead a two-tiered system in which the earliest clinical pharmacology stages of research—defined to include those closely supervised studies conducted to obtain basic information about pharmacology, toxicology, and pharmacokinetics, and preliminary information about safety and effectiveness—would be subject to less FDA regulatory control. The comments argued that during this "clinical pharmacology" stage FDA should rely more heavily than in the past upon the expertise of investigators and the safeguards employed by institutions conducting clinical pharmacology studies. The comments concluded that FDA should focus its review on the "clinical development" stages of research, which would include the later stages of research, in which large numbers of subjects are studied to develop evidence necessary to support a marketing application.

Except for the question of whether there ought to be "two" versus "three" phases, the approach of the final rule is generally consistent with that recommended by the comments, both in terms of how the phases of a clinical investigation are defined and how they are regulated. FDA agrees that the clinical investigation process should be divided into an early clinical pharmacology stage (Phase 1) and a later clinical development stage (Phases 2 and 3), and that FDA's control of the earliest studies should be significantly less than over the later stages.

With respect to the question of two versus three phases, to the extent that the entire process is organic and evolutionary, any division into phases or stages is somewhat arbitrary. However, the agency believes that the definition adopted corresponds as well as any with the significant divisions of the investigational process.

29. Several comments recommended that the proposed definitions of the phases delete all references to the size of the subject population that would usually be expected to participate in the three phases of a study. One comment expressed concern that the numbers used to characterize each of the phases for illustrative purposes might come to be viewed as rigid requirements or limits for the number of patients in each phase. Other comments objected that the definitions of the phases did not necessarily apply to studies of biologic drugs, "orphan" drugs, diagnostic products, dosage forms other than the oral dosage form, or to marketed drugs tested for a new use.

The purpose of including these definitions in the regulations is to provide a general yardstick for the development process for new drugs. The agency agrees that the description of the phases may not apply to certain classes of clinical investigations as well as it applies to studies of the classic, previously untested, drug in oral dosage form. However, that fact does not, in the agency's view, reduce the value of the descriptions as guidance in generally describing the nature of each phase. The agency assures sponsors that the description of the phases are not intended as rigid requirements, and that sponsors whose studies do not conform to the norms described in the regulation will not be disadvantaged in the review of their applications.

General Principles of the IND Submission (§ 312.22)

30. This section states that the agency's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phases 2 and 3, to help assure that the quality of scientific evaluation of drugs is adequate to permit an evaluation of drugs' effectiveness and safety. Accordingly, the agency's review of Phase 1 submissions focuses on assessing the safety of the investigations while the review of Phases 2 and 3 also includes an evaluation of the scientific quality of the investigation and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

31. Several comments took issue with the agency statement of its objectives in reviewing clinical investigations. One comment argued that it is inappropriate for FDA to review and otherwise regulate the scientific design of Phase 2 and Phase 3 studies to determine whether such studies are likely to yield data capable of meeting statutory standards of marketing approval. The comment argued that "it is in fact expert opinion [that] is necessary to determine if substantial evidence has been provided," that such conclusions "rarely can be made at the outset" of a clinical development study, and that FDA "should not interject itself into the sponsor's developmental program unless there exists risks relative to patients." On the other hand, another comment suggested that it is inappropriate not to consider the scientific quality of a study, even in Phase 1. The comment suggested that concerns about the safety and rights of human subjects and concerns about scientific validity of a study are, in fact, not distinguishable because, according to the comment, "experiments which are poorly designed scientifically expose subjects to unreasonable risks and are, by definition, unsafe."

FDA believes that the final rule, like the proposal, strikes the proper balance between these two extremes. First, the agency believes that its review of the quality of the sponsor's study design in the later stages of an investigation is in the public interest. Such review should preclude unnecessary exposure of human participants to risks in investigations that will ultimately have no scientific or regulatory value. In addition, by screening out poorly designed studies before they are conducted, FDA review should reduce

the time required to obtain the valid evidence to make a decision on a drug's availability. As discussed later in this preamble, however, FDA would not place a clinical hold on a Phase 2 or 3 study, because of study design, unless the design was so deficient that the study could not meet its stated objective of establishing the product's safety and effectiveness.

Agency authority to consider questions of study design in regulating clinical investigations is well-established. The premarketing approval provisions of the statute require that the evidence proferred to demonstrate a drug product's effectiveness consist of adequate and well-controlled trials. The most cost-effective time to make that determination is before a study begins. Indeed, it would be unreasonable for FDA not to advise a drug sponsor, in advance, if the agency determined that a particular study would not yield data capable of meeting statutory standards for marketing approval.

The decision to narrow the focus in Phase I review to issues of safety alone reflects the desirability of reducing regulatory impediments to scientific creativity at this early stage of drug development. Because approximately 80 percent of all early investigations do not lead to marketing applications, the investment of resources that would be needed to assure the best possible scientific design of such studies is not justified, so long as research subjects are not put at risk. Moreover, Phase 1 studies are generally not considered pivotal to marketing approval, but rather are superseded by the later Phase 2 and Phase 3 studies. Of course, Phase 1 issues of study design that impact on research subject safety will remain part of FDA's purview.

32. Several comments addressed the statement in proposed § 312.22(c) that, to aid communications and minimize paperwork, information and data in IND's should, with some exceptions, be submitted only in summary form. While expressing agreement with the thrust of the principle, several comments were not certain what the exceptions referred to in the proposed section were. These comments asked that FDA identify the specific data items that would require detailed information.

FDA believes that the statement fairly reflects the rule's overall approach to submission requirements. However, FDA concludes that the statement should be deleted as it provides no more guidance on submission requirements than can be obtained from an examination of the various specific provisions of the regulation. Additional guidance may also be obtained from relevant guidelines and from discussions with agency reviewers. FDA has revised the final rule accordingly.

33. One comment, while appreciating the need to eliminate unnecessary paperwork, contended that eliminating raw data from IND submissions would serve to delay, rather than expedite, completion of the IND. The comment contended that raw data are needed to check sponsor and investigator interpretations of data, to spot check, and otherwise to gain a better insight into the application. The comment stated that raw data are especially important in an IND process in which a decision to permit an investigation to begin must be made within 30 days of submission of the application.

The agency believes that the detail and comprehensiveness of information required to be submitted in the IND are adequate to permit successful oversight of the safety and quality of clinical studies. While the agency does not require submission of "raw data" to the IND, information that is of most direct relevance to agency review—including information on the most important animal tests, on previous human experience with the investigational drug, and on adverse experiences during the course of the study—must be submitted in sufficient detail to permit close scientific review. To require routine submission of raw data would not only impose additional burdens on study sponsors without any evident corresponding benefits to FDA, but could well impair FDA's oversight by overloading reviewers with extraneous and irrelevant information.

34. Proposed § 312.22(d) states that when a sponsor-investigator uses a drug that is already subject to a manufacturer's IND, the sponsor may ordinarily refer to the manufacturer's IND to provide the technical information supporting the proposed clinical investigation. One comment, noting that the preamble to the proposal indicated that such incorporation would occur only when permission is granted by the commercial sponsor, urged that the final regulation require the commercial sponsor's permission to be in writing.

FDA agrees that a sponsor-investigator should not be able to rely on proprietary information submitted by a commercial drug firm unless the sponsor-investigator has received authorization to do so. Therefore, FDA has revised the final regulation to condition such reliance on the sponsor-investigator obtaining appropriate authorization from the commercial sponsor.

35. Proposed § 312.22(d) only expressly discussed the possibility that a sponsor-investigator might incorporate by reference information contained in a commercial sponsor's investigational application. One comment noted that under some circumstances incorporation by reference of information in a marketing application might also be appropriate. The comment urged that the final regulation be revised to accommodate this possibility.

FDA agrees that under certain circumstances—for example, when a marketed drug is studied for a new indication—it would be appropriate to incorporate information contained in a marketing application into a sponsor-investigator's IND. FDA has revised the final regulation accordingly.

IND Cover Sheet (§ 312.23(a)(1))

36. The proposal contained a requirement that the sponsor identify in the application cover sheet the phase or phases of the clinical investigations to be conducted. One comment asked whether the requirement pertained only to those studies to be initiated 30 days after submission of the IND, or whether it also referred to those studies to be conducted under the IND in the future.

The cover sheet should reflect the phase or phases of the study that are intended to be covered by the IND submission. This submission (including protocols and supporting information) may be limited to the studies that will begin immediately after the IND goes into effect or may cover, at the sponsor's option, any or all of the remaining studies planned.

37. The cover sheet includes a commitment by the sponsor that the investigation will be subject to the initial and continuing review and approval of an institutional review board (IRB), and that investigators will not make any deviations from the research plan without IRB approval. Several comments asserted that a sponsor cannot make these commitments for an investigator. The comments suggested that the sponsor should only be required to make a commitment to inform all investigators of applicable requirements, and to monitor them in accordance with applicable regulations.

A sponsor's obligation to monitor its studies to ensure compliance with pertinent regulatory requirements, including IRB review requirements, has been part of the IND regulations for many years, and is now widely accepted as an appropriate sponsor responsibility. Therefore, FDA does not regard as unreasonable requiring the sponsor to commit to ensure compliance by investigators with pertinent IRB

review and approval requirements. FDA does not view this commitment as a guarantee by the sponsor of investigator compliance in every case, but rather as an undertaking to ensure that investigators are fully informed of their responsibilities and to adopt monitoring procedures to minimize the possibility of investigator noncompliance.

38. Proposed § 312.23(a)(1)(vii) would require the sponsor to list the name and title of the person responsible for evaluating adverse reactions or other evidence of risks obtained from clinical investigators. Several comments recommended that this requirement be deleted, suggesting that the evaluation of adverse reactions is normally a collective effort, involving a number of individuals from different disciplines. The comments suggested that, in many cases, it would be extremely difficult to identify a single individual responsible for decisionmaking in this area. One comment suggested that FDA's initial contact point on all issues relating to conduct of the investigation, including adverse reactions reporting, should be the person responsible for monitoring the conduct and progress of the clinical investigation whose name would already have been provided to the IND under § 312.23(a)(1)(vi).

The agency believes that the requirement should be retained. The identification of a person (or persons) responsible for evaluating information relevant to the safety of the drug will be of significant help to agency reviewers in obtaining more information from the sponsor about a safety report submitted under § 312.32, when such followup is necessary.

FDA acknowledges that the evaluation of safety information may involve more than one person. Therefore, if a number of persons from different disciplines are involved in the evaluative effort, FDA would have no objection to the sponsor identifying any one or more of these individuals. FDA does not believe that it is consistent with the requirement for the sponsor to identify here the person identified in § 312.23(a)(1)(vi) as charged with monitoring the conduct and progress of the investigation unless that person is also, in fact, responsible for review and evaluation of safety information.

As proposed, the regulation would have required the identification of the person responsible "for evaluating adverse reactions or other evidence of risk * * *." This has been revised to require the identification of the person (or persons) responsible for "review and evaluation of information relevant to the safety of the drug." The change conforms this section to the provisions in § 312.32 governing review and reporting of safety information.

IND Content and Format—General Investigational Plan (§ 312.23(a)(3))

39. Many comments opposed the proposed requirements for a general investigational plan (proposed § 312.23(a)(4); final § 312.23(a)(3)(iv)). Several comments suggested that the information submitted in the plan would also be available elsewhere in the IND application. On the other hand, other comments criticized the requirements for the plan as being too vague. One comment strongly disputed the need to provide the required information in the plan, arguing that the clinical development plan of a drug product is not within the realm of information needed for FDA, either to decide whether it is safe to proceed with a clinical study, or to evaluate the scientific merit of a particular clinical study. Additionally, the comment contended that the information requested for the plan is often not available at the time of a new IND submission. The comment concluded that the requirement may force sponsors to formulate plans prematurely at the time of IND submission rather than at a later stage, when sufficient data are available upon which a more concrete plan may be based.

FDA believes that many of these comments misunderstood the limited purpose of the general investigational plan, which is to give agency reviewers a very brief overview of the scale and kind of clinical studies to be conducted during the following year. This overview, which is general should be no more than two or three pages in length, will provide the necessary context for FDA reviewers to assess the sufficiency of technical information to support future studies and to provide advice and assistance to the sponsor.

FDA does not agree with those comments that suggest that the requirements for the general investigational plan are either too vaguely expressed or are redundant with respect to other requirements in the IND regulations. In general, the information submitted in the general investigational plan regarding the sponsor's short-term plans for clinical studies—the indications to be studied, the rationale for the study, the number of subjects to be involved—will not be available in the clinical protocols or elsewhere in the application.

FDA does view this requirement as forcing the sponsor to formulate plans prematurely. When development plans are not yet crystallized, the sponsor should simply so indicate in the appropriate place in the plan.

Finally, the agency has clarified the regulation to state that the general investigational plan is to be limited to the plans for the following year. As noted in the comments, it would be unreasonable to require a sponsor to formulate and describe its plans for a 4- and 5-year study on "day 1" of the initial trials.

40. One comment asked whether the brief description of the overall plan for investigating the drug would include plans for nonclinical investigations, or whether it would be confined to plans for clinical studies only. Another comment asked whether a sponsor would be required to adhere to the general investigational plan, or would be permitted to make adjustments during the course of the investigation.

The general investigational plan is intended to be limited to plans for clinical studies in the coming year. It is not the appropriate place to discuss plans for animal or other nonclinical tests.

FDA neither insists that a sponsor adhere to the general investigational plan nor does it necessarily require that the sponsor inform FDA of a deviation at the time the deviation is made. The sponsor is free to make changes in the plan during the course of the year as the need may arise, subject to the reporting requirements for protocol amendments and information amendments (§§ 312.30 and 312.31).

41. One comment recommended that the reference in the general investigational plan (proposed § 312.23(a)(4)(vi); final § 312.23(a)(3)(iv)(*f*)) to "special risks anticipated" should be made consistent with similar references with respect to information in the investigator's brochure (proposed § 312.23(a)(5)(v)) and information the sponsor is required to submit with respect to previous experience with the drug (proposed § 312.23(a)(9)(i)). The comments suggested that all three sections use the wording of proposed § 312.23(a)(9)(i): "Information that is relevant to the safety of the proposed investigation." Alternatively, the comment suggested that the three sections incorporate the wording in the current IND regulations: "All relevant hazards, contraindications, side effects, and precautions suggested by prior experiences."

Although FDA favors consistency whenever appropriate, the comment erroneously assumes that the information to be submitted in the three sections would be identical. In fact, each of the sections calls for somewhat

different information, and different requirements are therefore warranted.

The distinction between the "special risks" section of the general investigational plan and the "possible risks" provision in the investigator brochure is primarily one of scope and detail. Although both sections should contain safety information that may be relevant to precautions and special monitoring to be done during the clinical investigation, the agency expects the general investigational plan to be a more selective document than the investigator brochure. Accordingly, FDA believes that the "special risks" section of the general investigational plan should be limited to those risks that most concern the sponsor—the most serious and significant risks that can be anticipated on the basis of previous experience. FDA has revised the final rule to reflect this distinction.

Finally, the information to be reported in § 312.23(a)(9)(i) is limited to previous human experience with the investigational drug, in contrast to the information expected in the general investigational plan and the investigator brochure, both of which should include animal test data as well.

Protocols (§ 312.23(a)(6))

42. This section would require a protocol for each planned study. Two comments asked whether "planned study" meant a study definitely planned, or a study to be conducted in the future if the investigation followed the desired course. One of these comments noted that protocols may not yet have been completed for some studies to be conducted at later stages of the investigation.

As noted above, the sponsor may limit the IND submission to the study or studies to be conducted at the end of the 30-day review period, or may also include some or all of the studies to be conducted subsequently. To the extent that protocols for future studies have not yet been developed, the sponsor is under no obligation to submit them in the initial submission.

43. Several comments criticized the provision in proposed § 312.23(a)(6)(i), which requests that protocols for Phase 2 and Phase 3 investigations "be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset." One comment contended that in some cases it may not be possible to anticipate deviation at all, or it may not be possible to anticipate deviations in sufficient detail to provide for an alternative course of conduct. Comments suggested that inclusion of such contingency plans should be at the discretion of the sponsor and that such information should only be required "where feasible."

The final regulation, like the proposal, puts the inclusion in the protocol of contingency plans at the sponsor's discretion. Nevertheless, the agency strongly encourages submission of such plans as it believes there is much to be gained in thinking about and planning for possible alternative courses of action early in the protocol development process. Providing in the initial protocol for possible departures from the study design enhance the value and reviewability of study results. Such advance planning also permits both FDA and the sponsor to raise useful questions about study design and supporting information at the earliest possible time. Moreover, to the extent FDA is aware in advance of how a sponsor may need to depart from a planned protocol, misunderstandings between FDA and sponsors over such departures may be minimized.

The agency agrees with the comment that in some cases it may not be possible to anticipate the need to depart from the planned protocol and, in such cases, the sponsor would not be expected to submit plans for alternative or contingent courses of action.

44. Several comments objected to the requirement that the sponsor submit a curriculum vitae for each investigator. One comment suggested that instead of the curriculum vitae, which can extend to 30 or 40 pages, a sponsor should be able to submit a shorter data sheet on each investigator.

Under section 505(i) of the act (21 U.S.C. 355(i)), the agency is required to assure that the investigational drug will be provided to "experts qualified by training and experience to investigate" a new drug. To discharge that responsibility, FDA must have sufficient information about an investigator to show that he or she is qualified by reason of training and experience to conduct the proposed study. While this information is ordinarily most conveniently provided through a conventional curriculum vitae, the agency will accept any other statement of qualification that demonstrates the investigator's fitness to conduct the study. FDA has revised the final regulation accordingly.

45. Several comments contended that the names of each investigator, subinvestigator, and IRB should not be included in the protocol for the investigation, but should be included as a separate part of the study documentation. One comment claimed that when multicenter studies are conducted, it is more efficient for all investigators to conduct their studies using a master protocol that is individualized only for investigator name and address. The comment observed that, in multicenter trials, investigators are frequently added or changed during the course of the study.

To promote efficient review of an IND, all information pertaining to the protocol, including the names and qualifications of the investigators and identification of participating IRB's, should be presented together. However, whether the information pertaining to the investigators and IRB's is part of the protocol itself, or is an addendum to the protocol or accompanying document, is a matter on which the sponsor may use its discretion. When this issue arises, FDA will be willing to discuss such alternative ways of presenting the information.

When a multicenter study is conducted under a single "master" protocol, the sponsor is not required to resubmit the protocol for every new investigator added, but under § 312.30(d) may simply reference the protocol in an appropriate protocol amendment submission containing information on the new investigator, subinvestigators, or IRB.

46. Another comment suggested that information in the protocol on investigator qualifications redundantly repeated information on investigators provided in the investigator statement (Form FDA–1572).

While it is true that the investigator statement, including information on the investigator's qualifications, is provided by the investigator to the sponsor of the clinical investigation, the sponsor is not required to submit that statement to FDA. Therefore, it cannot take the place of information contained in the sponsor's submission to the agency. At the same time, FDA acknowledges that in the past some sponsors have submitted information to FDA on their investigators by simply attaching copies of the investigator statements from the investigators. The agency believes that such a practice is appropriate provided the investigator statements submitted by the sponsor contain sufficient information to demonstrate the investigators' qualifications to undertake the proposed studies.

47. One comment asked that the term "subinvestigator" be defined. Specifically, the comment questioned whether the term included nonphysicians, nurses, technicians, and

other assistance to the clinical investigator.

Studies frequently are conducted by a team of individuals who share responsibility for designing and conducting the investigation. The principal investigator is the responsible leader of that team. Subinvestigators include all other professionals who assist the principal investigator in the design and conduct of the investigation. Subinvestigators would not include those technicians and other assistance who assume no responsibility for the conduct of the study. FDA has revised the rule to reflect this concept of "subinvestigator."

48. Several comments objected to requiring the sponsor to identify the reviewing IRB for each participating investigator. One comment argued that information on IRB's may not be available at the time that an IND is filed. Another comment argued that it is inappropriate and impracticable to include the name and address of each reviewing IRB, contending that normally the investigator is the IRB contact. The comment asked whether, in requiring the identification of the IRB in the protocol, FDA intended that IRB approval be obtained before the pertinent protocol is submitted to FDA. Several comments concluded that FDA can always obtain the identification of IRB's if a need exists, but that such information should not be part of the protocol or sponsor's responsibility.

This requirement is based on FDA's regulatory responsibility to ensure that the safety, rights, and welfare of human test subjects are adequately protected. To carry out this responsibility, FDA conducts on-site inspections of both clinical investigators and IRB's. By identifying the reviewing IRB in the protocol submission, FDA is assured of having an up-to-date record of active IRB's, together with studies under their purview. FDA believes that requiring sponsors to include this information in their submissions constitutes a minimal burden and will substantially aid the agency in carrying out its mandate to monitor subject safety.

As noted in response to paragraph 67, the final rule requires that IRB approval precede the start of a clinical study but does not require that IRB approval be obtained before the IND is submitted to the agency. If information on the IRB is not available at the time the protocol is submitted, the sponsor may later add the information to the protocol through a protocol amendment.

49. One comment suggested that the protocol provisions be revised to include a requirement that the sponsor state the criteria by which effectiveness of the investigational drug will be judged. Another comment argued that the protocol should include a proposed method of analysis of results of the study.

The protocal section lists the essential elements that protocols for all studies possess in common. As not every protocol contemplates a specific method of analyzing study results or is intended to examine a drug's effectiveness, it would not be appropriate to list them in this section. The essential elements of a protocol for a study intended to demonstrate effectiveness are described in the regulation outlining the characteristics of an adequate and well-controlled investigation (21 CFR 314.126).

Chemistry, Manufacturing, and Control Information (§ 312.23(a)(7))

50. A comment agreed with FDA that the amount of chemistry, manufacturing, and control information should be less in the clinical pharmacology stage (Phase 1) than in later stages of drug development, but suggested that the proposed chemistry requirements for Phase 1 would still require more information than is necessary to assure subject safety in early research. Specifically, the comment urged that, rather than provide information on the "general method of preparation of the drug substance" for Phase 1 studies, sponsors should only be required to provide a brief outline in the form of a schematic diagram outlining the manufacturing process. Additionally, the comment recommended that sponsors should not be required during Phase 1 studies to provide detailed information on raw materials used in investigational products.

FDA does not agree that it is asking for more information than is actually needed to assure human subject safety in Phase 1 studies. In general, a schematic diagram of the process by which the drug substance is synthesized, while a useful symbolic representation of the method of drug synthesis, will not provide adequate information about the manufacturing process—including, for example, information on equipment used, work-up and isolation procedures, purification steps, tests for completion of reaction and yields—to permit FDA to make a number of key safety determinations, including determinations about the presence of contaminants and byproducts.

51. Several comments urged that the proposal be revised to indicate that complete stability data are not required prior to beginning clinical studies. These comments urged that the regulations permit the development of stability data concurrently with the conduct of the clinical investigations. One comment argued that in the closely controlled distribution system that is required for investigational drug accountability, corrective action for materials that no longer meet the appropriate standards for use is easily undertaken. The comment contended that the concurrent development of stability data is consistent with current good manufacturing practice. Two comments suggested that if data developed concurrently indicate that a drug product does not meet its acceptance standards during the entire period of the investigation, appropriate corrective action can easily be undertaken to replace the material. Several comments maintained that permitting concurrent stability testing would further the regulatory objective to speed up the drug testing and approval process.

The regulation does not preclude a sponsor from conducting stability tests on an investigational drug product concurrently with clinical investigations of the product. However, the agency does expect that, by the time a clinical study is begun, the sponsor will have submitted to FDA at least preliminary evidence (obtained from accelerated studies) to show that the product is likely to remain stable for the duration of the study. The applicable requirements for stability testing are set forth in 21 CFR 211.166 of the regulations describing current good manufacturing practice for finished pharmaceuticals. At the same time, sponsors should be aware that a decision not to complete stability tests before commencing a clinical study may jeopardize the value of study results should the tests ultimately show problems in the drug product's degradation or bioavailability.

While the regulations thus permit concurrent testing of investigational drug products, the agency believes that testing of the stability of the drug substance should be substantially completed before initiation of human clinical studies of the drug. This should not present significant difficulties to sponsors, as these tests are usually conducted while preclinical animal studies of pharmacology and toxicology are underway.

52. The proposed rule indicated that, as drug development proceeds, and as the scale of production of the investigational drug is changed from the limited pilot production appropriate for the initial clinical studies to larger scale production necessary for expanded clinical investigations, the sponsor should submit information amendments to supplement the initial information

submitted on the manufacturing and control processes. One comment argued that information amendments should only be required if the manufacturing formula changes, not every time the scale of production changes, since the scale does not change the compositional formula of the clinical supplies.

FDA does not agree. Although it is true that changes in scale may not affect a drug's composition, such changes may affect a drug's physical or biochemical characteristics and thus possibly affect the safety of proposed studies. Specifically, changes in scale may involve use of new kinds of production equipment or use of the same equipment in different ways to accommodate larger batch processing. These changes may significantly affect important chemical and physical properties of the drug, including the drug's content uniformity, hardness, moisture content, and dissolution. Utimately these sorts of changes can affect a drug's bioavailability and be of clinical significance.

53. One comment recommended that sponsors be required to provide information on the composition, manufacture, and control of any placebo used in a controlled clinical trial, including information demonstrating that the placebo is identical to the drug under study in all respects other than the presence of the active drug substance. The comment contended that the validity of a blinded study depends in part on the placebo being perceived as identical to the drug under study.

FDA agrees that information on placebos is needed to assure that the blinded nature of a study is not compromised by the failure of a placebo to mimic the odor, taste, texture, and other physical characteristics of the investigational drug. FDA has requested such information for a number of years.

In response to this comment, the agency has revised the final rule to require a brief, general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial. The agency, however, is not requiring a demonstration that, but for the presence of the active drug substance, the placebo is "identical in all respects" to the drug under study. This is because exact duplication of the investigational drug may not be possible. For example, the use of a coloring agent or an inactive bitter flavoring may be required to mimic characteristics of the drug substance so that the placebo will be perceived as identical to the drug under study.

54. As proposed, the rule would permit reference to the United States Pharmacopeia—National Formulary to satisfy relevant portions of the chemistry section. One comment noted that compendial requirements may in some cases not meet FDA's requirements. The comment urged that the rule make clear that in some circumstances reference to the formularies may not satisfy relevant requirements of the chemistry provisions.

As noted in the preamble to the NDA Rewrite final rule (50 FR 7459), although the agency believes that references to the official compendia may be relied on under proper circumstances to provide the required information, new developments in drug synthesis and advances in analytical technology may introduce new concerns about the chemistry of drug substances that are not adequately addressed by current compendial monographs. In those cases, FDA may need additional information about a drug substance to ensure that additives or byproducts of the synthetic process are properly controlled. Although a reference to official compendia will often satisfy the requirements, the final rule has been revised to indicate that FDA may require additional information to permit proper review of the application.

55. One comment claimed that the information on manufacturing facilities submitted in the IND in accordance with proposed § 312.23(a)(6) would be inadequate to determine whether the applicable IND termination provisions should be invoked, i.e., whether the facilities used for the manufacturing, processing, and packing of the investigational drug are adequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety.

FDA believes that the information required in § 312.23(a)(6) should ordinarily be adequate to determine whether the drug's manufacture and control may compromise subject safety. The required information includes descriptions both of the general method of preparation of the drug substance (§ 312.23(a)(7)(iv)(*a*)) and of the method of manufacturing and packaging of the drug product (§ 312.23(a)(7)(iv)(*b*)). If additional information is needed on the manufacture and control of the drug, FDA can either request the sponsor to submit the information, or under certain circumstances, can inspect the manufacturing site to determine compliance with applicable current good manufacturing practice (21 CFR Part 211).

56. One comment suggested using the word "strength" instead of "potency" in § 312.23(a)(7)(iv)(*a*) to be consistent with the language of 21 CFR Part 211.

FDA agrees and has revised the final rule accordingly.

Pharmacology and Toxicology Information (§ 312.23(a)(8))

57. The proposed pharmacology and drug disposition section would require information describing the pharmacological effects and mechanisms of action of the drug in animals and information on the absorption, distribution, metabolism, and excretion of the drug. One comment asked whether the information on the absorption, distribution, metabolism, and excretion of the drug required under proposed § 312.23(a)(8)(i) should, like the information on pharmacological effects, also be based on animal studies.

The pharmacology and toxicology section (§ 312.23(a)(8)) refers principally to data derived from animal studies, but could include human data for comparison, if available. Therefore, FDA expects that any information in the initial IND submission on the absorption, distribution, metabolism, and excretion of the drug will be derived from animal studies of the drug. As information is obtained on the pharmacokinetics of the drug in humans, the agency would expect such information to be reflected in the investigator brochure (§ 312.23(a)(5) (ii) and (iii)) and reported, as appropriate, in information amendments and annual reports.

58. Proposed § 312.23(a)(8)(ii)(*b*) would require the submission of full tabulations of data suitable for detailed review for each toxicology study that is intended primarily to support the safety of the proposed clinical investigation. Many comments objected to the requirement that full toxicological data be submitted. Several comments contended that this requirement is inconsistent with the principle that data in the IND should normally be submitted in summary form. Other comments expressed the belief that full data are not necessary in order to achieve the objective of assuring subject safety, arguing that the safety of subjects can be adequately protected by requiring submission of a summary in sufficient detail to permit scientific review, and allowing FDA access to full data when necessary.

FDA believes that, as a general rule, full tabulations of data from subacute and chronic studies and other studies intended primarily to support safety are crucial in permitting their scientific review. The agency has found that summaries, by heavy reliance on statistical averaging of data, may not reveal the actual magnitude of response

in some animals and do not provide for comparing the spectrum of responses in any one animal. Summaries, while helpful adjuncts to the pharmacological and toxicological review process, cannot substitute for full tabulations in providing adequate insight into the extent and course of drug effects in individual test animals.

Because FDA believes that full tabulations of such data are necessary in every case for an adequate review of the safety of proposed studies, it sees no merit in a procedure that would permit reviewers to obtain detailed information only on request. Such a procedure would likely only serve to delay the review process.

59. One comment asked for clarification of the meaning of "full tabulations" of toxicological data. The comment stated that it would object to a requirement that every data point collected in a study be tabulated, suggesting that such a requirement would create an unwarranted burden.

This section is intended to continue current practices with respect to submission of individual animal data. Thus, applicants are not required to submit laboratory notebooks, worksheets, and other documents relating to individual animals. However, the agency does expect the full tabulations to include every significant recorded observation, pathology finding, and laboratory measurement that relates to a scientific evaluation of the drug's safety for its proposed investigational use. This would ordinarily include all notable periodically measured toxic signs, as well as blood values, electrocardiograms, and any other measurements or observations that would contribute to the evaluation of the drug's toxic potential.

60. Several comments urged the adoption of specific pharmacological and toxicological testing requirements. Thus, for example, one comment urged that the regulation clearly require sponsors to test drugs that have not previously been tested in human subjects in at least two animal species prior to the commencement of clinical trials.

As noted above, the regulation is intended to describe in general terms an appropriate format and content for the initial IND submission. Because of the dynamism and complexity of the scientific issues involved, the agency does not believe that it would be either feasible or wise to specify in the regulation detailed, substantive pharmacology and toxicology testing requirements. Current FDA guidelines do specify the type of animal studies needed for new drug substances before commencement of human studies, and the agency is developing, and will soon make publicly available, an updated guideline that will outline the scope of animal testing submissions for the more common and expected circumstances.

Previous Human Experience with the Investigational Drug (§ 312.23(a)(9))

61. Section 312.23(a)(9)(iii) requires the sponsor to list the foreign countries in which the investigational drug has been marketed as well as those countries in which the drug has been withdrawn from the market for any reason relating to safety or effectiveness. One comment urged that this responsibility be limited to experience with the sponsor's own drug as "it may not be feasible for a sponsor to be fully aware of all actions taken by all firms worldwide."

FDA believes that it is not unreasonable to expect a commercial drug firm to make a good faith effort to determine the foreign marketing experience of a drug it seeks to market in the United States. Given the potential hazardous consequences that may follow from the use of unsafe or ineffective drugs, FDA would expect commercial sponsors to obtain the information for their own benefit, apart from regulatory requirements. Much of this information should already be available to the sponsor as a result of patent searches or other routine business practices. Because additional information on foreign marketing is readily obtainable through trade journals available in the United States, a comprehensive review of the pertinent information should not be unduly burdensome to the sponsor.

62. Proposed § 312.23(a)(9)(i) would require that any published material relevant to an assessment of the drug's safety and effectiveness be provided in full. One comment claimed that this requirement is inconsistent with the general principle that the sponsor should provide a summary of previous human experience. The comment argued that it would be possible to provide relevant information on a number of similar studies in a single narrative summary and that such a summary of the available literature would provide all the information the agency would need. One comment claimed, moreover, that a requirement for all literature could result in voluminous submissions under certain circumstances, especially if a sponsor were testing a combination product in which one component is a well-established drug.

The agency believes that some of these comments may have misinterpreted the proposed provision the purpose of which is to give agency reviewers easy access to those reports in the scientific literature that are most directly relevant to the safety and effectiveness of the drug for its proposed use. Reports of greatest relevance would include, for example, reports of the most serious or frequent drug-associated adverse reactions, reports of critical dose-response information, as well as reports of the results of controlled clinical trials. Publications from the scientific literature less directly relevant or exclusively relevant to other indications for use need not be submitted, although they should be included in the sponsor's bibliography. Thus, for example, a sponsor studying aspirin to reduce the risk of stroke would not be expected to submit to FDA studies relevant only to the drug's analgesic effects.

If a sponsor were testing a combination drug in which one of the components had already been lawfully marketed in the United States, the sponsor would not need to submit all the literature on the component's marketed use, but only publications of direct relevance to the proposed use (including publications relevant to component-component interactions). FDA has revised the final rule in § 312.23(a)(9)(ii) to make this requirement explicit.

For the reasons given, the agency does not believe that the provision should ordinarily be unduly burdensome or result in the submission of excessive numbers of publications from the scientific literature. Of course, if a sponsor is concerned about the extent of published literature to be submitted in a particular instance, the agency would be willing to discuss the issue with the sponsor in advance of the submission.

63. One comment stated that providing information for each component of a combination product the components of which have been previously investigated or marketed, is reasonable only if the requirement is understood to relate to the active drug components.

FDA agrees and has revised § 312.23(a)(9)(ii) accordingly.

Drug Dependence and Abuse Potential (§ 312.23(a)(10)(i))

64. Proposed § 312.23(a)(10) would require a sponsor of a drug with abuse potential to provide a description of "relevant clinical studies and experience and studies in test animals." One comment asked that this section be clarified to require that such information be supplied only if it is available and only for the later phases of a clinical investigation.

The comment misunderstands the intended function of this section, which is simply to establish a place in the IND for a sponsor to compile and present available information on the dependence or abuse potential of its drug. The provision does not establish substantive requirements with respect to clinical studies. Guidance on these substantive matters can be obtained from the published clinical guidelines issued by FDA and from the agency's scientific review divisions.

Material in a Foreign Language (§ 312.23(c))

65. One comment objected to the requirement that the sponsor submit a copy of each original literature publication for which an English translation is also submitted. The comment claimed that this requirement is of questionable value and is inconsistent with the principles of the Paperwork Reduction Act. The comment suggested deleting the requirement for routine submission and replacing it with a requirement that foreign language materials be made available to FDA on request.

FDA believes that it is reasonable to ask an applicant who relies upon a publication in a foreign language to submit both the foreign publication and an English translation of it. FDA believes it is under some obligation to verify the bases of documents it receives only in translation, and views sponsors' furnishing to FDA of the non-English original as the least burdensome method by which verification can be accomplished.

Protocol Amendments (§ 312.30)

66. One comment suggested that, to speed early clinical research, sponsors should not have to submit protocol amendments: (1) For modifications of a clinical pharmacology research protocol made on the basis of experience gained in the investigation; (2) for continuation of a human subject from Phase 1 to the subsequent phases of the investigation; or (3) in situations where the investigator concludes that immediate action is necessary to reduce or eliminate an apparent immediate hazard to a subject.

The final rule, like the proposal, does not require a sponsor to submit a protocol amendment for a change in a Phase I protocol that may affect the scope or scientific quality of an investigation, if it does not significantly affect the safety of subjects. Therefore, to the extent that a modification to a clinical pharmacology (Phase 1) protocol does not raise significant safety issues, it would not have to be reported in a protocol amendment. In addition, the protocol amendment provisions do not require a sponsor to file an amendment to continue a subject from one phase of the study to the next, assuming a protocol is in effect for the subsequent phase that covers administration of the investigational drug to that subject.

Finally, as noted in response to paragraph 69 below, FDA has revised the final rule to state that a sponsor may change a protocol to eliminate an apparent immediate hazard to a subject, provided FDA is subsequently notified of the action. The agency believes this clarification of the requirement meets the concerns of the comment.

67. As proposed, protocol changes that would require a protocol amendment under § 312.30(b) may only be implemented after the sponsor has submitted "the amendment to the IND following completion of review of the change by the IRB that is responsible for review and approval of the study." Several comments read this requirement as obliging the sponsor to ensure that an IRB reviewed and approved the change before submitting it in a protocol amendment to FDA.

FDA has revised § 312.30(b) to clarify that IRB review and approval may be obtained before or after submission of the protocol amendment to FDA, provided the sponsor and investigator ensure that the change that is the subject of the amendment is not begun until IRB review and approval has been obtained.

68. One comment argued that the rationale for requiring submission of a protocol amendment to report the addition of a new test or procedure to monitor for side effects or adverse events is unclear, since any effect of such action would be a positive one, increasing the safety precautions afforded the subject. The comment suggested that comparable considerations dictated that changes to enhance the scientific quality of studies should also not require a protocol amendment.

The purpose of a protocol amendment is to give the agency timely notice concerning the kinds of changes that bear directly on its review and monitoring responsibilities. The agency believes it is responsible for making an independent review of significant protocol changes even when their intended effect is to increase the safety of subjects. In this context, it should be noted that submission of a protocol amendment to FDA does not delay implementation of the change described in the amendment.

69. One comment noted that, for protocol changes designed to reduce the risks of injury, any delay in undertaking the change caused by the need to submit the change to FDA or to obtain IRB approval might jeopardize subject safety. The comments suggested that prior notification to FDA and prior approval by IRB's not be required for changes designed to eliminate hazards to study subjects.

The agency agrees that a protocol change intended to eliminate an apparent immediate hazard to human subjects should not be delayed because of a need to notify FDA or the reviewing IRB. FDA has revised final § 312.30(b)(2)(ii) to permit such changes, provided FDA and the reviewing IRB are subsequently notified.

70. One comment asked the agency to clarify a sponsor's responsibilities with respect to protocol changes that would not require submission of a protocol amendment, including, for example, a Phase 1 change that does not significantly affect subject safety.

The sponsor's responsibility depends on the nature of the change. Changes that are not required to be reported in a protocol amendment may still be reportable under another section of these regulations, or under the regulations governing review of marketing applications (Part 314). Thus, for example, a change in the scope of a Phase 1 investigation may not require a protocol amendment but should be reported in the next annual report in accordance with § 312.33(b). Other changes—minor modifications of a study design, for example—may not be reportable until the study is submitted in a marketing application, where it would be reported as part of the application under § 314.50(d)(5).

Finally, it should be noted that investigators may be required under § 56.109 to report to reviewing IRB's some protocol changes that are made during Phase 1 even though such changes need not be reported to FDA under these protocol amendment requirements.

71. Several comments expressed support for the provision in § 312.30(c) that would require a sponsor to notify FDA within 30 days of adding an investigator, but asked that the final rule make clear that a sponsor may ship an investigational drug to a new investigator at the time that the investigator is added by the sponsor to the study, and that the newly added investigator may begin his or her participation in the study prior to submission of the protocol amendment, so long as the amendment is submitted within 30 days of the commencement of the investigator's participation.

FDA has revised § 312.30(c) to make clear that, once the sponsor has added an investigator to a previously submitted study, the investigator may begin participation in the study. Notification to FDA is required within the next 30 days.

72. Several comments read § 312.30(d)(1)(i) as requiring a sponsor to describe in detail the differences between the new and the old protocols. The comments claimed that this provision would impose significant burdens without corresponding benefits. One comment claimed there are many cases where detailed explanations would not be needed. Finally, one comment suggested that, if a requirement to explain protocol changes is retained at all, a sponsor should only be required to highlight significant changes from previous protocols.

Proposed § 312.30(d)(1)(i) was not intended to require detailed explanations of the differences between old and new protocols. In fact, a detailed and undiscriminating enumeration of the differences would defeat the purpose of this requirement, which is to identify the most important differences between the old and new protocols and to alert FDA reviewers to major changes that may require additional supportive data, such as changes in dose, route of administration, or indication. What is expected is that the sponsor will briefly highlight the most clinically significant features of the new protocol, such as an increase in dose or duration of treatment, or a change in patient population. To clarify agency intent, FDA has revised § 312.30(d)(1)(i) to require, for each new protocol, a brief description of the most clinically significant differences between it and previous protocols. As so modified, the highlighting of the changes should not be a significant burden on sponsors, and will be of considerable help to FDA in directing reviewers' attention to the parts of a protocol most in need of scrutiny.

73. One comment asked for clarification of a sponsor's responsibilities when a new investigator is added to conduct a previously submitted protocol. The comment stated its assumption that FDA would still want all the information that is currently required, including a copy of the protocol itself.

In this situation, the agency does not believe a copy of the previously submitted protocol is necessary, if the protocol is adequately identified in the protocol amendment. However, FDA would expect the sponsor to submit the same information about the individual investigator that would be required if the investigator had been named at the time the protocol was initially submitted. These items of information are listed in § 312.23(a)(6)(iii)(*b*) and include, in addition to the investigator's name and qualifications, the name of each subinvestigator, the name and address of the research facilities, and the name and address of the reviewing IRB. FDA has revised § 312.30(d)(1)(iii) to clarify this requirement.

74. Several comments addressed the requirement in § 312.30(d)(2) that the sponsor reference in the protocol amendment the specific information relied upon to support the new protocol or protocol change. The comments claimed that the provision is overly broad and may be read to require extensive cross-referencing to virtually all data in support of every new protocol or protocol change. One comment urged that the section be deleted, claiming that, under most circumstances, new protocols or protocol changes rely not on specific information but rather are based upon the totality of the experience derived from earlier or ongoing clinical trials. Another comment suggested that the final rule be revised to require references only to specific information in support of significant differences in new protocols or in support of significant protocol changes.

In one sense, FDA agrees that every new protocol and protocol change relies ultimately upon the totality of previously submitted information. The intent of the provision, however, is to elicit reference to the specific technical information supporting the clinically significant aspects of the proposed change. Thus, if a sponsor intends to change the dosage form of the investigational drug, appropriate chemistry and manufacturing information supporting this change should be referenced. Or, if a sponsor proposes to increase significantly the duration of patient exposure to the drug, the sponsor should reference the appropriate animal tests that would support this increased human exposure. To the extent that FDA is apprised of the basis for a change in a protocol, it can more quickly and comprehensively review the change. Of course, if the change is one that plainly does not require specific technical support, the sponsor would not be expected to reference any supporting technical information. FDA has revised § 312.30(d)(2) accordingly.

75. Several comments complained that the agency had not justified the use of serial numbering of protocol amendments and expressed doubt about the utility of this policy. One comment claimed that serial numbering will make tracking more difficult than under the current system, and recommended that an attempt be made to develop a numbering system that will provide for easy access to individual protocols and investigators. The comment suggested that it may be possible, for example, to use prefixes or suffixes to identify the protocol of an investigator to which a specific protocol amendment applies.

As noted in the preamble to the proposal, the formatting requirements for amendments, including the requirements for serial numbering of amendments, are intended to make these submissions easier for FDA to process and review. Deficiencies in formatting have frequently produced a disorderly and sometimes unintelligible flow of amendments and other documents to the IND file. The changes are designed to rationalize this flow of information to permit agency reviewers to gain an understanding of the significance of amendments and their relationship to one another. The changes should also help reviewers determine the completeness of amendments to an IND.

While the agency does not believe that sequential numbering of amendments will somehow make tracking more difficult, FDA agrees with the comment that an identification method that separates protocol changes and new protocols from new investigators might be preferable to a simpler system. The final rule does not mandate the use of a particular method of serial numbering, and so individual sponsors are not precluded from adopting a more complex system. FDA would be happy to work with sponsors in developing a system of maximum usefulness.

76. Section 312.30(d)(3) specifies that if a sponsor desires FDA to comment on a protocol amendment submission, the protocol amendment should so indicate and should include the specific questions FDA should address. One comment suggested that FDA should be obliged to respond within 15 days to a sponsor's request to avoid impeding the progress of the investigation and to avoid the imposition of clinical holds due to deficiencies in a proposed protocol.

Because protocol amendments do not require prior agency approval before implementation, the lack of an agency response should not, in itself, impede the progress of an investigation. Nevertheless, FDA understands the importance of conscientiously reviewing and responding to sponsor requests for assistance, and will respond as quickly as is allowed by the complexity of the

questions, the availability of agency reviewers, and the demands of other priority matters.

Information Amendments (§ 312.31)

77. One comment recommended that proposed § 312.31(b) be revised to define what discipline categories should be used when information amendments are "numbered serially" by discipline.

FDA has revised § 312.31(b) to add examples of appropriate headings for information amendments.

IND Safety Reports (§ 312.32)

What is Reportable?

78. A number of comments expressed confusion about what would be reportable in an IND safety report. As proposed, § 312.32 would require a sponsor to report "Any serious adverse experiences or other information * * * not previously reported (in nature, severity, or incidence) that may suggest significant hazards, contraindications, side-effects, or precautions." One comment asked that the agency define the term "serious adverse experience." Other comments asked that the agency clarify the meaning of "not previously reported (in nature, severity, or incidence)." One comment suggested that the parenthetical phrase was unnecessary and should be deleted. Another comment argued that the severity or incidence of an adverse experience is more appropriately the basis for adverse reaction reporting of marketed drugs than it is for investigational drugs. That comment contended that the appropriate basis for adverse reaction reporting in the IND process should be whether an event is "alarming," alarming being defined as any event requiring the discontinuation of an IND.

FDA agrees that it will be useful to provide additional guidance on what information should be reported in an IND safety report. The goal of the safety report section is to ensure timely communication of the most important new information about experiences with the investigational drug. To better achieve that goal, FDA has revised the safety report requirement to require reporting of any "adverse experience associated with the use of the drug that is both serious and unexpected." To clarify further a sponsor's reporting obligation, the agency has further revised the final rule to codify definitions of "serious adverse experience" and "unexpected adverse experience."

Serious Adverse Experience

Under this final rule, "serious adverse experience" is defined to mean any experience that "suggests a significant hazard, contraindication, side effect, or precaution." The definition distinguishes human (clinical) experiences from drug-related experiences in laboratory animals. "Serious adverse experience," as it applies to human experience, is defined as any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. (This definition is identical to a proposed revision of the definition of "serious" adverse drug experience for purposes of postmarketing reporting of adverse drug experiences published in the **Federal Register** of December 30, 1986 (51 FR 47028).) In contrast, with regard to results obtained from tests in laboratory test animals, a serious adverse drug experience includes any experience suggesting a significant risk for human subjects, including any finding of mutagenicity, teratogenicity, or carcinogenicity.

The language "suggests a significant hazard, contraindication, side effect, or precaution" is taken directly from the current IND regulations, § 312.1(a)(6), and the IND proposal, § 312.32(b). Thus, the underlying standard for determining what is a serious adverse drug experience has remained constant over time. The additional examples of serious human adverse drug experience are taken from the NDA Rewrite final rule, § 314.80 (50 FR 7500), pertaining to reports for marketed drugs. These examples have been added in order to clarify the underlying standard and to provide continuity in reporting between the investigational and marketing stages.

Unexpected Adverse Experience

In proposing to require a sponsor to report adverse experiences "not previously reported (in nature, severity, or incidence)," FDA intended to ensure the timely communication of the most important new information about the drug. However, the agency has concluded that the "not previously reported" language is unsatisfactory in that it might be read as limiting safety reports to the first case of a particular adverse experience. This was not intended. While the report of the first case of an adverse experience may indeed be the most useful one in terms of alerting FDA to a potential safety problem, reports on the first case are usually not adequate to determine whether or not an experience is truly drug related, to evaluate its likely frequency, and otherwise to assess the significance of the risk posed. To avoid any possible misinterpretation of agency intent and to ensure continued reporting of cases of a serious adverse experience until the risk posed is reasonalby well characterized and understood, the agency has deleted the "not previously reported" phrase, and substituted for it a requirement that sponsors report "unexpected" experiences.

The final rule defines an "unexpected adverse experience" to mean any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure for the study. For those IND's for which an investigator brochure is not required (i.e., IND's conducted by sponsor-investigators), an unexpected adverse experience would include any experience that is not identified in nature, severity, or frequency in the "risks" information contained in the current application. This definition is analogous to that used in the NDA Rewrite for reporting adverse drug experiences on marketed drugs, where the term "unexpected" is defined as any serious adverse experience outside of the drug's approved labeling (see § 314.80(a); 50 FR 7500; February 22, 1985). Under the final rule, therefore, a serious adverse reaction that had been reported previously could still be unexpected.

To increase assurance that the significance of safety information will be placed in proper context, the final rule also requires that the sponsor identify all safety reports previously submitted by the sponsor concerning a similar adverse experience, and analyze the significance of the adverse experience in light of all previous similar safety reports.

Finally, FDA disagrees with those comments that suggest that it is inappropriate to base IND safety reporting on adverse experience severity or incidence. A study under an IND is allowed to proceed in part on the basis of the sponsor's characterization of the risks posed by the investigational drug. This characterization, usually described in some detail in the investigator brochure and elsewhere in the IND, is based primarily on the clinical and nonclinical experiences with the drug available at the time studies under the IND begin. As additional experience with the drug is obtained that either suggests new risks or casts previously identified risks in a new light, it is essential to FDA's safety monitoring responsibilities that the agency be promptly apprised of such information.

79. Under the final rule, a sponsor would be required to report each successive case of a serious and unexpected adverse experience until the risk posed by the experience is sufficiently well understood to be described in the investigator brochure or until an equally satisfactory resolution of the issue is reached (for example, a determination that the experience is not drug related). Ordinarily, reports of succeeding cases would, like the report of the first case, be submitted in IND safety reports as soon as possible and in no event later than 10 working days after the sponsor's initial receipt of the information. However, in some situations it may be desirable for the sponsor to "group" such cases at some different frequency, or to report such cases in a format not conventionally used for reporting a single case. Therefore, the agency has revised the final rule to authorize FDA to require a sponsor to submt safety reports in a format or at a frequency different than that normally required (§ 312.32(c)(3)). Section 312.32(c)(3) also permits the sponsor to propose and adopt an alternative reporting arrangement, if the alternative is agreed to by the director of the division of FDA's Center for Drugs and Biologics responsible for review of the IND.

Review Requirements

80. Several comments objected to the proposed requirement in proposed § 312.32(a) (now § 312.32(b)) that a sponsor "immediately" review all information relevant to the safety of the drug. One comment contended that the immediate review requirement was unrealistic, given that a sponsor may receive hundreds of medical journals within a short period of time, not all of which can be reviewed "immediately," and some of which may require translation into English.

FDA expects a sponsor to review all information it receives that may be relevant to the safety of its investigational drug in sufficient time to meet its reporting obligations. However, as noted below, FDA has deleted the proposed 3-working-day time frame for written reports of fatal or life-threatening experiences and has established a uniform, 10-working-day time frame for all written reports of serious and unexpected adverse experiences. (As noted below, sponsors are still required to give FDA an "early warning" by telephone of any information obtained from the sponsor's own clinical studies suggesting an unexpected fatal or life-threatening experience no later than 3 working days after receipt of the information.) This means, in effect, that sponsors who would have had no more than 3 working days to review and report safety information under the proposal will now have up to 10 days to complete their review and submit required reports. In light of this change, the agency believes a "prompt review" requirement is a more accurate characterization of a sponsor's reporting obligation and has revised § 312.32(b) accordingly.

81. One comment asked that FDA clarify when it would impute to a large, multi-national corporation knowledge of an adverse event gained by one of its employees. In particular, the comment wanted to know when FDA would deem a parent company to have "received" a report in a medical journal obtained by an employee of one of the parent company's subsidiaries.

FDA expects drug companies to review those reports that come to its attention in the normal course of business. Whether an employee's knowledge of a report of an adverse experience would be imputed to the sponsor will depend upon the factors surrounding the employee's knowledge of the report. As a general rule, however, FDA will consider a drug firm responsible for information known to its employees (including the employees of a division or separately incorporated subsidiary of the firm), and companies should adopt procedures to ensure that employees will expeditiously bring important information to the attention of company officials.

82. Several comments objected to the requirement that sponsors review and report in safety reports information about "related drugs." Suggesting that the term might be variously construed to include drugs with related chemical structures, drugs of the same pharmacological class, and drugs with the same intended therapeutic use, the comments criticized the term as vague and potentially subject to an overbroad interpretation. One comment complained that the provision would impose a greater reporting burden on IND sponsors than that imposed on holders of approved marketing applications.

The agency agrees that the category of "related drugs" may be overbroad, and that a requirement based on that category might well elicit much information of little relevance or value to FDA's safety evaluation of a particular investigational drug. Therefore, the agency has deleted the requirement that expressly calls for sponsors to report in safety reports information about related drugs. As revised, the regulation limits safety reports to those experiences that are associated with use of the particular investigational drug under study. This revision is not intended to suggest that safety information about related drugs is never important to evaluating the safety of an investigational drug. Indeed, a drug firm developing a new member of a structurally related class of drugs should monitor clinical reports on other members of that class. FDA's experience is that sponsors frequently do report to FDA significant and relevant safety information about such related drugs, and FDA strongly encourages continued reporting of this information to FDA in information amendments or annual reports.

Reporting Time Frames

83. FDA received a considerable number of comments concerning the proposed time frames for reporting IND safety reports. The proposal would have required the sponsor to submit a safety report to FDA no later than 3 working days after receiving information on a fatal or life-threatening experience, and no later than 10 working days after receiving information on any other serious adverse experience. Although most comments agreed on the need for timely reporting of adverse experiences, many contended that the reporting provisions, especially the 3-working-day time frame for fatal and life-threatening experiences, would not give sponsors enough time to review and assess the significance of safety information and would result in the submission of incomplete or misleading information. To remedy these perceived problems, several comments suggested giving sponsors up to 15 days from date of receipt of the initial safety information to make a safety report. Alternatively, other comments recommended that the reporting obligation run from the time that a sponsor received the "essential information" on the experience, or from the time the sponsor determined an event was drug related, rather than from the date of receipt of the initial, perhaps fragmentary, report of the experience. Finally, several comments suggested that safety information derived from foreign experience with investigational drugs should be reported less frequently than other safety information—one comment recommended 3-month intervals—because of the need for translation and because of the greater problems in investigating such experiences.

FDA has carefully considered these comments and has concluded that 3 working days may not be sufficient time to determine whether a death or life-

threatening experience should be reported in a written IND safety report under § 312.32(c). Therefore, FDA has revised the final rule to require that all serious, unexpected adverse drug experiences be reported in a written IND safety report to FDA as soon as possible and in no event later than 10 working days after the sponsor's initial receipt of the information. FDA believes that this change will ensure timely communication of the most important safety information, while giving sponsors a reasonable amount of time to review incoming safety information, to identify reportable information, and to prepare and transmit to FDA complete and accurate safety reports. Although FDA has changed the proposed 3-working-day reporting time for written reports of fatal and life-threatening experiences to 10 working days in order to improve the quality of the reports received (and therefore the likelihood that FDA would have sufficient data to take action, if necessary), FDA emphasizes that such information is required to be submitted "as soon as possible" in order to protect patient safety. Moreover, as described below, sponsors are also required to notify FDA by telephone of an unexpected fatal and life-threatening adverse experience, in advance of the written notification, to provide an early warning that a potential problem exists.

FDA does not agree with those comments that suggest that the reporting obligation should run from the time that the "essential" information on the event is collected as such a provision might unduly delay reporting of vital information. However, FDA understands that 10 working days may not be sufficient time in every case to determine conclusively whether the factors triggering a report under § 312.32(c) are present, i.e., for determining that an adverse event reported to the sponsor is associated with use of the drug and that the event may suggest a significant hazard, contraindication, side effect, or precaution. In those cases in which the sponsor's initial information may not be conclusive, FDA advises the sponsor to err on the side of caution, to submit the preliminary information, and to follow up this initial report with whatever more definitive information is subsequently obtained.

Finally, FDA declines to adopt a different time frame for reporting foreign safety information than the 10-working-day time frame adopted for all other safety information. As the relevance and importance of safety information should usually not depend on the source of the information, FDA concludes that an exception should not be made for foreign experiences.

84. The final rule requires the sponsor to report a serious and unexpected adverse experience if the experience is "associated with the use of the drug." The proposal defined this phrase to mean that "there is a reasonable possibility that the event may have been caused by the drug." One comment suggested that requiring a sponsor to determine whether an event was possibly caused by the drug introduced a new concept to adverse reaction reporting. Although supporting the concept, the comment suggested that a determination about diverse event causality would require more time than the proposal allowed.

FDA rejects this comment as it believes that 10 working days allowed under this final rule should generally be adequate time to make the required determination. Moreover, FDA does not regard the cited requirement as representing a significant departure from current requirements. Under the current regulation, the sponsor is required to report "any finding associated with the use of the drug that may suggest significant hazards, contraindications, side effects, and precautions pertinent to safety * * *." Implicit in this requirement is an expectation that the sponsor will report events that the sponsor believes may have been caused by the drug. The revision simply makes this expectation explicit. To the extent that assessing the causation of an adverse experience is considered a close call, FDA advises the sponsor to err on the side of reporting.

Telephone Call Requirement

85. A number of comments objected to the proposed requirement that sponsors transmit each IND safety report by telephone at the same time as a written safety report is submitted. Comments criticized the requirements as being unnecessarily burdensome on both FDA and sponsors. Several objected specifically to the proposed requirement that the sponsor contact each investigator by phone, one comment noting that there may be over 100 investigators in a single investigation. Another comment argued that telephone notification served no useful purpose because the same information conveyed by telephone would also be concurrently submitted in a written report prominently identified as an "IND safety report."

Those comments that did not urge rescinding the requirements in its entirety recommended scaling it back significantly. One comment suggested that telephone reporting should be required only when an adverse event is so alarming that the sponsor elects to discontinue the study. Other comments recommended that sponsors not be required to telephone investigators at all, or that the sponsor only be required to telephone investigators concerning the most significant new safety information.

FDA has revised § 312.32(c)(2) to limit the telephone call requirement to adverse experiences that are obtained from the sponsor's own clinical studies that suggest an unexpected fatal or life-threatening experience associated with use of the drug. The information would be required to be relayed by telephone only to the agency unless FDA also requests the sponsor to telephone all investigators. The change should ensure that a sponsor's reporting obligations are no greater than necessary for the timely communication of the most urgent safety information. Because drug-related deaths or life-threatening experiences are relatively rare occurrences during a clinical trial, the change should also keep the amount of information transmitted by telephone to a manageable level.

FDA emphasizes that the 3-day telephone alert is reserved for the most urgent circumstances. Thus, for purposes of this section, the term "life-threatening" means that the patient was, in the view of the investigator, at *immediate* risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening in this context even though drug-induced hepatitis can be fatal.

86. Two comments mistakenly interpreted the proposal as requiring IND safety reports for experiences that occur due to the natural course of the disease being treated.

As noted in the proposal, only adverse experiences "associated with the use of the drug" need be reported, i.e., those events for which there is a reasonable possibility that the event may have been caused by the drug. A death due to the natural course of a disease would not meet this criterion and thus would not have to be reported in an IND safety report. Such deaths, however, would be reported in the annual report. See § 312.33(b)(3).

Safety Report Format

87. One comment noted that the proposal did not specify a reporting

format for IND safety reports and suggested that the form used to report experiences with marketed drugs—the Form FDA–1639—be used.

This final rule does not prescribe the use of any specific format for reporting safety information. However, the agency notes that the one page form FDA–1639 is designed primarily as a means to permit individual physicians to make "spontaneous" reports concerning adverse drug reactions in patients under their care. The form is clearly inappropriate for reporting in a safety report information about animal tests. It is also in most cases not an appropriate means of transmitting information about human clinical experience during a clinical investigation, as more extensive information on individual adverse experiences is needed than can ordinarily be included in a one page report. Generally, while the kinds of data entries required in a FDA–1639 report for a marketed drug are also appropriate for reporting adverse experiences in IND safety reports, more detailed reporting is desirable, particularly for reporting clinical adverse experiences from Phase 1 and 2 studies. While FDA does not encourage use of the form, FDA believes the Form FDA–1639 may in some cases be acceptable for submitting IND safety reports about human clinical experiences during Phase 3 studies and would be happy to discuss use of the form with individual sponsors.

IND Study of a Marketed Drug

88. One comment urged that the regulations specify whether, when a marketed drug is used in a clinical study under and IND, an adverse experience associated with use of that drug product should be reported to the division in FDA's Center for Drugs and Biologics which is responsible for monitoring adverse reactions for marketed drugs or to the IND. The comment suggested that the adverse experience should be reported to only one application with appropriate cross-reference filed in the other application.

As a general rule, FDA agrees that adverse experiences associated with use of a drug that is subject to both an investigational new drug application and a marketing application need not be reported to both. Accordingly, the agency has in this final rule limited IND safety reporting for clinical studies of marketed drugs to those adverse experiences associated with the clinical study itself. Adverse experiences that originate from outside the clinical study (including, for example, "spontaneous" reports submitted to the drug firm by individual practitioners) need not be reported to the IND file provided such experiences are reported to the marketing application file in accordance with the applicable NDA regulations (21 CFR 314.80).

Followup Reports

89. Several comments addressed the issue of followup reports. One comment, noting that the regulation would require the sponsor to investigate all safety information received by it, asked FDA to clarify what level or degree of investigation would be required for various sources of safety information including, for example, clinical experiences in studies conducted under the IND, reports from the scientific literature, and reports on foreign experiences with the drug.

Regardless of the source of the safety information, FDA expects a sponsor to conduct as thorough an investigation as is feasible to interpret the adverse experience that is the basis for the initial safety report. Of course, some initial reports will require more followup than others. For example, reports of clinical experience in the sponsor's own IND studies or reports of formal clinical trials from the scientific literature might be sufficiently complete in themselves to require little, if any, followup. In contrast, a literature report of an adverse experience that does not tie the experience to an individual patient may require substantial followup. Reports of adverse experiences from foreign marketing experience may be sketchy or even uninterpretable, and a sponsor may be unable to obtain further information. Thus, the extent of followup will depend on the source of the safety information, on the amount of information already reported, and on the potential for obtaining additional useful information through diligent effort.

90. One comment urged FDA to require followup reports to be submitted within 60 days of the initial report (unless a shorter period is required by the agency for a specific adverse experience on grounds of safety), rather than "promptly" as had been proposed. Two comments suggested that the final rule be amended to require the submission of followup reports to IND safety reports "if needed."

Under the final rule, a sponsor is required to investigate all safety information received by it. Ordinarily, these investigations will not be completed within the time limit prescribed for the IND safety report. However, if such investigations are completed within the time frame prescribed, the sponsor should indicate this fact in the IND safety report. No further followup report would then be required. With respect to the suggested time period for the submission of followup reports to an IND safety report, FDA does not believe it should prescribe any specific time period, given the variety of experiences that may require followup. Therefore, the final rule will remain as proposed.

91. With respect to the provision requiring prompt reporting of "relevant information" in followup reports to an IND safety report, one comment asked FDA to clarify the term "relevant."

Determining the relevance of information is invariably a matter of judgment. In this case, relevant information is information that explains or clarifies the circumstances of the reported adverse experience. For example, each followup might include reports of autopsy findings or reports of the results of additional blood tests. FDA will provide additional guidance on followup on request.

91a. Finally, FDA has added a provision stating that a safety report submitted in accordance with these regulations does not necessarily reflect a conclusion by either the sponsor or FDA that the report constitutes an admission that the drug caused or contributed to an adverse experience. This "disclaimer" provision parallels similar provisions adopted in the NDA Rewrite (50 FR 7452; February 22, 1985) and in the medical device reporting regulation (49 FR 48272; December 12, 1984). The disclaimer provision was adopted in response to comments expressing concern about the legal liability consequences of reporting possible adverse experiences. FDA advises, as it has done previously, that although FDA does not intend for such a report to be viewed as an admission of liability, whether a court will treat a submission to FDA as an admission will depend on factors outside of the agency's control, such as the contents of the report.

Annual Reports (§ 312.33)

92. A number of comments asked that the agency give more detailed guidance on what information should be included in the annual report of an investigation's progress. In addition, comments were interested in knowing whether specifically identified items of information should be submitted in the annual report or in some other submission to the agency. For example, one comment, noting that there was no explicit mention in the annual report section regarding submission of reports from the scientific literature, asked whether such information should be reported in annual reports, safety

reports, or both. Along similar lines, several comments asked whether information on animal studies should be submitted in information amendments or in annual reports. Finally, one comment contended that the proposed annual report requirement for summaries of the previous year's clinical and nonclinical investigations was "unnecessary and burdensome," arguing that by the time the annual report was due such information would already have been reported to FDA in information amendments or other submissions.

FDA has carefully considered these comments and concludes that the submission requirements for annual reports, which are expressed in very general terms in the proposed rule, should be identified in the final rule in more detail. These changes, which are outlined below, should significantly increase the usefulness of these reports in providing both sponsors and FDA with insight into the status and progress of studies. The changes will also provide guidance to sponsors in determining whether information obtained during the course of the investigation should be submitted in information amendments or safety reports rather than in the annual report.

As proposed, § 312.33(a) called for a brief summary of the status of each of the clinical studies conducted (both those in progress and completed) during the past year, but did not specify the contents of such reports. To clarify this requirement, FDA has revised § 312.33 to require the sponsor to submit: (1) Brief "identifier" information for each study, and (2) a brief numerical analysis of patient exposure to the investigational drug in that study, i.e., the number of subjects planned for inclusion in the study, the number whose participation in the study was completed as planned, and the number who dropped out. The final rule also requires a brief description of the study outcome or interim results for each study—on a study-by-study basis—for which results are available. This should be a concise, one or two sentence statement of study results. For example, if the study made some important finding about pharmacokinetics, that should be so indicated. Likewise, if a placebo-controlled study distinguished or failed to distinguish between the investigational drug and the placebo, that too should be so stated.

In addition to these clarifications of the "status report" elements of the annual report, the final rule also elaborates on the proposed provision in § 312.33(b) requiring a brief summary of information obtained during the previous year's investigations. This section serves as a means to bring together data from individual studies and briefly communicate what was learned during the past year about the investigational drug's safety and effectiveness. The final rule specifically identifies five pieces of information to be included in the annual report relating to the clinical experience with the drug: (1) A summary showing the most frequent and most serious adverse experiences by body system; (2) a summary of the past year's safety reports; (3) a list of subjects who died during the past year; (4) a list of subjects who dropped out of clinical investigations during the past year; and (5) a brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions. Also, this provision requires a list of preclinical studies (including animal studies) completed or in progress during the past year and a summary of major preclinical findings. Finally, the sponsor is expected to submit a summary of any significant manufacturing or microbiological changes made during the past year.

The agency believes that there should be little overlap between the information submitted by the sponsor in information amendments, protocol amendments, or safety reports and information submitted in the annual report. As noted above, FDA expects annual reports in general to contain brief information summing up what was learned about the investigational drug during the past year. Annual reports thus provide a periodic overview of the investigation's progress. In contrast, amendment and safety reports contain specific information needed by the agency in determining whether to continue to allow the study to proceed.

93. Several comments recommended that the required lists of deaths and drop-outs include only deaths and drop-outs related to the safety of the investigational drug. One comment contended that to include nonsafety related deaths and drop-outs would require FDA's reviewers to sort through potentially long lists of subjects and extract from those the cases related to safety, and that this sorting process would create considerable work for both the sponsor and the agency without offsetting benefits. The comment recommended confining the lists of deaths and drop-outs to those subjects who suffered a drug-related adverse reaction and who were not previously identified in safety reports to FDA. Thus, according to the comment, every drug-related reaction would be submitted to FDA in either a safety report or an annual report.

Because of the difficulty of assessing the meaning of single adverse experiences—of determining, for example, whether the death of a subject in a study of a cardiovascular drug is due to the drug itself or to the natural course of the disease being treated—FDA believes it is important periodically to aggregate all such experiences, whether or not the individual events are thought to be drug related, for review and analysis. Such grouping may show an increased incidence of an adverse experience or other problem that would not be readily ascertainable in a review of single, discrete adverse experiences. Therefore, FDA believes that the list of deaths and drop-outs in the annual report should include all deaths or drop-outs, whether or not thought by the sponsor to be drug related.

94. Several comments objected to the requirement that the annual report contain an updated general investigational plan for the following year. One comment questioned the value of submitting in each annual report a wholly new description of the general investigational plan for the coming year. The comment claimed that it is difficult, if not impossible, to schedule clinical trials with precision and that artificial time frames like the "coming year" are, therefore, inappropriate. Another comment suggested that the requirement would increase the sponsor's burden in preparing annual reports and increase the amount of material that FDA must review. The comment recommended that the provision be revised to require only a description of significant changes in the investigational plan not covered by previously submitted amendments or other sections of the annual report.

As noted in the discussion of comments on the general investigational plan in paragraphs 39 through 41, FDA does not expect the general investigational plan to be a detailed description of future clinical studies, but rather a very brief summary of plans for clinical studies for the following year. As noted earlier, the purpose of the plan is simply to place individual studies within a larger context so that FDA reviewers are not operating in a vacuum. Moreover, the provision does not obligate the sponsor to invest resources into formulating plans that are not otherwise available; if at the time the sponsor submits the annual report, plans for the following year are not yet formulated, the sponsor need only so state in the submission. For these reasons, FDA believes the requirement

does not represent a significant burden and should be retained as proposed.

95. One comment asked whether, if the general investigational plan for the coming year is unchanged, the plan must be resubmitted.

FDA advises that if the plan for the following year is unchanged, the sponsor may simply refer to the previously submitted plan.

96. One comment asked whether the requirement for a brief summary of significant foreign marketing developments with the drug during the past year applied to the experience of other firms that may be marketing the same dosage form of the drug, or applied only to the sponsor's experience.

Reports of regulatory actions taken by foreign drug licensing authorities—such as license refusals, or withdrawals from the market for safety reasons—frequently signal potential problems with an investigational drug. As the relevance and significance of this information would usually not depend on the identity of the company marketing the drug, FDA believes a sponsor should report to FDA all significant foreign regulatory actions taken, whether or not the action was taken with respect to the sponsor's own drug. Finally, FDA would expect a sponsor to report significant actions taken not only with respect to the specific dosage form under study, but also with respect to other dosage forms of the drug, since such information may also be extremely valuable.

97. On its own initiative, FDA has revised § 312.33 to specify that the sponsor is required to submit the first annual report no later than 60 days after the anniversary date of the initial IND submission. FDA believes this provides needed guidance on the proper timing of annual reports and represents a reasonable time frame within which to prepare and submit such reports.

Identification of Patients

98. One comment expressed concern that the proposed regulation would not protect subjects' rights of privacy. The comment noted that several sections of the proposal would require the submission of a list of "deaths and drop-outs" and interpreted this to require the sponsor to identify subjects by name. The comment contended that the sponsor should not be expected to have this information in its files, and that, moreover, many sponsors go to great lengths to delete subject names from files. The comment contended that the regulation should permit the use of other identifiers, which could then be used in conjunction with the investigator's records to identify a subject by name.

As noted in the NDA Rewrite final rule (§ 312.80(h)), FDA does not expect a sponsor to maintain in its records the names and addresses of individual subjects. In reporting deaths and drop-outs, moreover, to protect subject confidentiality, sponsors should identify subjects by initials or some other sort of coding, rather than listing subjects by name and address. However, sponsors and/or participating investigators are still required to retain sufficient information about subjects to permit FDA to find the name and address of a subject should the need to do so arise.

Treatment Use of an Investigational New Drug (Proposed § 312.34)

98a. Elsewhere in this issue of the **Federal Register**, FDA is reproposing new rules governing treatment use of investigational new drugs. Comments received on this issue are addressed in that reproposal. Because there are no existing regulations governing treatment use, § 312.34 has been held in reserve.

Emergency Use of an Investigational New Drug (§ 312.36)

99. One comment from a professional medical association complained that the proposal did not specify the appropriate procedures for obtaining an investigational drug in an emergency and urged that the final rule include detailed guidance for the benefit of individual physicians. Another comment contended that if an emergency need for an investigational drug arises after normal working hours or on a week-end or holiday, a requirement that no emergency shipment may be made without FDA authorization could possibly delay initiation of vitally important therapy. This comment recommended that the provision be revised to permit emergency shipment of a drug without FDA authorization if: (1) No responsible agency official can be reached by telephone; (2) the sponsor obtains the authorization of the chairman of an appropriate reviewing IRB; and (3) FDA is notified of the shipment by telephone as soon thereafter as is practicable.

FDA advises that, even when a situation arises that in the judgment of a treating physician calls for the emergency use of an investigational drug, an IND is still necessary. The physician's first step should be to contact the manufacturer of the drug and determine whether the physician may be added as an investigator under the manufacturer's IND. Should the company elect not to add the physician to its IND, the physician should then contact the agency directly.

When contacting the agency, the physician will be placed in contact with an FDA medical officer familiar with the drug who will review the proposed circumstances for use. If the medical officer is satisfied that emergency use of the drug is justified, the medical officer may authorize its shipment and use in advance of any formal written submission to the agency.

Because the procedures governing "emergency IND's" may change from time to time, FDA has not codified the details of current practices into this final rule. However, the final rule does identify the specific review office to contact to get the process in motion. Also, FDA has prepared an informational sheet that describes in some detail the procedures to be followed to obtain emergency authorization to use an investigational drug. The informational sheet also describes an investigator's responsibilities in an emergency with respect to informed consent and IRB review requirements. This informational sheet is available from the Food and Drug Administration, Office of the Associate Commissioner for Health Affairs (HFY–20), 5600 Fishers Lane, Rockville, MD 20857 (301–443–6143).

Requests for emergency authorization that are received after normal duty hours are handled like those received during the working day, except that in such cases the initial contact will be FDA's duty officer or the agency answering service rather than the appropriate review office. Because this procedure has worked well, and has not, to the agency's knowledge, materially delayed shipment of urgently needed drugs, FDA does not believe there is a need for an alternative procedure.

100. One comment perceived an inconsistency between the emergency use provisions of the IND regulations and the provisions in the IRB regulations (21 CFR 56.104) governing the proper role of the IRB with respect to the emergency use of test articles. The IRB regulations permit the emergency use of an investigational drug without prior IRB review and approval provided that the IRB is notified of such use within 5 working days. This comment concluded that this provision of the IRB regulation represented sound policy and should override any conflicting sections of the IND regulations.

This comment erroneously characterized this provision of the IRB regulations as exhausting all FDA regulation of emergency use of investigational drugs. However, IRB review requirements are supplemental to the requirements for an IND. As noted

above, when a physician wants to obtain authorization to use an unmarketed investigational drug in an emergency, an IND is still required.

Withdrawal of an IND (§ 312.38)

101. Proposed § 312.38 sets forth procedures for withdrawing an IND by a sponsor. Two comments recommended that the final rule provide that IND withdrawal not result in the public availability of confidential data submitted by the sponsor. One comment contended that the act of withdrawing an IND, in itself, should not trigger the release of confidential data, since that data may have proprietary value with respect to related compounds or other possible indications for that same compound.

The public availability of all data and information in an IND for a new drug or antibiotic drug will be governed by § 314.430, which describes the rules for disclosing information submitted in a marketing application under Part 314. The rules for public disclosure of information for biological investigational drugs are set forth in 21 CFR 601.50 and 601.51. In general, these rules hinge public disclosure on whether the information requested is trade secret or confidential commercial or financial information, and not on whether the application is formally pending with the agency. Thus, the fact that an IND has been withdrawn is not, in itself, determinative of the public availability of information in the IND file.

102. One comment suggested revising § 312.38(b) to make clear the sponsor's responsibilities for disposing of an investigational drug once the investigation is ended.

The agency has added a new section (§ 312.59) to describe a sponsor's responsibilities for disposing of an investigational drug. Under that section, sponsors are required to assure the return or other authorized disposition of all unused supplies of an investigational drug whenever an investigator ends his or her participation in the investigation, or the investigation is terminated.

Administrative Actions

General Requirements for Use of an Investigational New Drug In a Clinical Investigation (§ 312.40)

103. One comment objected to retaining the system under which an IND goes into effect 30 days after FDA receives the IND unless FDA notifies the sponsors that the investigations covered by the IND may not begin. The comment acknowledged the need for expeditious review of investigational applications, but expressed concern that during substantial portions of the 30-day period the application may not actually be available for review by FDA's scientific reviewers because of the time needed to route the IND to the scientific reviewers. The comment recommended that, in light of this "delay," the 30-day period should be deemed to begin from the time that the application has actually been transmitted to the responsible reviewing officials.

Under longstanding practice, agency reviewers have had 30 days from date of receipt of the IND to review the submission. Agency reviewers are asked during this period to decide whether the information submitted in the IND supports initiation of the proposed clinical investigations. Only rarely has the agency found the 30-day period, which period includes the administrative time taken up in routing a submission from the file room that initially receives the IND to the designated scientific review team members, insufficient to conduct an adequate initial review. In those rare cases, the agency has invariably obtained the sponsor's agreement to delay its proposed studies pending completion of the agency review. FDA believes this system has worked satisfactorily and should not be changed.

Clinical Holds and Requests for Modification (§ 312.42)

104. Several comments supported codifying clinical hold procedures in the regulations. However, a number of comments objected to the proposed criteria for imposing a clinical hold and also to the proposed procedures under which clinical holds would be implemented. These specific objections are discussed in detail below.

105. One comment suggested that the standard for a clinical hold based on a finding that the investigator brochure is "misleading, erroneous, or materially incomplete" (proposed § 312.42(b)(1)(iii)) be reworded to require a finding that "the investigator brochure is materially misleading, erroneous, or incomplete."

The agency believes that any information in an investigator brochure that is "misleading" or "erroneous" is presumptively "material" in terms of significance, and therefore the explicit qualifier suggested by the comment is unnecessary. However, the "incompleteness" of an investigator brochure may be of minimal significance and, therefore, an insufficient basis for imposing a hold without a further finding that the deficiency is material with respect to the function of the brochure. Therefore, the agency concludes that this provision should be retained as proposed.

106. Under proposed § 312.42(b)(2)(ii), a clinical hold may be imposed on a Phase 2 or 3 study where "the plan or protocol for investigation is clearly deficient in design to meet its stated objectives." One comment objected to the omission of this grounds for clinical hold from the criteria applicable to Phase 1 studies. The comment contended that the safety of a study cannot be evaluated without a critical inquiry into its scientific merits and concluded that it would be difficult to assure subject safety absent a carefully drawn research protocol. In contrast, several comments objected to the retention of this criteria for studies in any phase. These comments contended that FDA's mandate does not extend to stopping a clinical investigation based solely on the agency's views of the scientific deficiencies of the investigation. Finally, one comment contended that it is inappropriate to interrupt the course of a planned clinical investigation, which may involve the investment of significant amounts of time and financial resources, unless there is a well-founded concern for the safety of study subjects.

As discussed in paragraph 31 above, FDA has both the authority and responsibility to establish conditions, including a review of study design, to ensure that a study that is conducted to develop evidence of a drug's safety and effectiveness is designed to achieve its objectives. Review of study design may prevent unnecessary mistakes, may assure the adequacy of a study, and may otherwise increase the likelihood that completion of the study will generate the kind of data needed to make a final determination about the drug's safety and effectiveness.

FDA is sensitive to the potential costs and disruptiveness of a clinical hold, and will not impose a hold because of design problems unless it finds the study to be "clearly deficient in design to meet its stated objectives." This intentionally places a substantial burden on FDA to show that a design defect is critical with respect to the purposes of the study. The criterion is a guarantee that FDA will not casually impose clinical holds for trivial or easily correctable design problems. When this standard is met, however, imposing a clinical hold will preclude exposure of human subjects to risks in an investigation that FDA concludes would ultimately have no scientific or regulatory value. It will also save substantial drug development time, in the long run, by preventing

continuation of a study that could not possibly support marketing approval.

The agency discussed previously its reasons for "narrowing" the focus of Phase 1 review to matters of subject safety alone. As noted in that discussion, the narrow focus reflects a desire to remove impediments to innovation at this early stage of drug discovery. While the narrower focus may mean that some poorly designed studies will be conducted that would otherwise have been placed on clinical hold, FDA believes the likelihood of this happening is slight, and that the safety considerations arising from such an occurrence are not significant in that FDA will still have reviewed the study for subject safety generally. On balance, therefore, FDA believes it appropriate to defer to sponsors on matters of Phase 1 study design.

FDA notes that a number of potentially safety-related criteria are listed as bases for terminations, but are not listed as bases for clinical holds. Thus, for example, while § 312.44(b)(1)(iii) authorizes FDA to terminate a study on finding that the methods, facilities, and controls used for manufacturing the drug "are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety," this factor is not listed among the bases for clinical holds under § 312.42(b). The omission of such specific criteria from the listed criteria for clinical holds is not intended to suggest that they would not be a basis for a clinical hold, if the particular deficiency posed an unreasonable and significant risk of illness and injury to human subjects. To the contrary, FDA would view the deficiency to be a proper basis for a clinical hold under the provisions of § 312.42(b) (1)(i) and (2)(i).

107. Several comments urged the creation of additional procedural safeguards and a better appeals mechanism relating to the imposition of clinical holds. One comment claimed that the promise in proposed § 312.42(c) that FDA will, before issuing the clinical hold order, attempt to discuss and satisfactorily resolve the matter with the sponsor, can be interpreted to mean anything from a casual attempt at telephone communication to a requirement for a formal meeting. Given the potential significance of a clinical hold for a sponsor's drug development plans, the comment urged that the sponsor be given 48-hour notice of a hold imposed for safety reasons and longer notice for holds imposed for nonsafety reasons. In either case, the comment urged that a sponsor be given the right to meet or talk by telephone with the responsible reviewing official before the hold goes into effect. Another comment, while conceding that it may be appropriate to impose an immediately effective hold where the safety and rights of human subjects are at stake, recommended that in all other cases a clinical hold not become effective until the sponsor has exhausted all appeals rights including, ultimately, the right to a regulatory hearing before the agency under Part 16.

The procedures governing the imposition of clinical holds are tailored to the needs of a regulatory process that gives reviewers little time to decide whether proposed studies should begin or ongoing studies continue: studies under an IND may begin 30 days after FDA is given notice by the sponsor, and these same studies, once begun, may be significantly changed in direction or scope under protocol amendments without any advance notice to FDA. The relative informality and flexibility of the clinical hold procedures, criticized by the comments, are thus, in the agency's view, dictated by the nature of the process.

While the agency is committed to making a good faith attempt to discuss and satisfactorily resolve deficiencies in an IND before considering the need to impose a clinical hold, it does not believe that it is obligated to establish procedural safeguards of the types suggested by the comments. The nature of the agency contact with sponsors will depend on the imminence of hazard to human subjects, on the availability of key agency and sponsor personnel, and on a variety of other factors.

For similar reasons, FDA believes that it cannot in the abstract specify the extent of notice that can appropriately be given a sponsor before making a hold effective.

108. Several comments urged that the clinical hold provisions make clear the agency's obligation to explain the reasons for a hold when it is imposed.

Agency practice has been to explain briefly the basis for a clinical hold when it is imposed, and to follow up this initial communication with a written explanation of the agency's action. FDA has revised the final rule to reflect this practice.

109. One comment urged that the procedures governing the resumption of a clinical investigation placed on clinical hold be revised to permit the order rescinding the hold to be made by or on behalf of the Division Director. (The proposal provided that such rescission order could only be made by the Division Director.) The comment also recommended that the clinical hold procedures specifically permit FDA to authorize resumption of a study by telephone or by other means of rapid communication.

FDA agrees with these suggestions and has revised the regulation accordingly.

110. Proposed § 312.45(a) would give the agency the authority to convert an IND to inactive status if all clinical investigations covered by the IND remain on hold for 1 year or more. Several comments recommended revising this to state that any IND on clinical hold will be placed on inactive status only in the event that the clinical hold is no longer contested by the sponsor of the investigation.

FDA believes that as a matter of administrative efficiency—to "clear the books"— it is appropriate that the agency retain the authority to place an IND on inactive status if all studies under the IND have been on clinical hold for at least 1 year. The 1 year between imposition of the clinical hold and transfer to inactive status should generally be more than sufficient time to raise and attempt resolution of the deficiencies that prompted the agency to place the studies on clinical hold.

It should be noted that inactivation of a study under the circumstances described by the comment is not automatic. Under § 312.45(a), if FDA seeks to place a study on inactive status, it must give the sponsor notice of the proposed action and an opportunity to respond as to why the IND should remain active. The fact that issues surrounding a clinical hold order remain under dispute may be a legitimate basis for a sponsor request to continue an investigation as "active."

111. One comment urged that FDA elaborate on the scope of a clinical hold. The comment claimed that it would not be reasonable to halt a study with six investigators when only one had been found to be inadequately qualified to participate in it.

If FDA finds that only one of several investigators named in an IND is not qualified to conduct the investigation, the clinical hold order would ordinarily be limited to the study conducted by that investigator. This concept is noted in § 312.42(a) of this final rule, which states that the clinical hold order may apply to one or more of the investigations covered by an IND.

To ensure that the sponsor is informed of the precise limits of the clinical hold order, FDA has revised the final rule to require the Division Director (or the Director's designee) to specify in the

initial communication to the sponsor the studies to which the hold applies.

As proposed, the clinical hold procedures (§ 312.42) gave FDA 15 days from the date of imposition of a clinical hold to provide the sponsor with a written explanation of the basis for the action. On reconsideration, FDA concludes that 15 days may not allow the agency sufficient time to provide the sponsor with a complete written explanation of the basis for its action. Accordingly, § 312.42(d) has been revised to require the agency to provide a written explanation "As soon as possible, and in any event within 30 days of the imposition of the clinical hold."

Termination (§ 312.44)

112. Under proposed § 312.44(b)(1)(iv), FDA would be able to terminate an investigation on a finding that clinical investigations are not being conducted in accordance with the plan or protocol submitted. One comment suggested that minor departures from these protocols and plans should not be the basis for terminating an IND, and recommended conditioning such actions on a finding that the investigations are being conducted in a manner "substantially different" from the plan or protocol submitted.

The agency agrees and has revised the final rule accordingly.

113. Under § 312.44(b)(2)(ii), FDA may terminate a Phase 2 or 3 investigation if it finds that the investigational plan is not reasonable as a bona fide plan to determine whether or not the drug is safe and effective for use. One comment urged that this standard not be used to prevent or preclude pilot studies or exploratory research that might not, taken alone, be satisfactory to establish safety and effectiveness. Another comment objected to the standard on the grounds that it would permit FDA to prevent clinical investigations "merely on the basis of the agency's opinion as to the value of what FDA anticipates will be their results." This comment urged that a determination under this provision require, in addition, a finding that a continuation of the investigation would subject human subjects to an unreasonable and significant risk of illness or injury.

Proposed § 312.44(b)(2)(ii) was intended to give FDA grounds for terminating an investigation that was not directed, overall, at evaluating safety and effectiveness of the drug. The criterion would not provide grounds for terminating an investigation simply because one or another study was considered inadequate. A bona fide investigational approach may well include pilot studies, open safety studies, and other studies that would not, by themselves, establish a drug's safety and effectiveness.

114. As proposed, § 312.44(b)(2)(iii) would authorize FDA to terminate a study on finding that "There is convincing evidence that the drug is effective for the purpose for which it is being investigated." This provision has been corrected in the final rule to read "There is convincing evidence that the drug is not effective for the purpose for which it is being investigated."

115. Under proposed § 312.44(d), FDA could immediately terminate an IND on finding that the continuation would present a significant danger to the public health. One comment suggested revising this language to condition an immediate termination on a finding of an "unreasonable, direct, and substantial danger to the health of individuals."

The agency believes that the immediate termination procedure should focus more directly on the health of individuals and therefore has revised § 312.44(d) in this final rule to condition such terminations on a finding of "an immediate and substantial danger to the health of individuals."

Inactive Status (§ 312.45)

116. Several comments objected to the provisions under which FDA could terminate an IND that has been on inactive status for 5 years. One comment suggested that the prospect of termination eliminates the principal value of inactive status to sponsors and will discourage them from seeking it.

FDA believes that the provision for terminating IND's that have been on inactive status for 5 years or more is reasonable to permit the agency to focus its resources upon clinical investigations that are actually being conducted and to keep government records current. Moreover, the termination procedure in § 312.44 is not automatic: under the procedure, the sponsor has an opportunity to respond to an agency proposal to terminate an IND with an explanation of why it should continue on inactive status. Finally, FDA does not believe sponsors will be adversely affected by termination of an IND that has long been inactive, both because the termination of an IND does not preclude a sponsor from proposing new studies in the future under another IND, and because the agency has, in the NDA Rewrite final rule, amended § 314.430 governing the disclosure of information in a terminated IND to assure the continued confidentiality of trade secret, confidential commercial, and financial information.

Meetings (§ 312.47)

117. Comments agreed with FDA's view that meetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. Noting, however, that under current practice there is sometimes a delay of several months in scheduling meetings, comments urged that meetings be held promptly after a request is submitted. Also, one comment urged that advance written information in support of a meeting should be kept to a minimum, and that requests for such information should balance the sponsor's costs in preparing the material against the expected results.

The agency agrees that sponsors should not be asked to prepare and submit more information in advance of a meeting than is needed to ensure a productive exchange of views at the meeting. This principle does not mean, however, that the amount of advance information can or should always be kept to a bare minimum. To the contrary, the successful conclusion of many meetings may demand a considerable investment of time and resources in developing background information. This is especially true for meetings such as an end-of-Phase 2 conference, whose primary purpose is to evaluate the adequacy and significance of data developed by the sponsor.

FDA also agrees that meetings are most useful if held promptly after requests for them are submitted and after the necessary advance information has been submitted. The agency will make every effort to schedule such meetings as early as is feasible and to the extent that agency resources permit.

118. One comment requested that the final regulation specifically authorize and encourage "pre-IND" meetings, i.e., meetings between sponsors and FDA prior to the actual submission of an IND. The comment contended that such meetings are often needed to answer questions about technical requirements for an IND and may be essential for planning a clinical study.

The final rule identifies two specific points during the drug development process when meetings between a sponsor and FDA can be particularly useful and productive: (a) at the end of Phase 2; and (b) at the end of Phase 3, but prior to submission of a marketing application. FDA has codified those two meetings because they are exceedingly valuable to both agency reviewers and sponsors and because they are useful for a vast majority of IND's. Although "pre-IND" meetings may be useful for a

particular case, FDA does not believe their utility will be so generalized as to warrant separate codification. The agency notes, however, that individual sponsors may request such meetings under § 312.47(a) as the need may arise. FDA encourages such meetings to the extent that they aid in the evaluation of the drug and associated scientific issues.

119. Two comments contended that many NDA approvals are delayed by questions and concerns about manufacturing and control information. The comments recommended that FDA expand the list of subjects for "pre-NDA" meetings to include these kinds of technical issues.

FDA has no objection to sponsors raising for discussion at "pre-NDA" meetings technical problems relating to the chemistry, manufacturing, and control segment of the marketing application. FDA has revised the final rule to make clearer FDA's willingness to discuss these and other technical matters at such meetings.

Sponsors should also be reminded that the NDA final rule (§ 314.50(d)(1)(iv)) has established a procedure specifically authorizing the early submission and review of chemistry, manufacturing, and control information. Under this procedure, applicants may submit the chemistry, manufacturing, and control part of the marketing application 90 to 120 days in advance of the rest of the application. This procedure may frequently be superior to the "pre-NDA" meeting as a means of resolving the highly technical issues involved.

Dispute Resolution (312.48)

120. The IND Rewrite proposal contained a new formal appeals process for resolving disputes between FDA and sponsors. The appeals process was first outlined in the proposed NDA Rewrite and was more fully described in a publicly available FDA Staff Manual Guide 4820.5. Under that process, drug firms could appeal requests by agency employees for specific additional studies or information, requests to modify or delay a study, or unfavorable agency responses to sponsors' requests for waivers or special technical approaches to scientific problems. The procedure became available for use for both IND's and NDA's through issuance of the Staff Manual Guide noted above.

FDA first received adverse comments on this appeals procedure in the NDA Rewrite rulemaking, and these objections were reiterated in the IND Rewrite rulemaking. The comments suggested that the appeals process was, on the one hand, too complex for resolving minor administrative and procedural disputes, and, on the other hand, too inflexible to handle efficiently major scientific and medical disputes, which, according to the comments, should be referable as a matter of right to one of FDA's standing advisory committees.

FDA in general agreed with these observations about the shortcomings of the formal appeals mechanism. The agency's view of the deficiencies of the process was underlined by the fact that the appeals process was rarely used successfully during the more than 1 year it was effective. For these reasons, in issuing the NDA Rewrite final rule, FDA abandoned the formal process in favor of a more comprehensive approach to dispute resolution. This approach entailed establishing a range of procedural alternatives, each tailored to a specific kind of dispute, and then referring sponsors to whichever of the available procedural mechanisms was best suited to the particular matter under discussion. FDA now concludes that a comparable dispute resolution mechanism should be adopted for the IND process and § 312.48 of this final rule has been revised accordingly.

There are three chief components of this new appeals process: (1) The use of an ombudsman to deal with administrative and procedural problems; (2) the codification of an informal process for resolving scientific disputes; and (3) the increased use of outside scientific advisers, when feasible and appropriate.

First, the final rule encourages sponsors to seek the help of a designated "ombudsman" to resolve administrative and procedural disputes arising during the course of an investigation. The function of the ombudsman is to investigate the facts and to facilitate a timely and equitable resolution of the issue. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings, obtaining timely replies to inquires, and obtaining timely completion of pending reviews. Details on the role of the ombudsman are set forth in a publicly available FDA Staff Manual Guide 4820.7. (Other elements of the new dispute resolution mechanism are described in the revised FDA Staff Manual Guide, "Appeals Process: Resolving Scientific Disputes Over Drug Applications" (CDB 4820.5).)

The second component of the dispute resolution mechanism emphasizes the value of informal communications between sponsors and DFA as the best means of resolving important technical and scientific issues quickly and amicably. If scientific or medical disputes arise, the final rule provides that applicants should first discuss the matter directly with the responsible reviewing officials. If these discussions do not resolve the matter, applicants may request an informal meeting with the appropriate reviewers and supervisors. Alternatively, disputes may be appropriately discussed at a more formal, "pre-NDA" or "end-of-Phase 2" meeting.

Finally, the new procedures recognize the advantages of utilizing the advice of outside scientific experts in the dispute resolution process, where it is practicable and feasible to do so. Section 312.48(c)(3) of the final rule therefore provides that, in requesting a meeting with the agency to resolve a scientific or medical dispute, sponsors may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other agency consultants, as designated by the agency. The applicant is also free to bring its own consultants.

Section 312.48(c)(3) of the final rule also provides that, for major scientific and medical policy issues not resolved by informal meetings, FDA may on its own initiative refers the matter to one of its standing advisory committees for its consideration and recommendations. Although § 312.48 does not provide the right to advisory committee review requested by some comments, FDA does intend to integrate outside experts more fully into the IND portion of the drug approval process. FDA believes that providing applicants a right to advisory committee review for any disputed issue is impractical from the standpoint of the potential number of controversial issues and the relatively infrequent number of advisory committee meetings. Moreover, utilization of outside advisory committees is committed to the discretion of the agency, and not properly delegated to members of the public. Nonetheless, by involving individual advisory committee members or consultants in the dispute resolution process on a more informal basis, FDA believes that the goal of interacting with the scientific community can be achieved without the delays, resouces, and scheduling problems associated with full advisory committee involvement.

Responsibilities of Clinical Investigators and Sponsors

122. As noted in the introduction, the proposed IND Rewrite was issued on the assumption that proposed Part 52 governing the obligations of sponsors and monitors and proposed Part 54 governing the obligation of clinical

investigations would be adopted as final rules before, or at the same time as, this final rule. As noted, because those proposals have not been made final, FDA has retained in new Part 312 most of those obligations of investigators and sponsors in existing Part 312 that were to be transferred to in Parts 52 and 54. While in general, the obligations of sponsors, monitors, and clinical investigators are the same as those set forth in the existing IND regulations, in three areas, FDA is adopting minor changes that relate to provisions first proposed in the September 27, 1977, and August 8, 1978, proposed rules. These areas are: (a) Obligations assigned to contract research organizations; (b) disclosure of study audits conducted by the sponsor; and (c) the standard for disqualifying clinical investigators. These changes apply to investigational new animal drugs as well as new drugs for human use. They will be discussed in turn.

Contract Research Organizations

The agency is adopting certain provisions relating to contract research organizations based on proposed Part 52 (see proposed § 52.5 at 42 FR 49623). A contract research organization is an independent organization that contracts with a sponsor of a clinical investigation to assume one or more obligations of the sponsor for the conduct of a clinical study. Use of contract research organizations has grown increasingly common in the United States. Adoption of these provisions represents a regulatory acknowledgment of this common practice.

The final rule: (1) Defines the term "contract research organization" (§ 312.3); (2) authorizes a sponsor to transfer any or all of the sponsor's obligations for the conduct of the clinical study to a contract research organization (§ 312.52(a)); (3) requires that the sponsor keep a written statement that outlines what obligations have been so transferred (§ 312.52(a)); and (4) describes the responsibilities of both the sponsor and the contract research organization, once having made such a transfer (§ 312.52 (a) and (b)). In addition, the final rule requires that the sponsor disclose in the IND whether any obligations have been transferred to a contract research organization, and, if so, that the sponsor list the obligations transferred. Finally, 21 CFR Part 314 is amended by adding new § 314.50(d)(5)(x) to conform Part 314 to Part 312 with respect to contract research organizations.

The agency is adopting identical changes concerning contract research organizations in the investigational new animal drug (INAD) and new animal drug application (NADA) regulations.

A number of persons commented on the provisions pertaining to contract research oganizations when proposed Part 52 was issued. A summary of these comments and the agency's responses follow:

i. Several comments objected to the proposed requirements that obligations transferred to a contract research organization be specifically described, stating that a general transfer of all obligations should be allowed. These comments argued that because a sponsor is often unable to describe specifically each aspect of an obligation transferred before a study begins, it would be unrealistic to have those obligations that were not specifically described considered not to have been transferred at all.

FDA agrees that when a sponsor transfers all its responsibility for the conduct of a study, a statement of this general transfer of obligations should be allowed. The regulation has been revised accordingly. Therefore, when a sponsor transfers all obligations regarding the conduct of a clinical study to a contract research organization, the written statement may indicate that a general transfer has been made and need not enumerate the specific obligations transferred. However, in other cases, i.e., when less than all obligations are transferred, specificity in describing the transfer of obligations of a sponsor to a contract research organization is essential. In such cases, because a contract research organization is required to comply with the specific regulation applicable to any obligations it assumes for a sponsor, a sponsor must be able to set forth specifically each obligation that it expects the contract research organization to assume. The specification of the transferred obligations ensures that the contract research organization knows exactly what its obligations are before beginning a clinical investigation.

While a contract research organization may assume any or all of the sponsor's responsibility for the conduct of a study, it should be emphasized that the transfer does not relieve the sponsor from responsibility for the quality and integrity of any data derived from the investigation that are submitted to FDA.

ii. One comment requested an explicit statement to the effect that if a contract research organization is subjected to administrative action, the sponsor will not also be subject to this same administrative action if the sponsor complied with all applicable requirements governing the transfer of obligations.

The agency considers such explicit language unnecessary because the written statement identifying what obligations have been transferred will clearly fix the individual sponsor/contract research organization responsibilities. The agency may, therefore, initiate action based upon failure to comply with a regulatory obligation against only the party that has assumed responsibility for, but has not fulfilled, a particular obligation. The agency does not contemplate taking administrative action against a sponsor based solely upon the failure of a contract research organization to perform obligations that have been transferred to it by the sponsor. Sponsors should, therefore, take special care that transferred obligations are described clearly.

iii. One comment asked whether the name of the specific monitor within the contract research organization must be submitted to FDA, along with the name and address of the contract research organization.

The name of the monitor is required to be submitted. See § 312.23(a)(1)vi) in this final rule.

Disclosure of Study Audits

Proposed Part 52 would have required that a monitor designated by the sponsor visit investigators periodically to, among other things, audit case report forms against individual subject records to assure the accuracy and completeness of the forms (see proposed § 52.20(b) at 42 FR 49623, 49624). While the agency believes that such audits are extremely important, it has concluded that it should not compel such reviews by regulation.

Rather, the agency has concluded that it should only require that a sponsor, in its submission to the agency of a report of a clinical investigation, state whether the investigator's subject records were audited or reviewed in the course of monitoring a clinical investigation. The agency is adding new § 314.50(a)(5)(xi) as a necessary conforming amendment to Part 314. The agency is also making an appropriate change to the NADA regulations by adding a new § 514.1(b)(8)(ix).

As noted above, although FDA has not made the auditing of subject records mandatory in this final rule, FDA concludes that it should know whether such a review has, in fact, been conducted. Knowledge that a sponsor has audited subject records may affect the detail with which FDA conducts its

own inspection of the supporting data. Morever, in those cases where an agency inspection is not conducted, e.g., in some foreign countries, whether the sponsor has audited the study is an important factor to be considered in evaluating the study. Thus, FDA believes that disclosure of which studies have been audited will significantly improve the efficiency of the agency's clinical investigator inspection program while representing a minimal additional burden on study sponsors.

Disqualification of Clinical Investigators

123. The agency is retaining all the current standards and procedures governing disqualification of clinical investigators, with only one modification. The existing regulations permit the agency to disqualify an investigator on a finding that "the investigator has repeatedly or deliberately failed to comply with the conditions of the exempting regulations * * * or has repeatedly or deliberately submitted false information to the sponsor of an investigation *and has failed to furnish adequate assurance that the conditions of the exemption will be met* * * *" (§ 312.1 (c)(2)) (emphasis added). This final rule deletes the provision allowing a clinical investigator to avoid disqualifications through the submisson of "adequate assurances" of future compliance.

This action is based on proposed Part 54, which would have similarly limited the grounds for disqualification (see proposed Part 54, Subpart K, at 43 FR 35227). Under the 1978 proposal, no provision for the submission of assurances was included whereby an investigator could avoid disqualification if the other criteria for disqualification were met. FDA received no comments on this approach.

Based on its more than 20 years of experience with the clinical investigator disqualification procedures, the agency believes that the disqualification procedure will operate more effectively and efficiently if it is limited to objective questions about whether there have been violations of FDA's regulations. The more subjective question of when assurances of future compliance are adequate should be addressed independently of the hearing proceeding. Under the procedures adopted in this final rule, assurances may be presented at several stages of a disqualification proceeding: (1) When the agency initiates a disqualification action, (2) at the informal conference with the Center for Drugs and Biologics offered before any hearing, (3) during the negotiations on a consent agreement, and (4) after an investigator has been disqualified, as part of the efforts to obtain reinstatement. See § 312.70 of this rule and the guidelines for reinstating the eligibility of clinical investigators to receive investigational articles, announced in the **Federal Register** of November 19, 1982 (47 FR 52228). Deletion of the submission of "adequate assurances" as a ground for avoiding disqualification will affect only proceedings for which a notice of opportunity for hearing is issued after the effective date of this rule.

FDA acknowledges that proposed Part 54 contained additional criteria for clinical investigator disqualification that are not being adopted in this final rule. These criteria related to the significance of the regulatory violation; i.e., whether the violations adversely affected the validity of the study or the rights or safety of test subjects. The 1978 proposal also provided that the disqualification sanction would not be used if other lesser regulatory actions would be adequate.

FDA believes that these criteria are so subjective as to make them extremely difficult to apply fairly in disqualification proceedings. The agency emphasizes, however, that the agency retains discretion on whether to initiate an action to disqualify a clinical investigator, and that the Commissioner will exercise that discretion and not disqualify an investigator if the violations are insignificant, or if lesser sanctions would be adequate.

124. Several comments received on proposed Part 54 questioned FDA's authority under the act to disqualify clinical investigators. Because these coments are relevant to the disqualification procedures that are described both in the existing regulation and in this final rule, they are summarized and discussed below. One comment argued that none of the sections of the act that FDA cited in the preamble to proposed Part 54, that is, sections 701(a), 505(i), and 507(d), explicitly provides for or even suggests disqualification. Two comments suggested that the unsuccessful efforts of Congress to enact legislation to grant the agency explicit authority to disqualify investigators implies that FDA lacks authority now to disqualify clinical investigators.

FDA believes that the agency clearly has authority to disqualify clinical investigators that violate FDA's regulations. A thorough discussion of this authority is found in the preamble to proposed Part 52 (43 FR 35221). FDA believes it is unnecessary to restate that discussion here. In sum, although the concept of disqualification is not explicitly mentioned in the act, the Supreme Court in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973) has recognized that FDA has authority that "is implicit in the regulatory scheme, not spelled out *in haec verba*" in the statute. As stated in *Morrow* v. *Clayton*, 326 F.2d 36, 44 (10th Cir. 1963):

> [I]t is a fundamental principle of administrative law that the powers of an administrative agency are not limited to those expressly granted by the [ir] statutes, but include, also, all of the powers that may be fairly implied therefrom.

See *Mourning* v. *Family Publications Service Inc.*, 411 U.S. 356 (1973) and *National Petroleum Refiners Association* v. *FTC*, 482, F.2d 672 (D.C. Cir. 1973). See also *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *National Nutritional Foods Ass'n* v. *Weinberger*, 512 F.2d 688, *cert denied*, 423 U.S. 827 (1975); *United States* v. *Nova Scotia Food Products Corp.*, 568 F.2d 246–248 (2d Cir. 1977); *American Frozen Food Institute* v. *Mathews* 413 F. Supp. 548 (D.D.C. 1976) *aff'd per curiam*, 555 F. 2d 1059 (D.C. Cir. 1977); *National Confectioners Ass'n* v. *Califano*, 569 F.2d 690 (D.C. Cir. 1978); *National Ass'n of Pharmaceutical Manufacturers* v. *FDA*, 637 F.2d 877 (2d Cir. 1981).

Congressional inaction on proposed legislation that would state expressly an agency's authority to act does not support an inference that the agency lacks implicit authority to act under existing legislation. *Red Lion Broadcasting Co.* v. *FCC*, 395 U.S. 367, 381–382 n. 11 (1969). See also *Leist* v. *Simplot*, 638 F.2d 283, 318 (2d Cir. 1980), *affirmed sub nom. Merrill Lynch, Pierce, Fenner & Smith* v. *Curran*, 456 U.S. 353 (1982).

The agency concludes it has ample authority for the promulgation of procedures that govern the disqualification of an investigator of any FDA-regulated product who fails to carry out the requirements of these regulations.

125. The statement of clinical investigator responsibilities in this final rule is essentially the same as that contained in former § 312.1 with the exceptions noted above. However, in the former regulation, as noted below, clinical investigator responsibilities were described in forms (Forms FD–1572 and FD–1573) that were signed by the investigator and obtained by the sponsor. While FDA believes that the forms adequately stated the investigator's responsibilities, the

agency has concluded that a clearer approach is to set forth investigator responsibilities in the body of the text (see § 312.60 et seq.).

126. FDA recognizes that some may view the decision by the Ninth Circuit Court of Appeals in the *United States* v. *Smith*, 740 F.2d 734 (9th Cir. 1984), which involved criminal charges against a clinical investigator, as raising questions about the agency's authority to promulgate enforceable regulations on the obligations of clinical investigators. After considering the court's opinion, FDA concludes that it has ample authority to issue such regulations. The agency points out that the court in *Smith* noted that under the regulation then in effect (former 21 CFR 312.1(c)), FDA could conduct an administrative hearing to revoke an investigator's entitlement to work with investigational new drugs.

Moreover, FDA believes that both the language of the statute and its legislative history demonstrate that issuance of this final rule is within the scope of authority delegated to the Secretary by Congress under sections 505(i) and 701(a) of the act (21 U.S.C. 355(i) and 371(a)). The statutory language makes clear Congress' intent that clinical investigators be subject to section 505(i) of the act, and that they be required to maintain records. The stated purpose of section 505(i) is to make investigational drugs available "solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." The experts referred to are, in fact, the clinical investigators covered by this final rule, who perform the tests for which the investigational exemption exists. Section 505(i) of the act states that the "Secretary shall promulgate [exempting] regulations * * * [for] drugs intended soley for investigational use by experts * * *." Thus, it does not contain any restriction on who may be subject to such regulations.

The plain meaning of the statute demonstrates that Congress intended the Secretary to have the discretionary authority to impose conditions on investigational drug use in addition to those conditions specified as examples in the statute. The Secretary was explicitly authorized by Congress to impose "other conditions relating to the protection of the public health" by this part of the statute. 21 U.S.C. 355(i).

The legislative history of section 505(i) of the act also demonstrates that Congress intended the Secretary to require clinical investigators to maintain investigational drug study records. Before passage of the Drug Amendments of 1962 (Pub. L. 87–781), Congress was aware that FDA had proposed regulations on new drugs for investigational use, including the requirement that investigators prepare and maintain records. See 27 FR 7990 (1962); 108 Congressional Record 17308 (1962) (remarks of Senator Eastland). The regulations were promulgated in 1963 (28 FR 179; January 8, 1963) and were codified in § 312.1. The House Committee Report specifically approved the proposed regulations and made clear what section 505(i) of the act was intended to accomplish.

> [This section] provides a firm legal basis for greater controls of the distribution of new drugs for investigational use. Existing law directs the Secretary to promulgate regulations providing for exempting new drugs from preclearance for safety on condition that they are labeled and intended soley for investigational use by experts qualified by scientific training and experience to investigate the safety of new drugs. * * * *These investigators are required to maintain records on the investigation. The Department has proposed strengthening regulations to provide greater safeguards in investigational drug use. The bill approves strengthening regulations* and provides that the regulations may require, among other things, * * * (3) the establishment and maintenance of adequate records, * * * to facilitate the evaluation of the safety and effectiveness of the new drug, when an application is filed * * *. [This section also] amends the prohibited-acts section of existing law, section 301(e), 21 U.S.C. § 331(e), to forbid the failure to establish or maintain any required record, either on an investigational use of drugs or on clinical experience. * * *

H. Rept. 2464, 87th Cong., 2d Sess. 9–10 (1962) (emphasis added).

FDA views as unreasonable an interpretation of section 505(i) of the act that excludes regulation of clinical investigation from the public health protections provided by the section. A clinical investigator who falsified or destroyed original records of a drug study, and who then submitted false records to a sponsor, would clearly cause the sponsor to maintain false records and to make false reports to FDA. Moreover, were an investigator not required to maintain his or her own records (as distinct from those maintained by the sponsor), FDA would in those cases frequently be precluded from even discovering the falseness of the reports and would then review and perhaps approve drug products on the basis of false data.

Thus, section 505(i) provides ample authority for FDA to adopt these regulations, which have the force and effect of law.

Investigator Statement (§ 312.53(c))

127. Proposed and final § 312.53(c)(1) transforms the investigator statement (Form FDA–1572) from a detailed description of the responsibilities of all parties to the investigation into a brief form that identifies the regulations governing conduct of a clinical investigation and commits the investigator to comply with these requirements. One comment expressed regret at this change, claiming that, as proposed, the clinical investigator would no longer have available a concise written statement of his or her obligations. The comment suggested that the regulations explicitly require the sponsor to provide the investigator with a written summary of all applicable responsibilities before the investigation begins.

FDA agrees with the comments on the usefulness of providing investigators with a written summary of their responsibilities in conducting a clinical investigation. The agency has therefore prepared an informational leaflet that summarizes investigator responsibilities imposed under this part and other relevant requirements of FDA's regulations. This leaflet can be obtained from the Legislative, Professional, and Consumer Affairs Branch (HFN–365), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 (301–295–8012).

Because FDA is making available a written summary of investigator responsibilities, the agency does not believe that this final rule should require sponsor distribution of similar materials to investigators.

128. Section 312.53(c) requires that the investigator statement identify the name and address of the IRB that is responsible for review and approval of the investigator's study. One comment suggested that it would be inappropriate and impracticable to include this information in the investigator statement.

FDA disagrees with this comment. An investigator is responsible for obtaining IRB approval of a clinical investigation before a study may be initiated, and for keeping the sponsor informed of such IRB approval and subsequent IRB actions concerning the study. FDA does not believe it is a significant additional burden to ask the investigator to inform the sponsor of the IRB's name and address. The cooperation of investigators in this matter will help the sponsor to meet its responsibility to keep the agency informed of the identity of all reviewing IRB's.

129. One comment asked that the proposed commitment of the investigator to "report to the sponsor immediately any unsuspected or serious

side effects that occur in the course of the investigation(s)" (proposed § 312.53(c)(1)(vi)(e)) be revised to require the reporting of any "unexpected or serious side effects."

FDA has revised § 312.53(c)(1)(vi)(e) to require the investigator to report adverse experiences in accordance with the provisions of § 312.64. Section 312.64 requires an investigator promptly to report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the regulation requires the investigator to report immediately. These provisions are taken almost verbatim from former § 312.1.

130. A comment objected to the provision in § 312.53(c)(3) that would require the sponsor to obtain a clinical plan from each participating investigator. The comment stated its assumption that the sponsor is ordinarily responsible for developing the plan, and that the sponsor normally provides the plan to participating investigators rather than the other way around. Another comment contended that the use of the term "clinical plan" is confusing, as it usually refers to the overall plan of the sponsor. The comment suggested using "protocol" or "clinical protocol" instead.

FDA agrees that the use of the term "protocol" alone may be less confusing and has revised § 312.53(c)(3) of the final rule accordingly.

The final rule is not intended to designate whether the investigator or the sponsor originate the protocol under which a study will be conducted. The inclusion of the protocol in the information given by the investigator to the sponsor simply provides added assurance that there has been a "meeting of the minds" between sponsor and investigator on the appropriate course for the study.

Informing Investigators (§ 312.55)

131. One comment contended that the intended relationship between the investigator notification requirements of § 312.32 dealing with notifying investigators of IND safety reports and those outlined in § 312.55(b) dealing with important safety information is unclear. The comment contended that § 312.55 should not require more with respect to notification than is required under the IND safety report requirement. The comment observed that proposed § 312.55(b) can be read to require that safety information other than that contained in the safety reports be conveyed to investigators on an immediate basis. If that is what was intended, the comment asked the agency to specify what other information should be conveyed to investigators and what need there is for conveying that additional information.

FDA did not intend that § 312.55(b) differ from § 312.32 with respect to investigator notification of important safety information. FDA has revised § 312.55(b) to clarify that important safety information shall be relayed in safety reports to the investigator in accordance with § 312.32.

Review of Ongoing Investigations (§ 312.56)

132. Proposed § 212.56 directed sponsors to "evaluate the evidence relating to safety and effectiveness of the drug as it is obtained from the investigators." One comment claimed that, since it is not ordinarily possible to evaluate evidence of effectiveness without breaking the code for blinded studies, the preamble to the final regulation should make clear that, for blinded studies, evidence is not considered "obtained" until the code is broken.

The agency views § 312.56(c) as requiring a sponsor to: (1) Immediately review all new data received from an investigator regarding the safety of the investigational drug, (2) periodically evaluate all data received from all investigators regarding the safety of the drug, and (3) periodically evaluate the data received from all investigators who have completed their portions of the investigation to ascertain whether the drug is proving to be effective for the intended use. As thus interpreted, a sponsor should not have to "break the code" of a blinded study to evaluate evidence relating solely to the effectiveness of the investigational drug.

133. If an investigation is discontinued for safety reasons, § 312.56(d) (§ 312.56(c) as proposed) requires the sponsor to notify all reviewing IRB's of the discontinuance. One comment asked whether the sponsor's obligation would be limited to notifying only those IRB's reviewing studies involving the specific dosage level and dosage form of the problem drug, or whether the obligation would extend to notifying all IRB's reviewing studies of the drug at any dosage level or in any dosage form. Two other comments suggested that the responsibility for notifying an IRB should belong with the investigator, not the sponsor.

The notification requirement in § 312.56(d) applies to all IRB's reviewing clinical investigations with the investigational drug. The notification provides added assurance that reviewing IRB's will be promptly informed of the most serious problems relating to their review.

With respect to the comments suggesting that the investigator, not the sponsor, has the responsibility for IRB notification, FDA recognizes that sponsors usually do not have direct contact with IRB's. FDA believes, however, that under extraordinary circumstances, such as when a sponsor discontinues a study because an adverse drug effect presents an unreasonable and significant risk to subjects, it is not unreasonable to ask the sponsor to notify all reviewing IRB's of the discontinuance. Direct contact between the sponsor and IRB in this situation will permit an IRB to obtain directly from the sponsor all the facts surrounding the sponsor's decision to discontinue the study, information that may not be available from the investigator.

134. Under § 312.56(d) (§ 312.56(c) as proposed), if a sponsor determines that its investigational drug presents an unreasonable and significant risk to subjects, the sponsor is required to discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination. One comment agreed that the 5-working-day time limit should apply to the entry of new subjects to the investigation, but argued that the provision should be revised to permit the investigator to take participating subjects off the drug "in a fashion consistent with the health and safety of the subjects."

Once a determination has been made that an investigational drug presents an unreasonable and significant risk to subjects—the trigger for discontinuance—the agency believes it is reasonable to expect sponsors to ensure that subjects are taken off the drug as quickly as possible. FDA believes that, as a general rule, 5 working days is sufficient time for patients to be taken off the drug in a fashion consistent with their health and safety. If, in the sponsor's view, there are extraordinary circumstances dictating that some subjects be continued on the drug, FDA will be willing on a case-by-case basis to discuss an extension of the 5-day time limit.

Inspection of Sponsor's Records and Reports (§ 312.58)

135. Proposed § 312.58(a) would require the sponsor to make available for FDA inspection and copying the records and reports that are required to be maintained by the sponsor under Part 312 and other applicable regulations.

One comment argued that reports made by a sponsor's monitor should not be subject to this provision because monitoring, as a quality assurance function, will work most efficiently if it is not subject to government audit. In this way, the comment contended, monitors' reports will be more candid and critical, and thus have more value to the sponsor in assuring that appropriate corrective actions are undertaken as needed.

FDA believes it should retain the authority to inspect records and reports relating to a sponsor's monitoring of clinical investigations under Part 312. Access to these materials helps the agency both to confirm that monitoring is actually taking place and to determine the nature of such monitoring. FDA also is not persuaded that the prospect of agency inspection of monitoring records and reports should significantly influence monitors in recording their observations and recommendations.

As proposed, § 312.58(a) would have required sponsors to make available to FDA's inspectors "reports required to be maintained under this part and under other applicable parts of this chapter." This might be read as not requiring a sponsor to make available a record or report that is not specifically enumerated in the regulations, even though it is clearly related to the conduct of a clinical investigation. To clarify agency intent, FDA has revised § 312.58(a) in the final rule to give the agency explicit authority to inspect and copy any record or report relating to a clinical investigation conducted under Part 312.

Imports (§ 312.110(a))

136. The proposal provided that an investigational drug may be imported if it complies with Part 312 and the consignee of the shipment is either the sponsor of the study or is an investigator named in the IND. One comment noted that a domestic agent may act as intermediary for a foreign sponsor, receiving the drug directly from the foreign sponsor, and monitoring and controlling its distribution. The comment suggested that shipment directly to this class of consignees be made expressly allowable.

The agency has no objection to the importation of a drug into the United States going through an agent of a foreign sponsor provided: (a) The intermediary is identified in the IND and (b) the IND describes what, if any, actions the intermediary will take with respect to the imported drug (e.g., repacking or relabeling). FDA has revised the regulation accordingly.

137. One comment asked that FDA give sponsors guidance on the procedures to be followed in importing a new drug for use in laboratory research or for tests in vitro.

The import into the United States of a drug intended for investigational use in laboratory research animals or tests in vitro must comply with the requirements set forth in proposed and final § 312.160 governing authorization to ship such drug. This section requires the shipper to ensure that the drug is properly labeled, that due diligence is taken to ensure that the drug is shipped only to experts regularly engaged in conducting tests in animals or in vitro, and that accurate records are kept of the drug's distribution. It should be noted that § 312.160 only governs compliance with the Federal Food, Drug, and Cosmetic Act; a sponsor may face import requirements under other laws and administered by other agencies, such as laws governing importation of controlled substances.

138. One comment suggested that the import provisions of proposed § 312.110(a) should be revised to allow a sponsor to import an investigational new drug for use as a control in a comparative study involving the sponsor's own drug without requiring a separate IND for the comparison drug. The comment suggested that the importation of the drug could be accommodated by allowing the sponsor to insert all necessary relevant information in the sponsor's existing IND file, thus obviating the need to create a separate IND for the imported drug.

As an administrative convenience and to ensure that information on both the investigational drug and the drug used as an active control are reviewed together, the two drugs should be included in the same IND. The sponsor should, of course, ensure that sufficient information is submitted on the control drug to permit an assessment of the drug's safety for use in the investigation, and to permit the drug to be used as a baseline of effectiveness against which to measure the effectiveness of the principal drug under study. (Sponsors are reminded that when an active treatment control is used, FDA expects such control to be a known effective therapy. See 21 CFR 314.126(b)(2)(iv).)

Exports (§ 312.110(b))

139. Proposed § 312.110(b)(1) would permit export of an investigational new drug if an IND is in effect for the drug and each person who receives the drug is an investigator named in the application. Several comments contended that, as written, this provision could be interpreted as prohibiting the intra-company export of investigational drugs, a practice which the comment suggested was common under the current regulations. The practice allows a shipment from the United States company to go first to its parent, subsidiary, or affiliate company in a foreign country for final distribution by the foreign affiliate to the clinical investigator. One comment stated that shipping through a foreign affiliate permits the sponsor to save multiple shipping expenses and to ensure proper storage conditions upon receipt. The comment stated its assumption that FDA did not intend to prohibit this practice and urged that the final regulation so state.

The agency has no objection to either a domestic or an export shipment of an investigational drug subject to an IND going through an intermediary on its way to the clinical investigator provided the IND identifies the intermediary and describes what actions, if any, the intermediary will take with respect to the drug. Of course, the IND would still be required to identify and give the qualifications for each participating investigator.

140. One comment questioned the applicability of the IND export provisions to the export of antibiotic drugs. The comment noted that, on its face, the export provisions apply to any investigational new drug including antibiotic drugs. The comment claimed that these provisions could be interpreted to mean that an unapproved antibiotic drug could not be exported except in accordance with the investigational export provisions. The comment claimed that this would be inconsistent with FDA's previously expressed view that the act does not require an IND for the export of an unapproved antibiotic drug intended for use in humans if the standards of section 801(d) of the act (21 U.S.C. 381(d)) are met. The comment asked for clarification of the agency's view in the final regulation.

The comment is correct in noting that antibiotic drug products, including investigational antibiotic drug products, may be exported under the provisions of section 801(d) of the act. FDA has added new § 312.110(b)(4) to state that, notwithstanding the export provisions of the IND regulations, an investigational antibiotic may be exported if its export conforms to the provisions of section 801(d) of the act.

141. It should be noted that, under the recently adopted Drug Exports Amendments Act of 1986, FDA is authorized to approve applications to

export unapproved drugs (including biological products). New section 802 of the Federal Food, Drug, and Cosmetic Act and section 351(h)(1)(A) of the Public Health Service Act describe the conditions that a drug firm must satisfy to obtain FDA approval to export unapproved products for commercial marketing abroad. FDA has revised § 312.110(b) to make clear that the IND export provisions do not preclude the export of products that are approved for export under the new law.

142. In the **Federal Register** of January 18, 1984 (49 FR 2095), FDA amended the IND regulations to streamline the process by which the agency may authorize the export of investigational new drugs that are not subject to an effective IND. Specifically, these revisions allow the agency to authorize export in two situations: (a) In response to a request submitted by a drug firm containing sufficient information to demonstrate that the drug is appropriate for investigational use, that the drug will be used for investigational purposes only, and that the drug can legally be used by the consignee in the importing country for the proposed investigational use; and (b) in response to a request submitted by an authorized official of the government of the importing country, submitted directly to FDA, that specifies that the government has adequate information about the drug for the proposed use, that the drug will be used for investigational purposes only, and that the drug can legally be used in the importing country. These two provisions have been incorporated into this final rule (§ 312.110(b)(2)).

Foreign Clinical Studies Not Conducted Under an IND (§ 312.120)

143. One comment noted that a foreign clinical investigation conducted under an IND is required to conform to FDA's current IRB regulations, whereas a foreign study not conducted under an IND is deemed acceptable if it complies with the ethical principles of the Declaration of Helsinki. The comment questioned the disparate treatment of these studies and suggested that the final rule should eliminate the distinction between them so that compliance with the ethical principles of the Declaration of Helsinki would meet the ethical requirements for any foreign study, whether conducted under an IND or not.

The distinction referred to in the comment is not a product of the new regulations, but rather carries forward the past requirement under former § 312.20. FDA believes this distinction is warranted for the following reasons.

First, the agency believes that any study under an IND, wherever it is conducted, should comply with all applicable requirements governing the conduct of clinical studies, including the requirement for institutional review. To exempt foreign studies under an IND from IRB requirements might encourage sponsors to remove clincial studies from the United States to countries with lesser standards of human subject protection. This would clearly not be in the interest of the public health.

While FDA is unwilling to create a different standard for foreign studies under an IND, the agency will accept in support of an IND or marketing application reports of foreign studies that are not under an IND (and not subject to institutional review), provided there are adequate alternative guarantees of human subject protection. This policy is based on a recognition that much important clinical research is conducted throughout the world, which meets the legal and ethical standards of the countries in which it is conducted, but which is carried on without the kind of institutional review required under FDA's requirements. To insist on absolute adherence to FDA's IRB requirements would obligate the agency to reject valid scientific data generated overseas. Thus, § 312.120 (like its predecessor § 312.20) permits FDA to accept a foreign study not subject to institutional review, provided the study was conducted in accordance with the Declaration of Helsinki or the laws of the foreign country in which the research was conducted, whichever affords the greater protection of the individual.

Finally, FDA notes that § 56.105 of the IRB regulations permits a waiver of IRB review where that is warranted. Thus, foreign research can be conducted under an IND even where IRB review is not available, provided a waiver from the agency is obtained in advance.

On its own initiative, FDA has revised § 312.120(b) to make clear that the data submission requirements for foreign studies in paragraph (b) apply not only to foreign studies intended to support an IND, but also to such studies when submitted in support of a marketing application. The revision conforms the final rule to previous agency policy.

144. Proposed and final § 312.120(b)(3) requires that case records from a foreign study be submitted if FDA so requests. One comment suggested that the laws and regulations of some foreign countries may not permit the submission of case records and urged that the final regulation provide for other means of assuring the validity of information in a foreign study.

FDA understands that a sponsor cannot disclose foreign records that are prohibited from disclosure by foreign law. Nevertheless, if the agency believes that access to records is necessary to verify certain data or to validate the study—and such records are not available because of foreign law—the sponsor and FDA will need to agree upon an alternative validating procedure if the agency is to rely on the data. Such alternative validation might entail the verification of data by a foreign drug regulatory body or other mutually agreed on procedure.

145. One comment supported FDA's proposals to accept foreign clinical studies in support of IND applications and applications for marketing permits, but urged that the assumption should be that these studies are acceptable unless FDA can demonstrate why the studies are not acceptable.

FDA disagrees with this comment's suggestion that the burden of proof should be on FDA to show why a foreign study is inadequate. As with domestic studies, the burden is on the sponsor to demonstrate that a study is valid. Nevertheless, FDA routinely gives sponsors its reasons for refusing to accept a study, whether foreign or domestic, and that practice will continue.

146. Section 312.120 requires a sponsor who wishes to rely on a foreign clinical study to submit a description of the research facilities used during the study. One comment recommended deleting the requirement, observing that such description is not required for studies under an IND.

FDA disagrees. An assessment of the adequacy of research facilities for a proposed investigation is an important factor in determining the reliability and validity of data generated by a study, wherever the study is conducted. For studies conducted under an IND, this assessment is frequently obtained through on-site inspections of the facilities identified in the IND. However, because of the difficulties in inspecting foreign research facilities and because of the likelihood that FDA will not otherwise be familiar with such facilities, FDA believes it is appropriate to require documentation of the adequacy of foreign facilities. The requirement should not represent a significant burden on sponsors, but will appreciably enhance FDA's review of the quality of foreign studies.

147. One comment recommended that FDA not require a sponsor wishing to rely on a foreign study to submit the

names and qualifications of members of that study's reviewing IRB or other independent review committee when such information is not required of a domestic study.

Information about the qualifications of such review committee members is important in assessing the competence of the committee to protect the interests of human subjects. While it is true that the sponsor of a study under an IND is not required to submit the names and qualifications of the members of an independent review committee, the information is routinely obtained through FDA on-site inspections of the IRB. To obtain comparable insight into the quality of institutional review for foreign studies not conducted under an IND, given that inspections of foreign review committees are usually not feasible, FDA believes it is appropriate to ask that the sponsor document the qualifications of the institutional committee members. FDA notes that this provision is not a new requirement, but has been part of FDA's regulations since 1975.

Availability for Public Disclosure of Data and Information in an IND (§ 312.130)

148. Proposed § 312.130 provided that the existence of an IND will not be disclosed or acknowledged. One comment urged that this section be revised to state that, unless such public disclosure is clear and a matter of public record, existence of an IND will not be disclosed by FDA without consulting with a sponsor. The comment argued that unless FDA has a clear record of a previous disclosure, the sponsor is most likely to know whether the existence of the IND has been publicly divulged.

FDA's longstanding policy has been not to disclose the existence of an IND unless its existence has previously been disclosed. Where there is any doubt about previous disclosure, the burden is placed on the requestor to demonstrate such disclosure. As this procedure for screening requests has worked well, FDA does not believe the suggested change is needed.

Drugs for Investigational Use in Laboratory Research Laboratories or In Vitro Tests (§ 312.160)

149. The proposal provided that if authority to ship a drug for use in laboratory research animals or in vitro is terminated, the person shipping the drug must recall or have destroyed the unused supplies of the drug. One comment contended that there should be no need to destroy supplies that may possibly be in short supply and suggested that the provision be revised to permit disposal of the drug in some other way.

FDA agrees with the comment and has revised the final rule by adding new paragraph (c) to § 312.160 to permit a shipper of a drug for investigational use in vitro or in research animals to authorize alternative disposition of unused supplies of the investigational drug, once the investigation is ended. The right to provide an alternative disposition is conditioned on the shipper assuring that the unused supplies will not expose humans to risks from the drug, either directly or indirectly.

List of Subjects

21 CFR Part 312

Drugs, Medical research.

21 CFR Part 314

Administrative practice and procedure, Drugs.

21 CFR Part 511

Animal drugs, Medical research, Reporting and recordkeeping requirements.

21 CFR Part 514

Administrative practice and procedure, Animal drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, 21 CFR Chapter I is amended as follows:

1. By reviewing Part 312 to read as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

Subpart A—General Provisions

Subpart B—Investigational New Drug Application (IND)

Subpart C—Administrative Actions

Subpart D—Responsibilities of Sponsors and Investigators

Subpart E—Miscellaneous

Subpart F—Drugs for Investigational Use in Laboratory Research Animals or in Vitro Tests

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); 21 CFR 5.10, 5.11.

Subpart A—General Provisions

§ 312.1 Scope.

(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part is exempt from the

premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

(b) References in this part to regulations in the Code of Federal Regulations are to Chapter I of Title 21, unless otherwise noted.

§ 312.2 Applicability.

(a) *Applicability.* Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 or 507 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

(b) *Exemptions.* (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in Part 56 and with the requirements for informed consent set forth in Part 50; and

(v) The investigation is conducted in compliance with the requirements of § 312.7.

(2)(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (*a*) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (*b*) it is shipped in compliance with § 312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (*a*) blood grouping serum; (*b*) reagent red blood cells; and (*c*) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with § 312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(c) *Bioavailability studies.* The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of § 320.31.

(d) *Unlabeled indication.* This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug or antibiotic drug product approved under Part 314 or of a licensed biological product.

(e) *Guidance.* FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

§ 312.3 Definitions and interpretations.

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part:

(b) The following definitions of terms also apply to this part:

"Act" means the Federal Food, Drug, and Cosmetic Act (secs. 201–902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301–392)).

"Clinical investigation" means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

"Contract research organization" means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

"FDA" means the Food and Drug Administration.

"IND" means an investigational new drug application. For purposes of this part, "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

"Investigational new drug" means a new drug, antibiotic drug, or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

"Investigator" means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

"Marketing application" means an application for a new drug submitted under section 505(b) of the act, a request to provide for certification of an antibiotic submitted under section 507 of the act, or a product license application for a biological product submitted under the Public Health Service Act.

"Sponsor" means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

"Sponsor-Investigator" means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

"Subject" means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

§ 312.6 Labeling of an investigational new drug.

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear

any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

§ 312.7 Promotion and sale of investigational drugs.

(a) *Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b) *Commercial distribution of an investigational new drug.* A sponsor or investigator shall not commercially distribute or test market an investigational new drug.

(c) *Prolonging an investigation.* A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

(d) *Sale of an investigational drug.* If the drug is to be sold, the sponsor should submit a notification to FDA providing a full explanation why sale is required and why the sale should not be regarded as the commercialization of a new drug for which an application is not approved.

§ 312.10 Waivers.

(a) A sponsor may request FDA to waive applicable requirement under this part. A waiver request may be submitted either in an IND or in an information amendment to an IND. In an emergency, a request may be made by telephone or other rapid communication means. A waiver request is required to contain at least one of the following:

(1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects of the investigation and that one of the following is met:

(1) The sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved;

(2) The sponsor's proposed alternative satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

Subpart B—Investigational New Drug Application (IND)

§ 312.20 Requirement for an IND.

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to § 312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to § 312.2(a) until the investigation is subject to an IND which is in effect in accordance with § 312.40.

§ 312.21 Phases of an investigation.

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. These three phases of an investigation are a follows:

(a) *Phase 1.* (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(b) *Phase 2.* Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(c) *Phase 3.* Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

§ 312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in § 312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

§ 312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1) *Cover sheet (Form FDA-1571).* A cover sheet for the application containing the following:

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of Part 56.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) The name(s) and title(s) of the person(s) responsible under § 312.32 for review and evaluation of information relevant to the safety of the drug.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

(ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) *A table of contents.*

(3) *Introductory statement and general investigational plan.* (i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

(ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).

(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (*a*) The rationale for the drug or the research study; (*b*) the indication(s) to be studied; (*c*) the general approach to be followed in evaluating the drug; (*d*) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (*e*) the estimated number of patients to be given the drug in those studies; and (*f*) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(4) [Reserved]

(5) *Investigator's brochure.* If required under § 312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6) *Protocols.* (i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with § 312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation—an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled

short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(*a*) A statement of the objectives and purpose of the study.

(*b*) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(*c*) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(*d*) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(*e*) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(*f*) A description of the observations and measurements to be made to fulfill the objectives of the study.

(*g*) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7) *Chemistry, manufacturing, and control information.* (i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(*a*) *Drug substance.* A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy relevant requirements in this paragraph.

(*b*) *Drug product.* A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product; and information sufficient to assure the product's stability during the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy certain requirements in this paragraph.

(*c*) A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

(*d*) *Labeling.* A copy of all labels and labeling to be provided to each investigator.

(*e*) *Environmental analysis requirements.* A claim for categorical exclusion under § 25.24 or an environmental assessment under § 25.31.

(8) *Pharmacology and toxicology information.* Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidelines are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) *Pharmacology and drug disposition.* A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) *Toxicology. (a)* An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration

or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(*b*) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under Part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations in Part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9) *Previous human experience with the investigational drug.* A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the durg has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (a)(9)(i) of this section should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

(10) *Additional information.* In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) *Drug dependence and abuse potential.* If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) *Radioactive drugs.* If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) *Other information.* A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

(11) *Relevant information.* If requested by FDA, any other relevant information needed for review of the application.

(b) *Information previously submitted.* The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(c) *Material in a foreign language.* The sponsor shall submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(d) *Number of copies.* The sponsor shall submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

§ 312.30 Protocol amendments.

Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made.

(a) *New protocol.* Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met: (1) The sponsor has submitted the protocol to FDA for its review; and (2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of Part 56. The sponsor may comply with these two conditions in either order.

(b) *Changes in a protocol.* (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:

(i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(*a*) The sponsor has submitted the change to FDA for its review; and

(*b*) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

(ii) Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with § 56.104(c).

(c) *New investigator.* A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is

added in the case of a treatment protocol under § 312.34. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

(d) *Content and format.* A protocol amendment is required to be prominently identified as such (i.e., "Protocol Amendment: New Protocol", "Protocol Amendment: Change in Protocol", or "Protocol Amendment: New Investigator"), to be serially numbered, and to contain the following:

(1)(i) In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.

(ii) In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.

(iii) In the case of a new investigator, the investigator's name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study as is required under § 312.23(a)(6)(iii)(*b*).

(2) Reference, if necessary, to specific technical information in the IND or in a concurrently submitted information amendment to the IND that the sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the IND, the sponsor shall identify by name, reference number, volume, and page number the location of the information.

(3) If the sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA's response should address.

(e) *When submitted.* A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

§312.31 Information amendments.

(a) *Requirement for information amendment.* A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:

(1) New toxicology, chemistry, or other technical information; or

(2) A report regarding the discontinuance of a clinical investigation.

(b) *Content and format of an information amendment.* An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), to be numbered serially by discipline, and to contain the following:

(1) A statement of the nature and purpose of the amendment.

(2) An organized submission of the data in a format appropriate for scientific review.

(3) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

(c) *When submitted.* Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

§312.32 IND safety reports.

(a) *Definitions.* The following definitions of terms apply to this section:

"Associated with the use of the drug" means that there is a reasonable possibility that the experience may have been caused by the drug.

"Serious adverse experience" means any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. With respect to results obtained from tests in laboratory animals, a serious adverse drug experience includes any experience suggesting a significant risk for human subjects, including any finding of mutagenicity, teratogenicity, or carcinogenicity.

"Unexpected adverse experience" means any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in nature, severity, or freuquency in the risk information described in the general investigational plan or elsewhere in the current application, as amended.

(b) *Review of safety information.* The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from clinical investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(c) *IND safety reports.* (1) *Written reports.* The sponsor shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with use of the drug that is both serious and unexpected. Such notification shall be made as soon as possible and in no event later than 10 working days after the sponsor's initial receipt of the information. Each written notification shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA division of the Center for Drugs and Biologics which has responsibility for review of the IND.

(ii) In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previouos, similar reports.

(2) *Telephone report.* The sponsor shall also notify FDA by telephone of any unexpected fatal or life-threatening experience associated with use of the drug in the clinical studies conducted under the IND no later than 3 working days after receipt of the information. Each telephone call to FDA shall be transmitted to the FDA division of the Center for Drugs and Biologics which has responsibility for review of the IND. For purposes of this section, life-threatening means that the patient was, in the view of the investigator, at *immediate* (emphasis added) risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

(3) *Reporting format or frequency.* FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the

change is agreed to in advance by the director of the division in the Center for Drugs and Biologics which is responsible for review of the IND.

(4) A sponsor of a clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with use of the drug that is not from the clinical study itself.

(d) *Followup.* (1) The sponsor shall promptly investigate all safety information received by it.

(2) Followup information to a safety report shall be submitted as soon as the relevant information is available.

(3) If the results of a sponsor's investigation show that an adverse experience not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor shall report such experience in a safety report as soon as possible after the determination is made, but in no event longer than 10-working days.

(4) Results of a sponsor's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

(e) *Disclaimer.* A safety report or other information submitted by a sponsor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse experience.

§ 312.33 Annual reports.

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

(a) *Individual study information.* A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) The total number of subjects initially planned for inclusion in the study, the number entered into the study to date, the number whose participation in the study was completed as planned, and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

(b) *Summary information.* Information obtained during the previous year's clinical and nonclinical investigations, including:

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trails, and information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under § 312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

§ 312.34 Treatment use of an investigational new drug. [Reserved]

§ 312.36 Emergency use of an investigational new drug.

Need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in accordance with § 312.23 or § 312.34. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to FDA by telephone or other rapid communication means. For investigational biological drugs, the request should be directed to the Division of Biological Investigational New Drugs (HFN–823), Center for Drugs and Biologics, 8800 Rockville Pike, Bethesda, MD 20205, 301–443–4864. For all other investigational drugs, the request for authorization should be directed to the Product Information Coordination Staff (HFN–46), Center for Drugs and Biologics, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4320. After normal working hours, eastern standard time, the request should be directed to the FDA Division of Emergency and Epidemiological Operations, 202–857–8400. Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization.

§ 312.38 Withdrawal of an IND.

(a) At any time a sponsor may withdraw an effective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with § 312.59.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

Subpart C—Administrative Actions

§ 312.40 General requirements for use of an investigational new drug in a clinical investigation.

(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:

(1) The sponsor of the investigation submits an IND for the drug to FDA; the

IND is in effect under paragraph (b) of this section; and the sponsor complies with all applicable requirements in this part and Parts 50 and 56 with respect to the conduct of the clinical investigations; and

(2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and Parts 50 and 56.

(b) An IND goes into effect:

(1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under § 312.42; or

(2) On earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND.

(c) A sponsor may ship an investigational new drug to investigators named in the IND:

(1) Thirty days after FDA receives the IND; or

(2) On earlier FDA authorization to ship the drug.

(d) An investigator may not administer an investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

§ 312.41 Comment and advice on an IND.

(a) FDA may at any time during the course of the investigation communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information.

(b) On the sponsor's request, FDA will provide advice on specific matters relating to an IND. Examples of such advice may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application.

(c) Unless the communication is accompanied by a clinical hold order under § 312.42, FDA communications with a sponsor under this section are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to the agency.

§ 312.42 Clinical holds and requests for modification.

(a) *General.* A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

(b) *Grounds for imposition of clinical hold*—(1) *Clinical hold of a Phase 1 study under an IND.* FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that:

(i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;

(ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;

(iii) The investigator brochure is misleading, erroneous, or materially incomplete; or

(iv) The IND does not contain sufficient information required under § 312.23 to assess the risks to subjects of the proposed studies.

(2) *Clinical hold of a Phase 2 or 3 study under an IND.* FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that:

(i) Any of the conditions in paragraph (b)(1)(i) through (iv) of this section apply; or

(ii) The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

(c) *Discussion of deficiency.* Whenever FDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of clinical hold FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.

(d) *Imposition of clinical hold.* The clinical hold order may be made by telephone or other means of rapid communication or in writing. The clinical hold order will identify the studies under the IND to which the hold applies, and will briefly explain the basis for the action. The clinical hold order will be made by or on behalf of the Division Director with responsibility for review of the IND. As soon as possible, and no more than 30 days after imposition of the clinical hold, the Division Director will provide the sponsor a written explanation of the basis for the hold.

(e) *Resumption of clinical investigations.* If, by the terms of the clinical hold order, resumption of the affected investigation is permitted without prior notification by FDA once a stated correction or modification is made, the investigation may proceed as soon as the correction or modification is made. In all other cases, an investigation may only resume after the Division Director (or the Director's designee) with responsibility for review of the IND has notified the sponsor that the investigation may proceed. In these cases resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfied the agency that the investigation(s) can proceed. Resumption of a study may be authorized by telephone or other means of rapid communication.

(f) *Appeal.* If the sponsor disagrees with the reasons cited for the clinical hold, the sponsor may request reconsideration of the decision in accordance with § 312.48.

(g) *Conversion of IND on clinical hold to inactive status.* If all investigations covered by an IND remain on clinical hold for 1 year or more, the IND may be placed on inactive status by FDA under § 312.45.

§ 312.44 Termination.

(a) *General.* This section describes the procedures under which FDA may terminate an IND. If an IND is terminated, the sponsor shall end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug. A termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND. Except as provided in paragraph (d) of this section, a termination shall be preceded by a proposal to terminate by FDA and an opportunity for the sponsor to respond. FDA will, in general, only initiate an action under this section after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described in § 312.42.

(b) *Grounds for termination*—(1) *Phase 1.* FDA may propose to terminate an IND during Phase 1 if it finds that:

(i) Human subjects would be exposed to an unreasonable and significant risk of illness or unjury.

(ii) The IND does not contain sufficient information required under § 312.23 to assess the safety to subjects of the clinical investigations.

(iii) The methods, facilities, and controls used for the manufacturing, processing, and packing of the

investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety.

(iv) The clinical investigations are being conducted in a manner substantially different than that described in the protocols submitted in the IND.

(v) The drug is being promoted or distributed for commercial purposes not justified by the requirements of the investigation or permitted by § 312.7.

(vi) The IND, or any amendment or report to the IND, contains an untrue statement of a material fact or omits material information required by this part.

(vii) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of serious and unexpected adverse experiences in accordance with § 312.32 or fails to make any other report required under this part.

(viii) The sponsor fails to submit an accurate annual report of the investigations in accordance with § 312.33.

(ix) The sponsor fails to comply with any other applicable requirement of this part, Part 50, or Part 56.

(x) The IND has remained on inactive status for 5 years or more.

(2) *Phase 2 or 3.* FDA may propose to terminate an IND during Phase 2 or Phase 3 if FDA finds that:

(i) Any of the conditions in paragraph (b)(1)(i) through (x) of this section apply; or

(ii) The investigational plan or protocol(s) is not reasonable as a bona fide scientific plan to determine whether or not the drug is safe and effective for use; or

(iii) There is convincing evidence that the drug is not effective for the purpose for which it is being investigated.

(3) FDA may propose to terminate a treatment IND if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (x) of this section apply; or

(ii) Any of the conditions in § 312.42(b)(3) apply.

(c) *Opportunity for sponsor response.* (1) If FDA proposes to terminate an IND, FDA will notify the sponsor in writing, and invite correction or explanation within a period of 30 days.

(2) On such notification, the sponsor may provide a written explanation or correction or may request a conference with FDA to provide the requested explanation or correction. If the sponsor does not respond to the notification within the allocated time, the IND shall be terminated.

(3) If the sponsor responds but FDA does not accept the explanation or correction submitted, FDA shall inform the sponsor in writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing before FDA under Part 16 on the question of whether the IND should be terminated. The sponsor's request for a regulatory hearing must be made within 10 days of the sponsor's receipt of FDA's notification of nonacceptance.

(d) *Immediate termination of IND.* Notwithstanding paragraphs (a) through (c) of this section, if at any time FDA concludes that continuation of the investigation presents an immediate and substantial danger to the health of individuals, the agency shall immediately, by written notice to the sponsor from the Director of the Center for Drugs and Biologics, terminate the IND. An IND so terminated is subject to reinstatement by the Director on the basis of additional submissions that eliminate such danger. If an IND is terminated under this paragraph, the agency will afford the sponsor an opportunity for a regulatory hearing under Part 16 on the question of whether the IND should be reinstated.

§ 312.45 Inactive status.

(a) If no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the sponsor or on FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor shall have 30 days to respond as to why the IND should continue to remain active.

(b) If an IND is placed on inactive status, all investigators shall be so notified and all stocks of the drug shall be returned or otherwise disposed of in accordance with § 312.59.

(c) A sponsor is not required to submit annual reports to an IND on inactive status. An inactive IND is, however, still in effect for purposes of the public disclosure of data and information under § 312.130.

(d) A sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment under § 312.30 containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, the plan shall reference such information. Additional information supporting the proposed investigation, if any, shall be submitted in an information amendment. Notwithstanding the provisions of § 312.30, clinical investigations under an IND on inactive status may only resume (1) 30 days after FDA receives the protocol amendment, unless FDA notifies the sponsor that the investigations described in the amendment are subject to a clinical hold under § 312.42, or (2) on earlier notification by FDA that the clinical investigations described in the protocol amendment may begin.

(e) An IND that remains on inactive status for 5 years or more may be terminated under § 312.44.

§ 312.47 Meetings.

(a) *General.* Meetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extent that they aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extent that FDA's resources permit. The general principle underlying the conduct of such meetings is that there should be free, full, and open communication about any scientific or medical question that may arise during the clinical investigation. These meetings shall be conducted and documented in accordance with Part 10.

(b) *"End-of-Phase 2" meetings and meetings held before submission of a marketing application.* At specific times during the drug investigation process, meetings between FDA and a sponsor can be especially helpful in minimizing wasteful expenditures of time and money and thus in speeding the drug development and evaluation process. In particular, FDA has found that meetings at the end of Phase 2 of an investigation (end-of-Phase 2 meetings) are of considerable assistance in planning later studies and that meetings held near completion of Phase 3 and before submission of a marketing application ("pre-NDA" meetings) are helpful in developing methods of presentation and submission of data in the marketing application that facilitate review and allow timely FDA response.

(1) *End-of-Phase 2 meetings*—(i) *Purpose.* The purpose of an end-of-Phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols, and to identify any additional information necessary to support a

marketing application for the uses under investigation.

(ii) *Eligibility for meeting.* While the end-of-Phase 2 meeting is designed primarily for IND's involving new molecular entities or major new uses of marketed drugs, a sponsor of any IND may request and obtain an end-of-Phase 2 meeting.

(iii) *Timing.* To be most useful to the sponsor, end-of-Phase 2 meetings should be held before major commitments of effort and resources to specific Phase 3 tests are made. The scheduling of an end-of-Phase 2 meeting is not, however, intended to delay the transition of an investigation from Phase 2 to Phase 3.

(iv) *Advance information.* At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, and, if available, tentative labeling for the drug. The recommended contents of such a submission are described more fully in FDA Staff Manual Guide 4850.6 that is publicly available under FDA's public information regulations in Part 20.

(v) *Conduct of meeting.* Arrangements for an end-of-Phase 2 meeting are to be made with the division in FDA's Center for Drugs and Biologics which is responsible for review of the IND. The meeting will be scheduled by FDA at a time convenient to both FDA and the sponsor. Both the sponsor and FDA may bring consultants to the meeting. The meeting should be directed primarily at establishing agreement between FDA and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. The adequacy of technical information to support Phase 3 studies and/or a marketing application may also be discussed. Agreements reached at the meeting on these matters will be recorded in minutes of the conference that will be taken by FDA in accordance with § 10.65 and provided to the sponsor. The minutes along with any other written material provided to the sponsor will serve as a permanent record of any agreements reached. Barring a significant scientific development that requires otherwise, studies conducted in accordance with the agreement shall be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

(2) *"Pre-NDA" meetings.* FDA has found that delays associated with the initial review of a marketing application may be reduced by exchanges of information about a proposed marketing application. The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. Arrangements for such a meeting are to be initiated by the sponsor with the division responsible for review of the IND. To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

(i) A brief summary of the clinical studies to be submitted in the application.

(ii) A proposed format for organizing the submission, including methods for presenting the data.

(iii) Any other information for discussion at the meeting.

§ 312.48 Dispute resolution.

(a) *General.* The Food and Drug Administration is committed to resolving differences between sponsors and FDA reviewing divisions with respect to requirements for IND's as quickly and amicably as possible through the cooperative exchange of information and views.

(b) *Administrative and procedural issues.* When administrative or procedural disputes arise, the sponsor should first attempt to resolve the matter with the division in FDA's Center for Drugs and Biologics which is responsible for review of the IND, beginning with the consumer safety officer assigned to the application. If the dispute is not resolved, the sponsor may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings and obtaining timely replies to inquiries. Further details on this procedure are contained in FDA Staff Manual Guide 4820.7 that is publicly available under FDA's public information regulations in Part 20.

(c) *Scientific and medical disputes.* (1) When scientific or medical disputes arise during the drug investigation process, sponsors should discuss the matter directly with the responsible reviewing officials. If necessary, sponsors may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Requests for such meetings shall be directed to the director of the division in FDA's Center for Drugs and Biologics which is responsible for review of the IND. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(2) The "end-of-Phase 2" and "pre-NDA" meetings described in § 312.47(b) will also provide a timely forum for discussing and resolving scientific and medical issues on which the sponsor disagrees with the agency.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may rely on, and may bring to any meeting, their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations.

Subpart D—Responsibilities of Sponsors and Investigators

§ 312.50 General responsibilities of sponsors.

Sponsors are responsibile for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

§ 312.52 Transfer of obligations to a contract research organization.

(a) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are

transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

(b) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

§ 312.53 Selecting investigators and monitors.

(a) *Selecting investigators.* A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.

(b) *Control of drug.* A sponsor shall ship investigational new drugs only to investigators participating in the investigation.

(c) *Obtaining information from the investigator.* Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:

(1) A signed investigator statement (Form FDA–1572) containing:

(i) The name and address of the investigator;

(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;

(iv) The name and address of any clinical laboratory facilities to be used in the study;

(v) The name and address of the IRB that is responsible for review and approval of the study(ies);

(vi) A commitment by the investigator that he or she:

(*a*) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

(*b*) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(*c*) Will personally conduct or supervise the described investigation(s);

(*d*) Will inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and institutional review board review and approval are met;

(*e*) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with § 312.64;

(*f*) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

(*g*) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

(vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under Part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

(viii) A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

(2) *Curriculum vitae.* A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

(3) *Clinical protocol.* (i) For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

(ii) For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

(d) *Selecting monitors.* A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation.

§ 312.55 Informing investigators.

(a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in § 312.23(a)(5).

(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with § 312.32.

§ 312.56 Review of ongoing investigations.

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA–1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of § 312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under § 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with § 312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those

investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by § 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.

§ 312.57 Recordkeeping and record retention.

(a) A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

(b) A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

§ 312.58 Inspection of sponsor's records and reports.

(a) *FDA inspection.* A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

(b) *Controlled substances.* If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR Part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

§ 312.59 Disposition of unused supply of investigational drug.

The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with § 312.57.

§ 312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of Part 50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in § 50.23. Additional specific responsibilities of clinical investigators are set forth in this part and in Parts 50 and 56.

§ 312.61 Control of the investigational drug.

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

§ 312.62 Investigator recordkeeping and record retention.

(a) *Disposition of drug.* An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under § 312.59.

(b) *Case histories.* An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational drug or employed as a control in the investigation.

(c) *Record retention.* An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

§ 312.64 Investigator reports.

(a) *Progress reports.* The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under § 312.33 to submit annual reports to FDA on the progress of the clinical investigations.

(b) *Safety reports.* An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.

(c) *Final report.* An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

§ 312.66 Assurance of IRB review.

An investigator shall assure that an IRB that complies with the requirements set forth in Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

§ 312.68 Inspection of investigator's records and reports.

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times,

permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to § 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

§ 312.69 Handling of controlled substances.

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

§ 312.70 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50, or Part 56, or has submitted to the sponsor false information in any required report, the Center for Drugs and Biologics will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered but not accepted by the Center for Drugs and Biologics, the investigator will be given an opportunity for a regulatory hearing under Part 16 on the question of whether the investigator is entitled to receive investigational new drugs.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50, or Part 56, or has deliberately or repeatedly submitted false information to the sponsor in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

(c) Each IND and each approved application submitted under Part 314 containing data reported by an investigator who has been determined to be ineligible to receive investigational drugs will be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval of any marketing application.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing under Part 16. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor of the determination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under Part 16 on the question of whether the IND should be reinstated.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the drug product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the drug product in accordance with the applicable provisions of the act.

(f) An investigator who has been determined to be ineligible to receive investigational drugs may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ investigatioal drugs solely in compliance with the provisions of this part and of Parts 50 and 56.

Subpart E—Miscellaneous

§ 312.110 Import and export requirements.

(a) *Imports.* An investigational new drug offered for import into the United States complies with the requirements of this part if it is subject to an IND that is in effect for it under § 312.40 and: (1) The consignee in the United States is the sponsor of the IND; (2) the consignee is a qualified investigator named in the IND; or (3) the consignee is the domestic agent of a foreign sponsor, is responsible for the control and distribution of the investigational drug, and the IND identifies the consignee and describes what, if any, actions the consignee will take with respect to the investigational drug.

(b) *Exports.* An investigational new drug intended for export from the United States complies with the requirements of this part as follows:

(1) If an IND is in effect for the drug under § 312.40 and each person who receives the drug is an investigator named in the application; or

(2) If FDA authorizes shipment of the drug for use in a clinical investigation. Authorization may be obtained as follows:

(i) Through submission to the International Affairs Staff (HFY-50), Associate Commissioner for Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, of a written request from the person that seeks to export the drug. A request must provide adequate information about the drug to satisfy FDA that the drug is appropriate for the proposed investigational use in humans, that the drug will be used for investigational purposes only, and that the drug may be legally used by that consignee in the importing country for the proposed investigational use. The request shall specify the quantity of the drug to be shipped per shipment and the frequency of expected shipments. If FDA authorizes exportation under this paragraph, the agency shall concurrently notify the government of the importing country of such authorization.

(ii) Through submission to the International Affairs Staff (HFY-50), Associate Commissioner for Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, of a formal request from an authorized official of the government of the country to which the drug is proposed to be shipped. A request must specify that the foreign government has adequate information about the drug and the proposed investigational use, that the drug will be used for investigational purposes only, and that the foreign government is satisfied that the drug may legally be used by the intended consignee in that country. Such a request shall specify the quantity of drug to be shipped per shipment and the frequency of expected shipments.

(iii) Authorization to export an investigational drug under paragraph (b)(2)(i) or (ii) of this section may be revoked by FDA if the agency finds that the conditions underlying its authorization are not longer met.

(3) This paragraph applies only where the drug is to be used for the purpose of clinical investigation.

(4) This paragraph does not apply to the export of an antibiotic drug product shipped in accordance with the provisions of section 801(d) of the act.

(5) This paragraph does not apply to the export of new drugs (including

biological products) approved for export under section 802 of the act or section 351(h)(1)(A) of the Public Health Service Act.

§ 312.120 Foreign clinical studies not conducted under an IND.

(a) *Introduction.* This section describes the criteria for acceptance by FDA of foreign clinical studies not conducted under an IND. In general, FDA accepts such studies provided they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the United States and/or marketing approval. Marketing approval of a new drug or antibiotic drug based solely on foreign clinical data is governed by § 314.106.

(b) *Data submissions.* A sponsor who wishes to rely on a foreign clinical study to support an IND or to support an application for marketing approval shall submit to FDA the following information:

(1) A description of the investigator's qualifications;

(2) A description of the research facilities;

(3) A detailed summary of the protocol and results of the study, and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

(4) A description of the drug substance and drug product used in the study, including a description of components, formulation, specifications, and bioavailability of the specific drug product used in the clinical study, if available; and

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under § 314.126.

(c) *Conformance with ethical principles.* (1) Foreign clinical research is required to have been conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" (see paragraph (c)(4) of this section) or the laws and regulations of the country in which the research was conducted, whichever represents the greater protection of the individual.

(2) For each foreign clinical study submitted under this section, the sponsor shall explain how the research conformed to the ethical principles contained in the "Declaration of Helsinki" or the foreign country's standards, whichever were used. If the foreign country's standards were used, the sponsor shall explain in detail how those standards differ from the "Declaration of Helsinki" and how they offer greater protection.

(3) When the research has been approved by an independent review committee, the sponsor shall submit to FDA documentation of such review and approval, including the names and qualifications of the members of the committee. In this regard, a "review committee" means a committee composed of scientists and, where practicable, individuals who are otherwise qualified (e.g., other health professionals or laymen). The investigator may not vote on any aspect of the review of his or her protocol by a review committee.

(4) The "Declaration of Helsinki" states as follows:

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of perdictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweight the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publications.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined With Professional Care (Clinical Research)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic methods.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain

the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

§ 312.130 Availability for public disclosure of data and information in an IND.

(a) The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an investigational new drug application for a new drug or antibiotic drug will be handled in accordance with the provisions established in § 314.430 for the confidentiality of data and information in applications submitted in Part 314. The availability for public disclosure of all data and information in an investigational new drug application for a biological product will be governed by the provisions of §§ 601.50 and 601.51.

(c) Notwithstanding the provisions of § 314.430, FDA shall disclose upon request to an individual to whom an investigational new drug has been given a copy of any IND safety report relating to the use in the individual.

§ 312.140 Address for correspondence.

(a) Except as provided in paragraph (b) of this section, a sponsor shall send an initial IND submission to the Central Document Room, Center for Drugs and Biologics, Food and Drug Administration, Park Bldg., Rm. 214, 12420 Parklawn Dr., Rockville, MD 20852. On receiving the IND, FDA will inform the sponsor which one of the divisions in the Center for Drugs and Biologics is responsible for the IND. Amendments, reports, and other correspondence relating to matters covered by the IND should be directed to the appropriate division. The outside wrapper of each submission shall state what is contained in the submission, for example, "IND Application", "Protocol Amendment", etc.

(b) Applications for the products listed below should be submitted to the Office of Biologics Research and Review (HFN–823), Center for Drugs and Biologics, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205: (1) Products subject to the licensing provisions of the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)) or subject to Part 600; (2) ingredients packaged together with containers intended for the collection, processing, or storage of blood or blood components; (3) urokinase products; (4) plasma volume expanders and hydroxyethyl starch for leukapheresis; and (5) coupled antibodies, i.e., products that consist of an antibody component coupled with a drug or radionuclide component in which both components provide a pharmacological effect but the biological component determines the site of action.

(c) All correspondence relating to biological products for human use which are also radioactive drugs shall be submitted to the Division of Oncology and Radiopharmaceutical Drug Products (HFN–150), Office of Drug Research and Review, Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, except that applications for coupled antibodies shall be submitted in accordance with paragraph (b) of this section.

(d) All correspondence relating to export of an investigational drug under § 312.110(b)(2) shall be submitted to the International Affairs Staff (HFY–50), Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

§ 312.145 Guidelines.

(a) FDA has made available guidelines under § 10.90(b) to help persons to comply with certain requirements of this part.

(b) The Center for Drugs and Biologics maintains a list of guidelines that apply to the Center's regulations. The list states how a person can obtain a copy of each guideline. A request for a copy of the list should be directed to the Legislative, Professional, and Consumer Affairs Branch (HFN–360), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Subpart F—Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

§ 312.160 Drugs for investigational use in laboratory research animals or in vitro tests.

(a) *Authorization to ship.* (1)(i) A person may ship a drug intended solely for tests in vitro or in animals used only for laboratory research purposes if it is labeled as follows:

CAUTION: Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.

(ii) A person may ship a biological product for investigational in vitro diagnostic use that is listed in § 312.2(b)(2)(ii) if it is labeled as follows:

CAUTION: Contains a biological product for investigational in vitro diagnostic tests only.

(2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for tests in vitro or in animals used only for laboratory research.

(3) A person who ships a drug under paragraph (a) of this section shall maintain adequate records showing the name and post office address of the expert to whom the drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery. Records of shipments under paragraph (a)(1)(i) of this section are to be maintained for a period of 2 years after the shipment. Records and reports of data and shipments under paragraph (a)(1)(ii) of this section are to be maintained in accordance with § 312.57(b). The person who ships the drug shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify records required to be maintained under this section.

(b) *Termination of authorization to ship.* FDA may terminate authorization to ship a drug under this section if it finds that:

(1) The sponsor of the investigation has failed to comply with any of the conditions for shipment established under this section; or

(2) The continuance of the investigation is unsafe or otherwise contrary to the public interest or the drug is used for purposes other than bona fide scientific investigation. FDA will notify the person shipping the drug of its finding and invite immediate correction. If correction is not immediately made, the person shall have an opportunity for a regulatory hearing before FDA pursuant to Part 16.

(c) *Disposition of unused drug.* The person who ships the drug under paragraph (a) of this section shall assure the return of all unused supplies of the drug from individual investigators whenever the investigation discontinues or the investigation is terminated. The person who ships the drug may authorize in writing alternative

disposition of unused supplies of the drug provided this alternative disposition does not expose humans to risks from the drug, either directly or indirectly (e.g., through food-producing animals). The shipper shall maintain records of any alternative disposition.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

2. The authority citation for 21 CFR Part 314 continues to read as follows:

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 353, 355, 356, 357, 371); 21 CFR 5.10, 5.11.

3. In § 314.50 by adding new paragraph (d)(5) (x) and (xi) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(d) * * *

(5) * * *

(x) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

(xi) If original subject records were audited or reviewed by the sponsor in the course of monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited or reviewed.

* * * * *

PART 511—NEW ANIMAL DRUGS FOR INVESTIGATIONAL USE

4. The authority citation for 21 CFR Part 511 continues to read as follows:

Authority: Secs. 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 512–516, 518–520, 601, 701, 706, and 801, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511–517 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 76 Stat. 794 as amended, 82 Stat. 343–351, 90 Stat. 539–574 (21 U.S.C. 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360b–360f, 360h–360i, 371, 376); secs. 215, 301, 351, 354–360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 241, 262, 263b–263n).

5. In § 511.1 by revising paragraph (c)(2) and by adding new paragraphs (b)(4) (vi) and (f), to read as follows:

§ 511.1 New animal drugs for investigational use exempt from section 512(a) of the act.

* * * * *

(b) * * *

(4) * * *

(vi) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

* * * * *

(c) * * *

(2) If, after evaluating all available information, including any explanation presented by the investigator, the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the conditions of the exempting regulations in this section or has repeatedly or deliberately submitted false information to the sponsor of an investigation, the Commissioner will notify the investigator and the sponsor of any investigation in which he has been named as a participant that the investigator is not entitled to receive investigational use new animal drugs with a statement of the basis for such determination.

* * * * *

(f) *Contract research organizations.* (1) For purposes of this part and Part 514, "contract research organization" means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

(2) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be in writing and, if not all obligations are transferred, shall describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

(3) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

PART 514—NEW ANIMAL DRUG APPLICATIONS

6. The authority citation for 21 CFR Part 514 continues to read as follows:

Authority: Secs. 512 (i), (n), 701(a), 52 Stat. 1055, 82 Stat. 343–351 (21 U.S.C. 360b (i), (n), 371(a)); 21 CFR 5.10, 5.11.

7. In § 514.1 by adding new paragraph (b)(8)(viii) and (ix), to read as follows:

§ 514.1 Applications.

* * * * *

(b) * * *

(8) * * *

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, the application is required to include a statement containing the name and address of the contract research organization, identifying the clinical study, and listing the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

(ix) If original subject records were audited or reviewed by the sponsor in the course of monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited or reviewed

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Dated: March 16, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

Dated: March 16, 1987.

Don M. Newman,

Acting Secretary of Health and Human Services.

[FR Doc. 87–6064 Filed 3–18–87; 12:05 pm]

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March 19, 1987

Part VIII

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 312

Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment, Use, and Sale; Reproposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 312

[Docket No. 82N-0394]

Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale

AGENCY: Food and Drug Administration.

ACTION: Reproposed rule.

SUMMARY: The Food and Drug Administration (FDA) is reproposing procedures to make investigational new drugs available to desperately ill patients before general marketing begins. These procedures are intended to facilitate the availability of promising new drugs to patients as early in the drug development process as possible, and would apply to patients with immediately life-threatening or other serious diseases for which no satisfactory alternative therapies exist. The procedures for immediately life-threatening diseases would apply, for example, to advanced cases of Acquired Immune Deficiency Syndrome (AIDS) and certain uncontrollable cardiac arrhythmias, while the procedures for other serious diseases would apply, for example, to Alzheimer's and multiple sclerosis. FDA is also reproposing conditions under which drug manufacturers may sell investigational new drug products. With the revolution in biotechnology, it is important to recognize the need to provide sufficient incentives for the rapid development of drug and biological agents. Accordingly, the new procedures would allow sale of drugs, when no satisfactory alternative therapy is available, when the drugs are provided for treatment use to large numbers of patients prior to general marketing.

FDA is reproposing these issues for public comment. While these issues have been aired at great length and have received substantial analysis, FDA, in an abundance of caution and with the desire to have all groups have the opportunity for full participation, is undertaking this extra action.

DATE: Written comments by April 20, 1987.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Steven H. Unger, Center for Drugs and Biologics (HFN-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8049.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of June 9, 1983 (48 FR 26720), FDA published proposed regulations governing the investigational new drug (IND) development process. This set of proposed regulations is commonly referred to as the IND Rewrite. These regulations cover the full range of the IND process, including the contents of IND applications, FDA procedures for reviewing IND's, meetings between FDA reviewers and drug sponsors, and reporting by sponsors of adverse drug reactions observed during clinical trials. The IND Rewrite proposal also addressed the conditions under which patients could obtain investigational drugs primarily for treatment use, and the conditions under which investigational drugs may be sold.

Elsewhere in this issue of the **Federal Register**, FDA is publishing a final rule addressing all portions of the IND Rewrite proposal, except for the provisions concerning treatment use and sale of investigational drugs, which are being reproposed here. Although FDA believes that it could justify publishing these provisions also as a final rule at this time, due to the increasing public interest in the availability of investigational drugs for treatment use, and in an abundance of caution, the agency is providing an additional opportunity for public comment. FDA is providing 30 days for public comment. FDA believes that the compelling public health advantages to be gained from issuing a final rule as quickly as possible constitute good cause under 21 CFR 10.40(b)(2) for providing less than the normal 60 day comment period. The agency plans to issue a final rule by May 18, 1987. FDA is proposing that any final rule based on this proposal be effective 30 days after the date of its publication in the **Federal Register.**

I. Contents of the Reproposal

FDA is reproposing 21 CFR 312.34 (Treatment use of an investigational new drug) and 21 CFR 312.7(d) (Sale of an investigational drug). These provisions, as reproposed, are summarized as follows:

Treatment Use

Under the reproposal, treatment use of an investigational drug would be permitted where the drug is intended to treat an immediately life-threatening or otherwise serious disease; there is no satisfactory alternative drug or other therapy available to treat the disease; the drug is under investigation in a controlled clinical trial under an IND in effect for the trial; and the sponsor of the controlled clinical trial is pursuing marketing approval of the investigational drug with due diligence.

The reproposal also provides two additional sets of criteria, depending upon whether the drug is intended to treat an immediately life-threatening disease or a disease that is serious but not immediately life-threatening. In the case of a "serious" disease, the reproposal provides that the Commissioner may deny a request for treatment use if he or she finds there is insufficient evidence of safety and effectiveness to support such use. In contrast, under the reproposal, for a drug intended to treat an "immediately life-threatening" disease, the Commissioner may deny a request for treatment use if he or she finds that, on the basis of clinical data or other reliable scientific evidence in the IND file, the drug clearly does not provide a therapeutic benefit; or the drug would expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury. The reproposal also adds conforming amendments to the clinical hold section of the regulation.

Sale

The reproposal presents two distinct contexts for the sale of an investigational drug: First, during a clinical trial; and second, under a treatment protocol/IND. Under a reproposal, for sale of an investigational drug during a clinical trial, prior FDA approval is required, and such approval would be granted only upon a showing that sale is needed for the sponsor to undertake or continue the clinical trial. In contrast, the reproposal would authorize sponsors to charge for investigational drugs made available to patients under a treatment protocol/IND, so long as the sponsor complies with certain designated safeguards against commercialization and notifies FDA 10 days prior to the commencement of such sale. Prior FDA approval of the sale in this context would not be required.

The reproposal also contains a provision allowing FDA to withdraw authorization for sale if the price charged is manifestly unfair or if the conditions underlying the initial authorization for sale are no longer satisfied.

These reproposed provisions on treatment use and sale are discussed further below in conjunction with public comments submitted in response to the June 9, 1983, proposal.

II. Response to Comments

A. Treatment Use of Investigational Drugs

1. One comment contended FDA did not have legal authority to permit the use of investigational drugs for treatment and in emergencies. The comment asserted that such uses were inconsistent with the grant of statutory authority in section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) allowing FDA to exempt from the otherwise applicable provisions of the law new drugs intended "solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs."

In allowing for the use of investigational drugs for treatment, FDA is officially recognizing in its regulation longstanding agency practice. FDA believes the comment too narrowly construes the statutory language in section 505(i) of the act. Section 505(i) of the act gives FDA broad discretionary authority to promulgate regulations governing the clinical investigation of new drugs to protect the rights, safety, and welfare of human subjects and otherwise to promote the public health. In implementing this grant of authority, FDA has properly responded to a demand from health professionals to permit limited use of investigational drugs to treat diseases for which there are no satisfactory alternative treatments. The agency believes that the treatment IND/protocol provision, as would be codified under this reproposal, appropriately balances the requirement that use of a drug under section 505(i) of the act be investigational with the public demand for some treatment of promising investigational drugs, and is clearly consistent with the public health mandate of the statute.

The requirement for a treatment IND/protocol calls for the submission of information in advance of treatment for the protection of subjects, and for the submission of safety reports and other information following administration of the drug that provide information on matters concerning the drug's safety and efficacy. Thus, FDA believes that there is a sufficient investigational aspect to these treatment uses to justify agency authorization of such uses.

The language of section 505(i) of the act, in the agency's view, is intended to ensure that unapproved new drugs are not commercialized before marketing approval, and not to prohibit some use of an investigational drug in a "hybrid" treatment-investigational setting. To read the language as prohibiting absolutely the use of an investigational drug for treatment might also call into question agency authorization of a large fraction of studies, most of which also have both an investigational and a treatment purpose. Given the clear intent of the statute that marketing approvals be based on data obtained from such studies, that result could not have been intended.

Finally, FDA notes that the legislative history of the new drug provisions demonstrates that Congress intended to encourage FDA to make promising investigational drugs available to seriously ill patients who are not treatable with alternative therapies. For example, Congress, in enacting in January 1983 the Orphan Drug Amendments (Pub. L. 97–41) to the Federal Food, Drug, and Cosmetic Act, clearly assumed the existence of treatment use for investigational drugs. As seen in section 528, the act instructs the Secretary of Health and Human Services (and, by delegation, FDA) to encourage sponsors of orphan drugs to make their drugs available under treatment protocols, i.e., "to design protocols for clinical investigations of the drug which may be conducted under the [IND] to permit the addition to the investigations of persons with the disease or condition who need the drug to treat the disease or condition and who cannot be satisfactorily treated by available alternative drugs." This statute fully supports the existence of and need for procedures that will permit some seriously ill persons to be treated with investigational drugs.

2. Many comments discussed the proposed criteria that FDA would use in determining whether to authorize use of an investigational drug for treatment. Several comments recommended alternative criteria to those proposed. One comment contended that the proposed criteria were simply too vague. Another comment indicated that FDA should accept the assessment of need for the drug by the patient's personal physician as sufficient justification for allowing treatment use. Another comment contended that if the proposed criteria were met, an investigational drug would satisfy the conditions for marketing approval, thus obviating the need for further studies. Another comment suggested that in determining whether there is sufficient evidence of a drug's safety and effectiveness to justify its proposed use, FDA should clarify that the only sort of evidence deemed "sufficient" would be evidence derived from controlled studies.

As discussed in the preamble of the proposed rule, an important goal of treatment protocols/IND's is to provide promising new drugs to patients with serious disease conditions for which there are no alternative therapies. This reproposal, like the proposed rule, is intended to improve physician (and patient) access to these investigational drugs by expressly authorizing the practice in regulations and clarifying what steps are necessary to obtain an investigational drug for treatment use. The treatment use program would protect against both the commercialization of investigational drugs, prior to marketing approval, and the use of investigational drugs for disease conditions that either are not serious or immediately life-threatening or for which there are alternative therapies. By restricting treatment use to serious and immediately life-threatening disease conditions and specifying what criteria must be met for treatment use for each, the program fulfills FDA's responsibility to protect the rights, safety, and welfare of human subjects and otherwise to promote the public health. The criteria for such use represent a significant improvement over previous, unwritten guidelines in specifically identifying the universe of eligible drugs and establishing reasonable guidelines for agency action.

FDA does not agree that criteria either significantly more stringent or more relaxed would adequately meet the need for a treatment use program. Significantly more stringent criteria for immediately life-threatening diseases, such as proof of a drug's safety and effectiveness, which can only be developed near the end of the investigational process, would not serve the purpose of allowing treatment use at an earlier stage than that provided by commercially approved drugs. Requiring a degree of proof only slightly less than is necessary for general market distribution would unnecessarily restrict a drug that could provide real benefits in the particular case under treatment.

On the other hand, where a disease is not serious or immediately life-threatening or there is insufficient evidence of safety and effectiveness, allowing a drug to be used for treatment would allow use that is too widespread given the lack of knowledge about the benefits and safety of the drug. Thus, the need for a treatment use program to bring promising new drugs to patients who particularly need them calls for standards designed to achieve the goal, such as those contained in this reproposal, of safety and therapeutic benefit for a specific category of patients.

FDA agrees that the criteria, as originally proposed, were in some respects overly general or too vague,

and that it is appropriate to provide more specific guidance, where possible, on the circumstances under which treatment use would be allowed. Consequently, the criteria provision in the reproposal is more specific and elaborates on the proposed provision by breaking out two cases of disease conditions that warrant distinction and specifying the criteria appropriate to each. The two cases are those in which the disease is immediately life-threatening and those in which the disease is serious, but not immediately life-threatening. This distinction is made because the consequences of denying treatment use for a patient in an immediately life-threatening situation are much graver than for a patient with a serious, but not immediately life-threatening condition. The criteria to deny treatment use for an immediately life-threatening disease, in turn, recognize this distinction by specifying that denial of treatment use must be predicated on evidence that the drug clearly does not provide a therapeutic benefit or the drug would present an unreasonable and significant additional risk of illness or injury. On the other hand, the denial of treatment use for serious, but not immediately life-threatening, disease conditions can be based on a finding of insufficient evidence of safety and effectiveness to support such use. However, in both cases, there must be no satisfactory alternative drug or therapy available.

What constitutes an immediately life-threatening illness cannot be rigorously defined. The medical judgment of the sponsor or treating physician must carry considerable weight in deciding whether an illness poses a sufficient threat to justify treating patients with a drug for which safety or effectiveness has not been demonstrated fully. Generally, an immediately life-threatening illness is one that poses a significant threat of the patient's dying unless the course of the disease is promptly altered to reduce that possibility. As used in this context, the term "immediately" refers to the need to treat the illness quickly, without implying any particular time within which death is expected to occur (though such time is expected to be reasonably short). The term "life-threatening" extends both to situations in which it is certain that a patient's disease will result in death and to situations in which death is a highly probable outcome of the disease.

For all treatment IND's, the reproposal clarifies that the drug must be under IND investigation in a controlled clinical trial, and that the sponsor is pursuing marketing approval with due diligence. These provisions are designed to ensure there is no incentive to prolong the investigational status of a drug subject to treatment IND, especially where the drug is to be sold to patients under § 312.7(d), as reproposed. The term "due diligence" is intended to refer to an applicant's good faith effort to seek timely and expeditious marketing approval through action meant to advance the progress of the IND or subsequent marketing application.

FDA disagrees with the comment that a physician's assessment alone should be sufficient justification for allowing treatment. The final rule relies heavily on the joint assessment of the physician and sponsor; however, FDA's statutory responsibility necessitates that it retain authority to review the appropriateness of IND treatment use and to ensure that such use does not constitute the commercialization of an investigational drug.

FDA disagrees with the notion that a drug that meets the criteria in § 312.34(b) would also meet the requirements for marketing approval. The regulation requires that the sponsor submit sufficient evidence of a drug's safety and effectiveness to justify its treatment use for serious disease conditions, but does not demand that the sponsor submit the same definitive, statutorily sufficient evidence of a drug's safety and effectiveness required for NDA approval. Thus, a sponsor could satisfy the criteria for treatment IND authorization by presenting evidence that is supportive of a drug's effectiveness for its treatment use, yet not meet the statutory standard of effectiveness, i.e., substantial evidence consisting of adequate and well-controlled clinical investigations, or the statutory standard for safety, required for open marketing of the drug under the New Drug Approval process. In the case of treatment use for immediately life-threatening diseases, the evidence may not even be sufficient to meet the standard for treatment use of a serious disease.

With respect to the comment suggesting that only evidence from controlled studies be used in determining whether there is sufficient evidence of a drug's safety and effectiveness to justify its proposed use, FDA advises that it will rely on all data available at the time the request for treatment use is received by the agency.

In the case of a drug for a life-threatening illness, for example, it is expected that data from controlled clinical trials will ordinarily be available at the time a treatment IND is requested. Even so, there may be circumstances where little data are available concerning the therapeutic benefit of a drug, particularly if Phase 1 studies have just ended or Phase 2 testing has only recently begun. In the case of an immediately life-threatening disease for which there is no adequate therapy available, the reproposal requires that the Commissioner have adequate support for a determination that there is an unreasonable and additional risk or clearly no therapeutic benefit in order for the Commissioner to deny treatment use. In making such a determination, the Commissioner obviously must have sufficient information, and must make use of all available information. It follows that, under the reproposal, it is expected that the Commissioner will be provided with sufficient data to make the specified determination. Once treatment use has been authorized, in the circumstance in which additional data later become available to provide a basis for the Commissioner to determine that the drug either clearly has no therapeutic benefit or presents an unreasonable and significant additional risk, the Commissioner may proceed under reproposed § 312.42(b)(3) to place the treatment IND on clinical hold.

Finally, agency experience has shown that patients are served most efficiently if the treating physician requesting an investigational drug for treatment use works through the sponsoring pharmaceutical company (under a treatment protocol to an existing IND) rather than applying directly to FDA for a separate treatment IND. Accordingly, although the reproposal contains procedures for either route, the treating physician would be required first to attempt obtaining the drug from the IND sponsor under a treatment protocol before submitting a separate treatment IND to FDA.

3. One comment expressed concern about FDA's stated willingness under certain circumstances to waive IRB review of treatment IND's and treatment protocols. Noting that review of the adequacy of informed consent is one function of the IRB, the comment wondered whether, if FDA finds that IRB review of a treatment use is unnecessary for the protection of subjects, the investigator would still be required to obtain his or her subject's informed consent. In addition, several other comments asserted that IRB review was necessary for the protection of both the patient and investigator and that no alternative method of assuring patient protection would provide adequate incentives to real patient protection. In contrast, one comment

suggested that all treatment uses should be granted a "blanket" exemption from IRB review requirements.

FDA emphasizes that it will only waive IRB review if it finds that there are adequate alternative means of assuring the protection of subjects' safety, welfare, and rights. In the proposal, FDA stated that it might on its own initiative waive IRB review because the agency believes that in the treatment IND/protocol context there may frequently be adequate alternative guarantees of subject protection. These guarantees include the required findings FDA must make in authorizing a treatment IND/protocol, that the necessary evidence is available to support the proposed treatment use, and that the potential risks of the drug are commensurate with the seriousness of the patient's disease. All of these findings are analogous to findings that an IRB is required to make. In addition, given that the physician's primary goal in using an investigational drug under a treatment IND or protocol is to provide the best available therapy to an individual patient, there is less likelihood than in a conventional investigation that concerns about the patient will be subordinated to concerns about the investigation. The less likelihood that a subject's interest may be subordinated, the less need there may be for a neutral, objective, third party to oversee the investigation. Finally, FDA will insist on assurances that adequate informed consent is obtained, regardless of whether IRB review is obtained or waived. The requirement for informed consent is independent of the requirement for IRB review and is not subject to waiver except in extraordinarily unusual circumstances. These factors lead FDA to conclude that waiver of IRB review of treatment IND's/protocol may frequently be warranted.

4. Proposed § 312.34(c) [reproposed as § 312.35(b)] provides that the supplying of an investigational drug to a licensed medical practitioner by a sponsor of a separate clinical investigation shall be deemed to authorize the incorporation-by-reference of the technical information contained in the supplying sponsor's IND into the medical practitioner's IND. One comment argued that, given the confidentiality of much of the information in an IND and the often highly competitive nature of new drug development, it would be inappropriate not to insist that authorization for incorporation be affirmatively documented by a letter from the sponsor. Another comment claimed that the sponsor should always be the party to control information to be referenced by another party. This comment claimed that there is no mechanism whereby FDA can verify the source of an investigational drug that may also be commercially available for other therapeutic uses. In contrast, one comment approved of the "deemed incorporated" provision, but concluded that the provision was deficient in failing to give the consignee-physician access to pertinent information in the commercial sponsor's IND file. The comment urged that the final rule ensure that the treating physician have access to all information in the commercial sponsor's IND that may be relevant to the treatment use of the drug. The comment claimed that a policy permitting nondisclosure would enable a commercial sponsor to withhold negative information about its drug from the physician and would, therefore, be incompatible with the physician's proper treatment of the patient and with the right of the patient to be fully informed.

FDA calls attention to the fact that, under the reproposal, most physician access to investigational drugs for treatment use would come through the sponsor. In the infrequent event that the physician is directly applying for a treatment IND, FDA believes it appropriate to consider a commercial drug firm that chooses to supply its investigational drug to a physician-sponsor to have consented to the information in the drug firm's IND being consulted by FDA in assessing the physician's IND. It is essential that FDA have access to this information in its review of the physician's treatment IND submission. The comments, however, misunderstand the significance of the "deemed incorporated" provision. First, it should be emphasized that the provision would not compromise the confidentiality of commercially valuable information in the drug firm's IND as the information incorporated-by-reference would be available solely to FDA for its review: The provision does not authorize disclosure of the incorporated information to the physician or to any third party. Second, if a drug firm remains concerned about the potential implications of the provision, the firm can either choose not to provide the drug to the physician, or preferably can choose to accommodate the physician's request for treatment use of the drug under a company developed treatment protocol.

As the treatment IND provisions are only available for unmarketed drugs, FDA can with some confidence assume that an investigational drug in the treating physician's possession was shipped from a drug firm that holds a commercial IND on the drug. Therefore, FDA believes that it should be able to "verify" the source of a drug.

Finally, with respect to the request that the physician-consignee be given access to the information on the investigational drug, the agency expects the supplying drug company to provide the physician with a copy of the same investigator brochure that it gives its own investigators. The brochure, which contains a summary of all information relevant to the investigational use of the drug, should be adequate to ensure the drug's proper use by the physician. The agency believes that individual treating physicians should no more need access to the technical information in the drug firm's IND than would investigators conducting controlled studies for the sponsor under that IND.

5. One comment urged that a physician who obtains an investigational drug under a treatment IND be required to relay important safety information obtained during the treatment use to the drug company that supplied the drug.

First, it should be emphasized that individual physician-sponsors of treatment IND's are, like sponsors of commercial IND's, required to submit safety reports to FDA in accordance with § 312.32. FDA also strongly encourages a physician who obtains drugs under his or her own treatment IND's to provide such safety information to the drug company that supplies the physician with the investigational drug. However, FDA does not believe it practical to require such concurrent reporting of safety information. The fact that some physicians may not provide such information to their drug firm suppliers is one reason why the agency would prefer a drug firm with a drug eligible for treatment use under § 312.34 to make the drug available under its own treatment protocol. Use of treatment protocols increases the likelihood that useful safety information generated by the treatment use will be properly collected, interpreted, and forwarded to the sponsor and FDA.

6. One comment urged that FDA list the information required to support a treatment protocol.

FDA advises that the information required to support a treatment protocol is that listed in § 312.35(a)—essentially a copy of the protocol itself and a copy of the brochure to be given each treating physician. Most, if not all, other information supporting the treatment protocol should already be in the drug firm's commercial IND and may be incorporated-by-reference.

B. Sale of Investigational Drugs

7. Many comments objected to the proposed change to the policy on sale of investigational drugs. Under the proposed policy, sale would not be allowed except upon the written approval of the Director of the Center for Drugs and Biologics. One comment claimed that there was no statutory authority for FDA to become involved in matters relating to the sale of investigational drugs. The comment maintained that current FDA requirements on sale have worked well and urged FDA to retain those requirements. Another comment, while not specifically objecting to the proposed policy, urged that the final rule require FDA to respond to a sponsor's request within a specified time limit. One comment urged the adoption of a very stringent standard for determining whether the sale of an investigational drug would be appropriate. Conversely, another comment suggested the sale be routinely allowed so long as the proposed sale price was not greater than necessary to recover costs of manufacture, research, development, and handling.

The agency disagrees with the comment claiming it does not have statutory authority. In the case of drugs subject to the Public Health Service Act, the authority for regulating the sale of an investigational biological drug is clear. Under section 351 of the Public Health Service Act (42 U.S.C. 262), no person may "sell, barter, or exchange, or offer for sale" a biologic drug product unless the product is subject to a biological product license. In the case of drugs that are not biological products, and thus subject to the new drug provisions of the Federal Food, Drug, and Cosmetic Act, the authority for regulating the sale of such investigational drugs is equally clear. Under the Federal Food, Drug, and Cosmetic Act, the Secretary of Health and Human Services (and, by delegation, FDA) has the responsibility for promulgating regulations to exempt from the otherwise applicable statutory provisions governing the shipment of new drugs, "drugs intended solely for investigational use * * *." In the agency's view, the sale of drugs under most circumstances, whether it be by a sponsor or investigator, suggests that it is being commercialized, a practice that is presumptively inconsistent with the drug's use solely for investigational purposes. Therefore, the agency believes that it is reasonable and within its statutory authority to prohibit a sale of an investigational drug unless it can be demonstrated that the proposed sale is consistent with the drug's investigational status and does not commercialize the drug prior to its approval.

The agency notes that this policy on sale and the general prohibition against commercialization are not policies newly adopted in the IND Rewrite rulemaking, but have been part of the IND regulations since 1963. FDA believes, however, that if sale were not permitted when appropriate, research and development in the drug industry and the medical field might be curtailed, in turn unnecessarily delaying or eliminating certain improvements in health care. Prohibitive costs would become a disincentive to new drug development if the sponsors did not have adequate assurance that sale is permitted when warranted.

The reproposal, like the proposal, prohibits the following: promotion of an investigational new drug; commercial distribution of an investigational new drug; and prolonging an investigation. The reproposal adds a provision that allows FDA to withdraw the sale authorization if the price being charged for an IND is manifestly unfair or the drug is promoted or otherwise commercialized. FDA believes this added provision is necessary to protect against abuses of sale authorization that might arise when the drug is the only treatment or therapy available.

As proposed, the authority to approve sale of investigational drugs for clinical trials belonged exclusively to the Director, Center for Drugs and Biologics. On reconsideration, FDA has revised the rule to authorize the directors of the review offices to approve sale requests in place of the Director.

As noted above, one comment suggested that FDA should specify a time frame in which responses to sale requests would be made. The procedure in the proposed rule for all investigational new drugs required application and written approval by FDA. In this reproposal, in the case of sale of a drug intended for treatment use, notification by the sponsor is required and after 10 days sale would be allowed unless FDA disapproves. For clinical trial sale requests, as in the proposed rule, sale would be allowed only after FDA approves sale. This distinction is justified for two reasons. First, affirmative approval would unnecessarily delay the availability of treatment use drugs that have met the criteria for treatment use. Second, the costs of IND's for clinical trials are standard costs of doing business while costs of treatment use drugs will be costs incurred beyond those needed to obtain marketing approval.

The cost of a drug used in clinical studies is normally absorbed by the sponsor as a cost of doing business. This is because clinical studies are required to obtain marketing approval from FDA, and because such studies might be undertaken even if FDA approval were not required. The traditional notion that clinical trial costs are a cost of doing business should hold unless the sponsor provides adequate explanation for the sale and receives affirmative FDA approval. For example, an explanation of specific modern advances in science and technology that create an environment of extremely high costs could warrant the sale of drugs used in clinical trials. In addition, permitting sale in such cases should permit greater competition in drug development by permitting small and fledgling companies to test products that are extremely expensive to produce, providing all ethical concerns are met.

In light of this greater justification burden, i.e., demonstrating why the costs should not be absorbed as a cost of doing business, FDA does not believe it should commit to respond to requests for sale of drugs in clinical trials within a specified time frame. Nevertheless, FDA is committed to expediting review of these requests within the constraints imposed by available resources and other priorities.

However, in the case of sale for treatment use, if both an attending physician and the relevant sponsor conclude that an investigational drug should be made available for treatment and such drug meets the treatment use criteria in § 312.34(b), it would be detrimental to disallow or delay the sale of the drug. There might be no incentive for a sponsor to supply investigational drugs for treatment use, thus denying the drug to patients who, in the exercise of their informed judgment, choose to avail themselves of this treatment. Similarly, any delay in the authorization of sale could cause a delay in the availability of the drug that would be inappropriate in light of the circumstances, i.e., a serious or immediately life-threatening disease condition for which there is no alternative therapy.

Although sale would be allowed under specified conditions in this reproposal, it would be inappropriate to introduce into the sale provision specific price controls or a procedure in which the agency becomes a price regulator. The sponsor is in the best position to know the costs involved in the manufacturing of a drug. However, there

is a potential that undue advantage may be taken of seriously or terminally ill patients, particularly due to the absence of alternative treatments, by charging exorbitant prices. Accordingly, to curb any possible abuse, under the reproposal FDA could withdraw authorization for sale of a drug, distributed under either a clinical trial or a treatment IND, if it determines that a charge for the drug is manifestly unfair.

In summary, the sale provision in the reproposal does not unduly restrict sale nor does it allow unrestricted sale. In all instances of investigational drug sale, the prohibitions against promotion and commercialization still apply. In addition, FDA has the authority to withdraw sale authorization if any abuses occur, including promotion and commercialization. FDA believes the policy as set forth in this reproposal would appropriately provide for sale when the circumstances of a particular investigational drug so warrant.

8. One comment asked that the sale provisions be clarified to assure that FDA does not regulate hospital charges imposed for the costs of handling, storing, and administering investigational drug products.

The sale provisions pertain to the direct sale of the drug itself, not to incidental charges imposed for services ancillary to the distribution or administration of the drug. Thus, the provision does not apply to charges imposed by hospital pharmacies for handling investigational drug products.

9. One comment suggested that if a physician wants to conduct an independent investigation under a treatment IND, the firm supplying the physician the drug should be permitted to charge the physician for the product. On the other hand, another comment, believing that FDA policy already allowed firms to sell products to physicians sponsoring treatment IND's, argued against that policy by suggesting that permitting sale of an investigational drug reduces the commercial sponsor's incentives to do the necessary work to prepare a marketing application.

When a commercial firm ships an investigational drug to a treating physician for use under the physician's treatment IND, the commercial firm may make reasonable charges for the drug in accordance with the specific provisions of § 312.7(d). It should be noted that the supplier is still subject to the general prohibitions in § 312.7(b) against commercializing an unapproved investigational drug, and any sale of the drug by the firm would be examined in that context.

III. Economic Impact

The agency has examined the economic impact of this proposed rule and has determined that it does not require either a regulatory impact analysis, as specified in Executive Order 12291, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96–354). These proposed procedures would facilitate the availability of promising new drugs to patients who need treatment. The proposed revisions would also modify conditions under which investigational drugs may be sold. Generally, these revisions would have a favorable impact on drug sponsors, investigators, physicians, and patients, while adequately protecting the safety of human subjects.

The proposed procedures would expedite public access to certain promising new drugs. For consumers, these new procedures would make many drugs for immediately life-threatening and other serious diseases more widely and quickly available than occur under existing regulations. These procedures would also benefit treating physicians because the drug sponsor would normally file the necessary paperwork to FDA for them. Finally, these procedures would benefit sponsors of unusually expensive drugs and/or sponsors whose size and resources make it difficult to finance new drug development. Under the reproposal, such companies would be able to recover some of their expenses for research sooner than is possible under current regulations. Therefore, the agency certifies that this proposed rule, if promulgated, will not have a significant economic impact on small entities as defined by the Regulatory Flexibility Act.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Paperwork Reduction Act of 1980

Sections 312.7 and 312.35 of this proposed rule contain collection of information requirements. As required by section 3504(h) of the Paperwork Reduction Act of 1980, FDA has submitted a copy of this proposed rule to the Office of Management and Budget (OMB) for its review of these collection of information requirements. Other organizations and individuals desiring to submit comments on the collection of information requirements should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Rm. 3208, New Executive Office Building, Washington, DC 20503, Attn: Desk Officer for FDA.

Interested persons, may, on or before April 20, 1987, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this reproposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 312

Drugs, Medical research.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, it is proposed that Part 312 be amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR Part 312 continues to read as follows:

Authority: Secs. 501, 502, 503, 505, 506, 507, 701, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 353, 355, 356, 357, 371); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); 21 CFR 5.10, 5.11.

2. In § 312.7 by revising paragraph (d) to read as follows:

§ 312.7 Promotion and Sale of Investigational Drugs

* * * * *

(d) *Sale of an investigational drug*—(1) *Clinical trials under an IND.* Sale of an investigational drug in a clinical trial under an IND is not permitted without prior written approval of the Director of the Center for Drugs and Biologics, the Director of the Office of Drug Research and Review, or the Director of the Office of Biologics Research and Review, as the case may be, upon a full written explanation by the sponsor that sale is required in order for the sponsor to undertake or continue the clinical trial.

(2) *Treatment protocol or treatment IND.* A sponsor or investigator may sell an investigational drug for a treatment use under a treatment protocol or treatment IND that is in effect for the treatment use provided (i) the sale does not constitute commercial marketing of

a new drug for which a marketing application has not been approved; (ii) the drug is not being commercially promoted or advertised; and (iii) the sponsor of the drug is actively pursuing clinical studies and marketing approval with due diligence. FDA must be notified in writing, in an information amendment submitted under § 312.31, 10 days prior to the commencement of sale of such a drug. Prior approval of the sale by FDA is not required.

(3) *Withdrawal of authorization for sale.* (i) If FDA determines that the price charged for an investigational drug authorized to be sold is manifestly unfair, FDA may withdraw authorization for the sale of the drug until the price is reduced or the charge eliminated.

(ii) Authorization to sell an investigational drug under paragraph (d)(1) or (2) of this section may be withdrawn by FDA if the agency finds that the conditions underlying the authorization are no longer satisfied.

3. By adding § 312.34 to read as follows:

§ 312.34 Treatment use of an investigational new drug.

(a) *General.* A drug that is not approved for marketing may be under clinical investigation for an immediately life-threatening or other serious disease condition in patients for whom no satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment protocol. Ordinarily, in the case of a serious disease, a drug may be made available for treatment under this section after Phase 2 investigations have been completed; however, in the case of an immediately life-threatening disease, or in other appropriate circumstances, FDA may permit such use earlier in the investigational process. Administration of an investigational drug under this section serves both to provide treatment and the investigational purpose of gathering additional data on the drug's safety and effectiveness. For purposes of this section, the "treatment use" of a drug includes the investigational use of a drug for diagnostic purposes.

(b) *Criteria.* (1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:

(i) The drug is intended to treat a serious or immediately life-threatening disease;

(ii) There is no satisfactory alternative drug or other therapy available to treat the disease;

(iii) The drug is under investigation in a controlled clinical trial under an IND in effect for the trial; and

(iv) The sponsor of the controlled clinical trial is pursuing marketing approval of the investigational drug with due diligence.

(2) *Serious disease.* For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if he or she finds there is insufficient evidence of safety and effectiveness to support such use.

(3) *Immediately life-threatening disease.* For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if he or she finds that:

(i) On the basis of clinical data or other reliable scientific evidence in the IND file, the drug clearly does not provide a therapeutic benefit; or

(ii) The drug would expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

(c) *Clinical hold.* FDA may place on clinical hold a proposed or ongoing treatment protocol or treatment IND in accordance with § 312.42.

4. By adding § 312.35 to read as follows:

§ 312.35 Submissions for treatment use.

(a) *Treatment protocol submitted by IND sponsor.* A sponsor of a clinical investigation of a drug who intends to sponsor a treatment use for the drug under § 312.34 shall submit to FDA a treatment protocol. A treatment use under a treatment protocol may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the treatment use described in the protocol may begin.

(1) A treatment protocol is required to contain the following:

(i) The intended use of the drug.

(ii) An explanation of the rationale for use of the drug, including, as appropriate, either a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.

(iii) A brief description of the criteria for patient selection.

(iv) The method of administration of the drug and the dosages.

(v) A description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk.

(2) A treatment protocol is to be supported by the following:

(i) Informational brochure for supplying to each treating physician.

(ii) The technical information that is relevant to safety and effectiveness of the drug for the intended treatment purpose. Information contained in the sponsor's IND may be incorporated by reference.

(iii) If a waiver from IRB review and approval requirements is desired, a request for the waiver. (FDA may on its own initiative waive IRB review requirements under Part 56, if it finds such review unnecessary for the protection of subjects to be treated.)

(b) *Treatment IND submitted by licensed practitioner.* (1) If a licensed medical practitioner wants to obtain an investigational drug subject to a controlled clinical trial for a treatment use, the practitioner should first attempt to obtain the drug from the sponsor of the controlled trial under a treatment protocol. If the sponsor of the controlled clinical investigation of the drug will not establish a treatment protocol for the drug under paragraph (a) of this section, the licensed medical practitioner may seek to obtain the drug from the sponsor and submit a treatment IND to FDA requesting authorization to use the investigational drug for treatment use. A treatment use under a treatment IND may begin 30 days after FDA receives the IND or on earlier notification by FDA that the treatment use under the IND may begin. A treatment IND is required to contain the following:

(i) A cover sheet (Form FDA–1571) meeting § 312.23(g)(1).

(ii) Information (when not provided by the sponsor) on the drug's chemistry, manufacturing, and controls, and prior clinical and nonclinical experience with the drug submitted in accordance with § 312.23. A sponsor of a clinical investigation subject to an IND who supplies an investigational drug to a licensed medical practitioner for purposes of a separate treatment clinical investigation shall be deemed to authorize the incorporation-by-reference of the technical information contained in the sponsor's IND into the medical practitioner's treatment IND.

(iii) A statement of the steps taken by the practitioner to obtain the drug under a treatment protocol from the drug sponsor.

(iv) A treatment protocol containing the same information listed in paragraph (a)(1) of this section.

(v) If a waiver from IRB review and approval requirements is desired, a

request for the waiver, as provided in paragraph (a)(2)(iii) of this section.

(vi) A statement of the practitioner's qualifications to use the investigational drug for the intended treatment use.

(vii) The practitioner's statement of familiarity with information on the drug's safety and effectiveness derived from previous clinical and nonclinical experience with the drug.

(viii) Agreement to report to FDA safety information in accordance with § 312.32.

(2) A licensed practitioner who submits a treatment IND under this section is the sponsor-investigator for such IND and is responsible for meeting all applicable sponsor and investigator responsibilities under this part and Parts 50 and 56.

5. In § 312.42 by adding paragraph (b)(3) to read as follows:

§ 312.42 Clinical holds and requests for modification.

* * * * *

(b) * * *

(3) *Clinical hold of a treatment IND or treatment protocol—(i) Proposed use.* FDA may place a proposed treatment IND or treatment protocol on clinical hold if it is determined that:

(A) The pertinent criteria in § 312.34(b) for permitting the treatment use to begin are not satisfied; or

(B) The treatment protocol or treatment IND does not contain the information required under § 312.35(a) or (b) to make the specified determination under § 312.34(b).

(ii) *Ongoing use.* FDA may place an ongoing treatment protocol or treatment IND on clinical hold if it is determined that:

(A) There becomes available a satisfactory alternative drug or other therapy to treat the disease for which the investigational drug is being used;

(B) The investigational drug is not under investigation in a controlled clinical trial under an IND in effect for the trial, or a clinical study under the IND has been placed on clinical hold;

(C) The sponsor of the controlled clinical trial is not pursuing marketing approval with due diligence;

(D) If the treatment IND or treatment protocol is intended for a serious disease, there is insufficient evidence of safety and effectiveness to support such use; or

(E) If the treatment protocol or treatment IND was based on an immediately life-threatening disease:

(*1*) On the basis of clinical data or other reliable scientific evidence in the IND file, the drug clearly does not provide a therapeutic benefit; or

(*2*) The drug would expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

* * * * *

Frank E. Young,
Commissioner of Food and Drugs.

Don M. Newman,
Acting Secretary of Health and Human Services.

Dated: March 16, 1987.

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