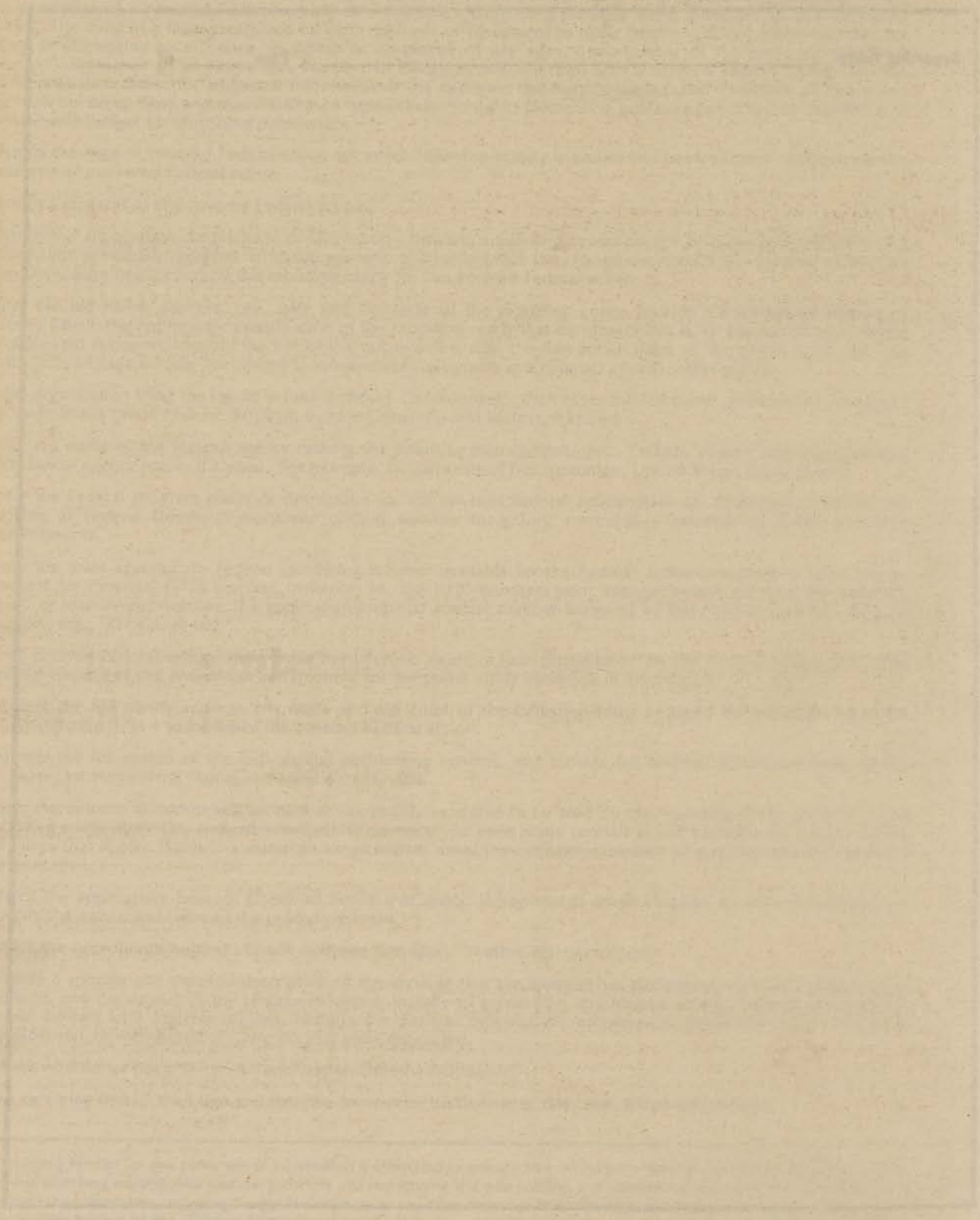
DISCLOSURE OF LOBBYING ACTIVITIES
CONTINUATION SHEET

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Friday
August 3, 1990

Part V

Department of Health and Human Services

Health Care Financing Administration

42 CFR Part 493

Clinical Laboratory Improvement Act Programs; Fee Collection; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

42 CFR Part 493

[HSQ-177-P]

RIN 0938-AE28

Clinical Laboratory Improvement Act Programs; Fee Collection

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Proposed rule.

SUMMARY: This proposed rule would implement provisions of section 353 of the Public Health Service Act (as amended by the Clinical Laboratory Improvement Amendments of 1988) by requiring laboratories to pay fees on a biennial basis for issuance of provisional certificates, certificates of waiver, certificates of accreditation, or certificates and to fund activities to determine compliance with the requirements established by the Department of Health and Human Services (HHS) for laboratory testing and issuance of certificates and renewal of certificates. It would also establish the methodology used to determine the amount of the fees charged for certificates of waiver, provisional certificates, certificates of accreditation, or certificates and activities to establish application procedures and determine compliance with applicable certification requirements.

DATES: To ensure consideration, comments must be mailed or delivered to the appropriate address, as provided below, and must be received by 5 p.m. on October 2, 1990.

ADDRESSES: Mail comments to the following address: Health Care Financing Administration, Department of Health and Human Services, Attention: HSQ-177-P, P.O. Box 26676, Baltimore, Maryland 21207.

If you prefer, you may deliver your comments to one of the following addresses:

Room 309-G, Hubert H. Humphrey Building, 200 Independence Avenue SW., Washington, DC, or

Room 132, East High Rise Building, 6325 Security Boulevard, Baltimore, Maryland.

Due to staffing and resource limitation, we cannot accept facsimile (FAX) copies of comments. In commenting, please refer to file code HSQ-177-P. Comments received timely will be available for public inspection as they are received, beginning approximately 3 weeks after publication of this document, in room 309-G of the Department's offices at 200 Independence Avenue SW., Washington, DC on Monday through Friday of each week from 8:30 a.m. to 5 p.m. (phone 202-245-7890).

Please address comments on information collection requirements to: Office of Management and Budget, Office of Information and Regulatory Affairs, Room 3002, New Executive Office Building, Washington, DC 20503, Attention: Allison Herron, HCFA Desk Officer.

COPIES: To order a copy of this proposed rule, please cite HSQ-177-P, CLIA '88: Fee Collection (Stock No. 069-001-00021-1). The cost for each copy ordered is $1.50. To order by mail, enclose a check made out to the Superintendent of Documents, or enclose your Visa or Master Card number and expiration date and send it to the Superintendent of Documents, Washington, DC 20402-9325. Credit card orders can also be placed by calling (202) 783-3238 or by faxing to (202) 275-0019.

FOR FURTHER INFORMATION CONTACT:
Jeffrey A. Clark, (301) 966-6802 (regarding fee amounts).
Rhonda Whalen, (301) 966-6801 (regarding operational issues).

SUPPLEMENTARY INFORMATION:

I. Background

A. Federal Oversight

Before the establishment of HCFA in 1977 and the signing of an interagency agreement, the Public Health Service (PHS) was responsible for the Clinical Laboratories Improvement Act of 1967 (CLIA '67) program. Currently, under an interagency agreement and a memorandum of understanding (MOU) with the PHS, through the Centers for Disease Control (CDC), HCFA has inspection and administrative responsibility for both the Medicare and CLIA programs. In addition, HCFA has responsibility for the development of the Federal requirements for laboratories but relies heavily on the PHS, and specifically CDC, and the Food and Drug Administration for technical and scientific expertise in the establishment of regulations. The most recent MOU between HCFA and CDC further delineates responsibilities by specifying that HCFA is responsible for developing regulations that relate to Medicare and CLIA.

B. Legislative History

Currently, under Public Law 90-174 (CLIA '67) laboratories engaged in testing in interstate commerce must meet the requirements of section 353 of the Public Health Service Act (42 U.S.C. 263a) in order to be licensed or remain licensed for testing in interstate commerce. In October 1988, Public Law 100-578 (Clinical Laboratory Improvement Amendments of 1988 (CLIA '88)) amended section 353 of the Public Health Service Act (PHSA) to expand the authority for the regulation of laboratories with some provisions having varying effective dates depending on whether or not the laboratory was subject to CLIA '67 on December 31, 1988. The provisions that are the subject of this proposed rule have the following effective dates: The fee provisions (section 353(m) of PHSA) are effective for all laboratories January 1, 1989; the application provisions (section 353(d) of PHSA) are effective for all laboratories January 1, 1990; the provision in section 353(g)(2) relating to inspection and the provision in section 353(f)(1)(C) relating to personnel qualifications are effective January 1, 1990 for laboratories that were subject to CLIA '67 on December 31, 1988, and on July 1, 1991 for all other laboratories.

Prior to the 1988 amendments, only those laboratories performing interstate testing were subject to the provisions of CLIA '67. CLIA '67 included a provision that authorized the Secretary of HHS to collect fees from approved laboratories for the issuance and renewal of CLIA licenses. The fee was set at $25 for each test category with a $125 cap on the amount any laboratory would be required to pay. However, the fee was ultimately eliminated because the administrative costs required for collection exceeded the revenue derived from the fees.

The CLIA '88 amendments require that any entity performing laboratory testing have a certificate, certificate of accreditation, or certificate of waiver and comply with the standards for laboratory testing established by HHS. In addition, section 353(m) of the PHSA, as amended by CLIA '88, requires the HHS to impose fees for the issuance and renewal of certificates, certificates of waiver, and accreditation certificates and for determining program compliance. Although the fee required for issuance and renewal of a certificate of waiver is to be only a nominal fee, the overall fees for certificates and certificates of accreditation must be sufficient to cover the general costs of administration incurred by HHS in carrying out the provisions of section 353 of the PHSA, including evaluating and monitoring approved proficiency testing programs and accreditation bodies and implementing and monitoring compliance with the requirements of section 353 of the

PHSA. The fees imposed for determining compliance must also be sufficient to cover the costs incurred by HHS in inspecting laboratories that are not accredited and in performing proficiency testing of laboratories that do not participate in approved testing programs. Section 353(m) also requires that the fees imposed vary by group or classification of laboratory, based on such considerations as HHS determines are relevant.

HHS is also required, under section 353(n) of the Public Health Service Act, on April 1, 1990, and annually thereafter, to compile and make available to physicians and the general public information that HHS determines is useful in evaluating the performance of a laboratory. This information must include a listing of laboratories whose certificates have been revoked, suspended or limited and those laboratories that have been subjects of intermediate sanctions, exclusion from Medicare or Medicaid, injunctions or withdrawal of accreditation. Additionally, sections 353(e)(2)(D) and 353(e)(3) of the PHSA require HHS to evaluate annually the performance of each approved accreditation body and submit an annual report to Congress that describes the results of that evaluation.

Section 6141 of the Omnibus Budget Reconciliation Act of 1989 (Pub. L. 101–239) requires that laboratories participating in the Medicare program comply with CLIA 88 requirements. Only laboratories that have a current unrevoked and unsuspended certificate of waiver, provisional certificate, certificate, or certificate of accreditation will be eligible for reimbursement in the Medicare or Medicaid programs or both.

C. Additional Background

HCFA issued a separate proposed rule on May 21, 1990 (55 FR 20896) that would establish three categories of laboratories based on testing performed. The categories proposed are: Certificate of Waiver, Level I, and Level II laboratories. The criteria we would use to determine a laboratory's classification are discussed in detail in that proposed rule. However, depending on the content of that final rule, we anticipate that large numbers of laboratories will qualify for certificates of waiver, thereby avoiding inspection fees. That proposed rule would also establish standards to assure consistent performance by laboratories of valid and reliable laboratory examinations and procedures.

In another proposed rule, HCFA will publish the criteria for the evaluation and approval of private and nonprofit organizations, accreditation programs, and State programs. Laboratories accredited or approved by these programs will pay separate fees set by the accrediting bodies or States. They will pay the Federal government only a fee for the certificate or certificate of waiver and a small share of the administrative costs of studies, validation surveys, etc. While this proposed rule discusses provisional certificates, certificates, certificates of waiver, and certificate of accreditation for accredited or State approved laboratories, only provisional certificates and certificates for existing CLIA '67 licensed laboratories will be issued initially when this rule is effective.

Also, although the proposed rule is written to reflect our plans for the final rule implementation with respect to the issuance of certificates, rather than provisional certificates, to those laboratories licensed under CLIA '67 as of December 31, 1988, we plan to initiate interim procedures for issuing CLIA '88 provisional certificates to those laboratories. We are instituting provisional certificates for laboratories licensed under CLIA '67 because, for the majority of these laboratories, their CLIA '67 licenses will expire June 30, 1990, and issuance of licenses under CLIA '67 is no longer valid. We are in the process of establishing the interim procedures and will be notifying CLIA '67 licensed laboratories shortly of the procedures to be followed to receive a provisional certificate. Provisional certificates issued to CLIA '67 licensed laboratories would be valid for a period of not more than 2 years and should allow HHS sufficient time to publish this rule in final, implementing the interim procedures for issuance of CLIA '88 certificates to those laboratories that as of December 31, 1988 were licensed under CLIA '67. Any laboratory that was issued a CLIA '67 license after December 31, 1988 would be issued a provisional certificate. However, after this rule becomes final, we would not propose to issue a certificate to those laboratories until the rule implementing the CLIA '88 standards becomes final.

For laboratories that were exempt from CLIA '67 based on low volume testing or accreditation by the College of American Pathologists (CAP) or licensed by New York State, we propose to issue provisional certificates. Issuance of provisional certificates to CLIA '67 low volume exempt laboratories will allow HHS sufficient time to establish the requirements for issuance of certificates of waiver that may be applicable to these laboratories. We propose to delay conducting inspections of these low volume exempt laboratories until we establish the health and safety standards, including the certificate of waiver provision, in a separate rule. Issuance of provisional certificates to those laboratories subject to CLIA '67 and issued an exemption based on licensure by New York State or accreditation by CAP will allow HHS sufficient time to establish the criteria for recognition of accreditation and State licensure programs. If (after the CLIA '88 standards are published in final and the criteria have been established for recognition of accreditation and State licensure programs) the New York State and CAP programs are recognized, those laboratories would be subject to the provisions for certificates of accreditation. If the New York State licensure program, CAP program, or any other accreditation program is not recognized, the laboratory would be subject to the certification requirements, unless it qualifies for a certificate of waiver. In any case, those laboratories issued CLIA '67 exemptions based on accreditation or licensure would not be subject to inspection under CLIA '88 until the final rules establishing the CLIA '88 standards and implementing the CLIA '88 provision for recognition of accreditation and State programs are published and effective. Certificates of waiver and certificates of accreditation will be issued after the other final rules are effective.

This document proposes interim steps for implementing the certification and fee collection requirements until categories of laboratories are established and the program for determination of compliance is fully operational. It also proposes requirements for certificates of waiver and certificates of accreditation when those regulations are effective.

II. Provisions of the Proposed Rule

This proposed rule would implement section 353(m) of the PHSA by establishing regulations at 42 CFR part 493, subpart F. As proposed at §493.602, it would set forth requirements all laboratories must meet in order to apply for and be issued a certificate under CLIA '88. It would also set forth the methodology for determining the amount of the fees for issuing provisional certificates, certificates, certificates of waiver, and certificates of accreditation, and for the proposed fee schedules for determining compliance with the standards.

This subpart would apply to all entities that perform laboratory testing. This rule would not apply to any

component or function of a laboratory that has been certified by the National Institute on Drug Abuse for the performance of forensic urine drug testing. While the regulation would not list them, "all entities that perform laboratory testing" includes but is not limited to the following—

(a) Laboratories located in physicians' offices (including group medical practices);
(b) Laboratories located in HMOs;
(c) Accredited, nonaccredited and Federal hospitals providing laboratory services;
(d) Laboratories located in skilled nursing facilities;
(e) Laboratories in intermediate care facilities (including intermediate care facilities for the mentally retarded);
(f) Laboratories located in rural health clinics;
(g) Laboratories located in ambulatory surgical centers;
(h) Laboratories located in end-stage renal disease facilities;
(i) Independent laboratories, as defined in § 488.52 of this chapter;
(j) Laboratories exempted from CLIA '67 based on accreditation by the College of American Pathologists, laboratories exempted from CLIA '67 based on New York State licensure, and low volume-exempt laboratories;
(k) Industrial laboratories;
(l) Insurance laboratories;
(m) City, State, and county laboratories;
(n) Federal clinics;
(o) Critical care units;
(p) Laboratories associated with tissue banks and tissue repositories; and
(q) All other laboratories such as Planned Parenthood Clinics, mobile laboratories, and any other facility or entity, including pharmacies and health fairs, that perform qualitative or screening laboratory test procedures or examinations of materials derived from the human body.

However, laboratories that perform research testing on human specimens, but do not report patient specific results for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, an individual patient are exempt from the CLIA '88 regulations.

Under CLIA '67 approximately 1,000 laboratories were exempt from Federal regulation because:

- The laboratories were accredited by the College of American Pathologists (CAP) or approved under the New York State program of laboratory standards enforcement; or
- The laboratories performed fewer than 100 tests in a given category.

CLIA '88 does not provide exemptions based on approval by CAP or New York State or on the volume of testing performed. Therefore, all laboratories are subject to the provisions of section 353 of the PHSA, including payment of fees. CLIA '88 does authorize the recognition of private accreditation programs and State licensure programs for clinical laboratories. Following recognition of accreditation or State licensure programs, laboratories participating in an approved accreditation program or licensed through a recognized State program will not be subject to payment of the individual laboratory inspection fee but will be subject to payment to cover the costs of monitoring a random sample of laboratories for the purpose of evaluating the accreditation program's standards and to a certificate of accreditation fee.

We would establish an exception for those components or functions of laboratories that are certified by the National Institute on Drug Abuse (NIDA) under Executive Order 12564 and section 503 of Public Law 100–71. Components or functions of laboratories that are not certified by NIDA would be subject to these proposed rules. If a laboratory conducts both NIDA certified forensic urine drug testing and other laboratory tests, the laboratory would be subject both to NIDA certification for the forensic urine drug testing and these proposed rules for all other tests, including other urine drug testing, performed by the laboratory. This is consistent with past requirements. Any laboratory not certified by NIDA that engaged in interstate commerce, whether or not it performed forensic testing, was required to have a CLIA '67 license.

In § 493.610, we would, based on section 353(b) of PHSA, prohibit solicitation or acceptance of materials derived from the human body for laboratory examination or other procedure unless the laboratory has an effective provisional certificate issued by HHS or a certificate, certificate of waiver, or certificate of accreditation issued by HHS applicable to the specialty or subspecialty of services offered by the laboratory. In addition, in accordance with section 6141 of Public Law 101–239, laboratories seeking payment in the Medicare program must meet the CLIA '88 requirements and must possess, therefore, a current unrevoked and unsuspended certificate of waiver, provisional certificate, certificate, or certificate of accreditation to be eligible for payment in the Medicare or Medicaid program or both.

In § 493.614, we would outline the procedure a laboratory must follow to obtain a provisional certificate, certificate, certificate of accreditation, or certificate of waiver. (While we discuss certificates of waiver and certificates of accreditation, they will not be issued until requirements for these certificates are established in regulations. In the meantime, we will issue only provisional certificates, and certificates for CLIA '67 licensed laboratories.) We propose to automatically send an application to all laboratories currently licensed and to those laboratories exempted (New York State approved, CAP-accredited and low-volume exempt laboratories) under CLIA '67 and to those laboratories that are Medicare/Medicaid approved. All other laboratories would be required to contact HHS or its designee (at an address to be provided in the final rule) for an application.

We would require that a separate application be made for each laboratory location using a form(s) prescribed by HHS and that the application be signed by the owner, operator or authorized representative of the laboratory.

Based on section 353(d)(1)(A) of the PHSA, the application would require information that describes the characteristics of the test procedures and examinations performed by the laboratory including—

(a) The names of the test procedures and examinations performed and the total number of test procedures and examinations performed annually;
(b) The methodologies for the test procedures and examinations performed; and
(c) The qualifications (educational background, training, and experience) of the personnel directing and supervising the laboratory and performing the test procedures and examinations.

For those laboratories that hold CLIA '67 licenses, we will evaluate the information contained in their applications for compliance with personnel requirements that have been set forth in the final rule published on March 14, 1990 (55 FR 9533).

Based on the information provided in the application, the certificate issued would be applicable to one or more specialty or subspecialty of services to include the tests performed by the laboratory.

These requirements would create a substantial reporting burden for laboratories, both in initial application and in updating certificates. HHS has little choice because the statute specifies these requirements in fine detail. We solicit suggestions on any ways that burden can be minimized while meeting the legislative requirements. For example, should laboratories be allowed to indicate on application forms that there are several methodologies that they potentially use to perform a particular test, without regard to the methodology most commonly used, in order to avoid the

need to update the certification if one of these methodologies is later added? Could or should the most common tests and methodologies within each specialty be listed on application forms to avoid the need to enter their names by hand? Could preprinted forms be used to summarize the education, training, and experience of each employee on one line rather than submitting a resume on each employee? HHS will carefully review all public comments. Then a standard application with definitions and instructions satisfying CLIA '88 intent will be developed by HHS and reviewed by the Office of Management and Budget under the Paperwork Reduction Act of 1980.

In § 493.618, we would require, based on section 353(d)(1) (B) through (D) of PHSA, that in submitting an application for a provisional certificate, a certificate of waiver, certificate of accreditation, or a certificate, a laboratory must agree to the following:

(a) To make records available and submit reports to HHS as HHS may require.

(b) To permit routine inspections by HHS as specified in Subpart N of 42 CFR part 493, except that the effective date of this requirement for laboratories not subject to section 353 of the PHSA as in effect on December 31, 1988, is July 1, 1991. This requirement would not apply to laboratories issued certificates of waiver.

(c) Except for certificate of waiver laboratories, to treat proficiency testing samples in the same manner as it treats materials derived from the human body referred to it for laboratory examinations or other test procedures in the ordinary course of business.

(d) To provide HHS with satisfactory assurances, through an attestation statement signed by the laboratory owner, operator, or authorized representative, that the laboratory will be operated in accordance with the requirements established by the Secretary under section 353 of the PHSA.

The exception provided in (b) above reflects the exception provided in PHSA and means that laboratories not subject to CLIA '67 are not subject to inspections until July 1, 1991.

We propose, in § 493.622, that if HHS denies a laboratory's application for a provisional certificate, certificate, certificate of accreditation, or certificate of waiver or limits its applicable certificate, the laboratory would be given a statement of the grounds on which the denial or limitation is based and an opportunity for a hearing in accordance with procedures set forth in part 498.

If a laboratory that is seeking a certificate of any kind for the first time has its application denied or the applicable certificate limited, it would not be able to conduct business as a laboratory under the PHSA unless the denial or limitation is overturned at the conclusion of the administrative appeals process. We reach this conclusion because, while the statute generally requires a prior hearing in the case of certificate revocations or suspensions, this provision does not encompass the initial denial of a certificate. If a laboratory cannot satisfy the statute's minimal requirements for initial applications, it ought not have the same procedural protections offered by the statute to those laboratories that have not only satisfied those requirements, but that have at least once satisfactorily passed an on-site inspection as well.

As mentioned in section I.C., HHS is proposing to implement interim procedures and policy for the issuance of certificates and collection of fees until it is able to fully implement the requirements of CLIA '88. In § 493.626, we propose to issue a provisional certificate to each laboratory that was not licensed under section 353 of the PHSA as in effect on December 31, 1988, provided that the laboratory meets the application requirements detailed above and pays the applicable fee discussed later in this proposed rule. Following the full implementation of CLIA '88, a provisional certificate would be issued initially to any new laboratory not eligible for a certificate of waiver including a laboratory that is seeking accreditation. The provisional certificate would be issued prior to operation, upon payment of the provisional certificate fee, to permit new laboratories to test specimens and to allow time for HHS to determine compliance with the CLIA '88 standards. Prior to expiration of the provisional certificate, HHS would notify the laboratory of the applicable requirements to obtain a certificate of waiver, a certificate of accreditation, or a certificate and of the amounts of the fees for issuing these certificates and, if applicable, the amount of the fee for determination of compliance. After fee payment, HHS would, if necessary, evaluate the laboratory to determine compliance with the CLIA '88 requirements and, if compliance is confirmed, would issue a certificate. Thereafter, the laboratory would be billed a fee on a biennial basis for a certificate and, if applicable, a fee for the cost of determining compliance.

We also propose that a provisional certificate would be valid for a period of not more than 2 years. If necessary, a provisional certificate would be re-issued until such time as an inspection to determine program compliance can be conducted, or the laboratory demonstrates it qualifies to receive a certificate of waive or certificate of accreditation. We also propose that the provisional certificate would not be renewable. However, HHS would reissue a provisional certificate to any laboratory that HHS or its designee has not had an opportunity to evaluate for compliance with the requirements for certification.

If a laboratory fails to comply with the applicable requirements as specified in the notification by HHS, HHS would suspend or deny Medicare payments, if applicable, and initiate revocation or limitation of a laboratory's provisional certificate and would deny the application for a certificate, certificate of accreditation or certificate of waiver. In this case, HHS would provide the laboratory with a statement of the grounds on which the revocation and denial is based and with an opportunity for a hearing. If the laboratory requires a hearing, the expiration date of the provisional certificate would be extended until a hearing decision by an Administrative Law Judge (ALJ) is issued. The Medicare payments would be suspended or denied pending the hearing decision because the Act authorized termination of payments under Medicare for those laboratories that fail to meet the requirements, with the opportunity for a hearing to occur subsequent to payment suspension or denial. Under CLIA '88, laboratories that do not meet the requirements would be notified of the basis for noncompliance determination and offered an opportunity for a hearing prior to any adverse action, unless HHS determines that the laboratory's deficiencies are such that they constitute an imminent and serious threat to human health.

The statutes differ with respect to hearing procedures ostensibly because suspension or termination of Medicare payments would not affect the laboratory's ability to provide services to non-Medicare patients, whereas suspension or revocation of a CLIA certificate would preclude a laboratory from the performance and reporting of any tests on human specimens regardless of the source of payment.

In § 493.630, we propose to issue a certificate to each laboratory that was licensed under CLIA '67 as of December 31, 1988, provided the laboratory meets the application requirements detailed above and pays the applicable fees discussed later in this proposed rule.

In § 493.631, we have specified the requirements for certificates of waiver

and, in § 493.632, we have specified the requirements for certificates of accreditation, even though the criteria for waiver tests and for recognition of accreditation and State licensure programs will be published in separate rules. These sections are provided to illustrate the different types of certificates HHS plans to issue and the proposed requirements for issuances of a certificate of waiver and certificate of accreditation.

We propose that the certificate, certificate of waiver, or certificate of accreditation issued would be applicable to only those test procedures and examinations performed by the laboratory that were included on the laboratory's application. In accordance with section 353(b) of the PHSA, a laboratory may not perform any test procedure or examination within a specialty or subspecialty that is not included on the laboratory's certificate, certificate of waiver, or certificate of accreditation. Laboratories must notify HHS prior to the performance of any test not included as a waiver test for performance by certificate of waiver laboratories or any test not included on the laboratory's certificate. A laboratory may not perform any "new" test or examination until it has requested and been issued an appropriate revised certificate that covers the examination or procedure. Additionally, we would require that the laboratory must notify HHS or its designee within 6 months of any deletions and/or changes in methodologies for any test procedure or examination for which the laboratory has been issued a certificate, certificate of waiver, or certificate of accreditation. These requirements are specified in section 353(d)(1)(A)(ii) of PHSA. There are no limitations on the tests a laboratory issued a provisional certificate may perform.

We also propose that HHS will initiate revocation or limitation of a laboratory s certificate, certificate of waiver, or certificate of accreditation for failure to comply with applicable requirements. For those laboratories licensed under CLIA '67 on December 31, 1988, the applicable health and safety requirements are contained in part 493. The applicable health and safety requirements for laboratories not licensed under CLIA '67 as of December 31, 1988, will be published in a separate rulemaking. If a determination is made that the laboratory is not in compliance with applicable requirements, the laboratory would be given a statement of grounds on which the revocation or limitation action is based and an opportunity for a hearing. The effective date of the revocation or limitation would not be earlier than the date of decision by an ALJ, unless we find that conditions at the laboratory pose an imminent and serious risk to human health. In such cases, we would suspend or limit the laboratory's certificate before the hearing is held. Failure to meet the applicable requirements could also result in loss of Medicare approval or intermediate sanctions to be specified in a separate proposed rule.

In the interest of administrative efficiency, we are proposing in § 493.634 that a laboratory must notify HHS or its designee within 30 days if changes occur in the laboratory's ownership, name, location, or director.

In § 493.638, we propose that a laboratory must pay a fee for the issuance of a provisional certificate, certificate of waiver, certificate of accreditation, or a certificate, as applicable. We propose that the total fees collected must be sufficient to cover the general cost of administering the laboratory certification program, including evaluating and monitoring proficiency testing programs and accreditation bodies and implementing and monitoring compliance with section 353 of the PHSA. For a certificate of waiver, the fee includes the cost of issuing a certificate of waiver, collection of fees, and analyzing applications to determine if a laboratory should be issued a certificate of waiver. For a certificate of accreditation, the fee includes the cost of issuing a certificate of accreditation, collection of fees, and analyses of standards and administrative policies of programs of accrediting organizations. The fees for the issuance of a provisional certificate, certificate of waiver, certificate of accreditation, or certificate will be assessed biennially. (Our proposed methodology for determining the amounts of the fees is discussed later in this preamble.)

We also propose that the fee would be set annually on a calendar year basis and would be based on schedules, or ranges, of laboratory test volume and scope of specialties tested, with the amounts of inspection fees in each schedule a function of the average hourly rates for the required activities and the average length of time required for the activity. The amount of the fee applicable to the issuance of a provisional certificate or to the issuance or renewal of a certificate would be the fee amount in effect at the time the application is received. Upon receipt of an application for a provisional certificate or an application (or renewal request) for a certificate, certificate of waiver, or certificate of accreditation, we would send the laboratory a notice advising it of the amount of the fee. We also intend to inform the public of the fee amounts each year by publishing a notice containing that information in the Federal Register.

Laboratories would not be subject to the payment of fees until the effective date of the final rule. HCFA would assess fees prospectively after implementation of the final rule. Following implementation of the final rule, laboratories licensed under section 353 of the PHSA as of December 31, 1988 would be notified by mail of the appropriate fee for determination of compliance and issuance of a certificate, and all other laboratories would be notified of the provisional certificate fee.

No certificate (other than for existing laboratories licensed under section 353 of the PHSA as of December 31, 1988) or certificates of waiver will be issued (and therefore no inspection fees or certificate or certificate of waiver fees collected) until the final rule setting forth the criteria for certificates and certificates of waiver is published and effective. Likewise, no certificate of accreditation fees will be assessed until the accreditation rule is final and effective and accreditation and State licensure programs are approved.

In § 493.639, we propose that if after a certificate, certificate of accreditation, or a certificate of waiver is issued a laboratory adds services and requests that its certificate or certificate of accreditation be upgraded, or certificate of waiver be changed or eliminated, the laboratory must pay a fee to cover the cost of issuing an appropriate revised certificate. We propose to base this fee on the actual cost to issue the revision to the laboratory. (Note that an additional fee is also required under § 493.643(e) if it is necessary to fund activities to determine compliance with additional requirements.)

In § 493.643, we propose that a laboratory that was licensed under section 353 of the PHSA as of December 31, 1988 must pay a fee to cover the cost of determining program compliance. Again, we have included the reference to certificates of waiver and certificates of accreditation in this section so that it would continue to be applicable once we begin issuing those types of certificates. We also propose that effective July 1, 1991, the other laboratories would be subject to a fee to determine their compliance with Federal requirements. We would not begin collecting this fee from these laboratories, however, until applicable criteria and standards are established in

final regulations. Further, the laboratory would not be assessed this fee if it qualifies for a certificate of waiver or certificate of accreditation. We propose to include in this fee the cost of: conducting onsite surveys, evaluating qualifications of personnel, monitoring proficiency testing, documenting deficiencies, evaluating laboratories' plans to correct deficiencies, and State and Federal surveyor preparation for and attendance at ALJ hearings. Laboratories will not be required to pay the cost of investigating followup surveys and sanction activities if allegations are not substantiated. Although the amount of the fee will be determined annually, inspections will be conducted biennially. Therefore, the fee covers a 2-year period. The methodology used to determine the amount of the fee is discussed later in this preamble.

For purposes of determining the amount of the fee a laboratory that must be inspected must pay, we propose to initially establish ten fee schedules. Each laboratory, regardless of its type of testing (a classification of laboratory based on the complexity of testing that is the subject of a separate proposed rule), would be placed into one of the ten following schedules based on the laboratory's scope and volume of testing. The schedules have been established based on the experience of Federal laboratory surveyors and other experts in HCFA to estimate appropriate parameters for classifying laboratories. In addition, we analyzed data from the Federal government's national data base that captures facility-specific information on laboratories, in an attempt to establish parity among the ten schedules listed.

We analyzed the various sizes and workloads of laboratories that are currently participating in the Medicare/Medicaid program and concluded that the average costs to inspect laboratories of various sizes are represented by the benchmarks set forth. These are averages based on a relatively limited amount of experience since the universe of the total number of regulated laboratories will eventually be much greater. As we obtain experience in future years, we will analyze the data and develop new estimates. We are interested in receiving comments on the formal methodology, process, and schedule to be used in updating these estimates.

We intend to use these schedules for purposes of collecting fees from laboratories before inspections actually take place. This will enable us to make this part of the implementation of CLIA '88 financially self-supporting as the Congress has directed.

We plan eventually to modify these schedules after sufficient time has elapsed to establish the fee amount in each schedule based upon an hourly rate per surveyor in each State, which reflects better the actual time and resources necessary to determine the laboratory's compliance with the requirements. We propose consideration of scope and volume of testing since they influence the time and resources required to determine program compliance.

Schedule A—The laboratory performs tests in no more than 3 specialties of service with a total annual volume of not more than 10,000 laboratory tests.

Schedule B—The laboratory performs tests in at least 4 specialties of service with a total annual volume of not more than 10,000 laboratory tests.

Schedule C—The laboratory performs tests in no more than 3 specialties of service with a total annual volume of more than 10,000 but not more than 25,000 laboratory tests.

Schedule D—The laboratory performs tests in at least 4 specialties with a total annual volume of more than 10,000 but not more than 25,000 laboratory tests.

Schedule E—The laboratory performs tests in at least 1 specialty with a total annual volume of more than 25,000 but not more than 50,000 laboratory tests.

Schedule F—The laboratory performs tests in at least 1 specialty with a total annual volume of more than 50,000 but not more than 75,000 laboratory tests.

Schedule G—The laboratory performs tests in at least 1 specialty with a total annual volume of more than 75,000 but not more than 100,000 laboratory tests.

Schedule H—The laboratory performs tests in at least 1 specialty with a total annual volume of more than 100,000 but not more than 500,000 laboratory tests.

Schedule I—The laboratory performs tests in at least 1 specialty with a total annual volume of more than 500,000 but not more than 1,000,000 laboratory tests.

Schedule J—The laboratory performs tests in at least 1 specialty with a total annual volume of more than 1,000,000 laboratory tests.

We would define a test as a test procedure or examination for a single analyte. Each profile (that is, group of tests) would be counted as the number of separate procedures; for example, a chemistry profile consisting of 18 tests would be counted as 18 separate test procedures or examinations. We are counting each test procedure or examination separately, because inspection would include assessments of quality control activities by test procedure, and evaluation of proficiency testing is conducted on individual tests. Thus the determination of compliance is based on assessment of individual tests rather than groups of tests or profiles. We specifically invite comments on the appropriateness of the number of specialties and tests we propose to use as thresholds. We also invite comments on our definition of a test and its feasibility, particularly in the area of quantitative testing.

We also propose that initially for purposes of determining a laboratory's fee schedule classification, the specialties and subspecialties currently used for Medicare, Medicaid and CLIA '67 be used to describe a laboratory's services. These specialties and subspecialties are:

- The specialty of Microbiology, which includes one or more of the following subspecialties:
  - (a) Bacteriology.
  - (b) Mycobacteriology
  - (c) Mycology.
  - (d) Parasitology.
  - (e) Virology.
- The specialty of Serology, which includes one or more of the following subspecialties:
  - (a) Syphilis serology.
  - (b) General immunology.
- The specialty of Chemistry, which includes one or more of the following subspecialties:
  - (a) Routine chemistry.
  - (b) Endocrinology.
  - (c) Toxicology.
  - (d) Urinalysis.
- The specialty of Hematology.
- The specialty of Immunohematology, which includes one or more of the following subspecialties:
  - (a) ABO grouping and Rh typing.
  - (b) Unexpected antibody detection.
  - (c) Compatibility testing
  - (d) Unexpected antibody identification.
- The specialty of Pathology, which includes the following subspecialties:
  - (a) Cytology.
  - (b) Histopathology.
  - (c) Oral Pathology.
- The specialty of Radiobioassay.
- The specialty of Histocompatibility.
- The specialty of Cytogenetics.

In a separate proposed rule that addresses the Federal health and safety standards based on a complexity model of regulation to implement CLIA '88, we are offering an opportunity for comment on the appropriateness of the specialties and subspecialties of service. In that proposed rule, the requirements concerning proficiency testing, quality control, quality assurance and personnel that relate to specialties and subspecialties of service are defined.

We also propose that if after a certificate is issued a laboratory adds services and requests that its certificate

be upgraded, the laboratory must pay an additional fee if, in order to determine compliance with additional requirements, it is necessary to conduct an inspection, evaluate personnel, or monitor proficiency testing participation. We propose to base the additional fee on the actual resources and time necessary to perform the activities.

In § 493.645, we propose that in addition to the certificate fee, a laboratory that is issued a certificate of accreditation would also be assessed a fee to cover the cost of evaluating individual laboratories to determine overall whether an accreditation program's standards and inspection policies are equivalent to the Federal program. An annual random sample of 5 percent of all accredited laboratories would be inspected in order to compare inspection findings of HCFA or its agents with the findings of the accreditation organizations. All accredited laboratories will share in the cost of these inspections. These costs are the same as those that would be incurred when inspecting nonaccredited laboratories.

Additionally, we propose that, in the case of a laboratory that has been issued a certificate of accreditation, if it is necessary to conduct a complaint investigation, impose sanctions or conduct a hearing, the affected laboratory would be assessed a fee to cover the cost of these activities. Sanction activity costs for State surveyors and sanction activity costs for the Federal government (which include testimony of Federal experts and costs for ALJs and attorney representation) would be in addition to the certificate of accreditation fee. If a complaint investigation results in a complaint being unsubstantiated or if an HHS adverse action is overturned at the conclusion of the administrative appeals process, the cost of the inspection would not be imposed upon the laboratory. The inspection fee would not be assessed until after a laboratory concedes the existence of the deficiencies or an ALJ rules in favor of HHS.

In § 493.646, we propose to notify laboratories by mail of the appropriate fee(s) and instructions for submitting the fee(s), including the due date for payment and the United States Department of Treasury designated commercial bank to which payment must be made. These fees, when finally calculated, would be nonrefundable, and provisional certificates, certificates of waiver, certificates of accreditation, and certificates would not be issued until the applicable fees have been paid.

With respect to program financing, CLIA '88 requires the establishment of a fully self-supporting program through the assessment of fees. The activities mandated by CLIA '88 that would be considered in the determination of fees that laboratories will be required to pay include:

- Determining compliance with the requirements through onsite inspections, evaluating personnel qualifications and monitoring proficiency testing performance.
- Performing proficiency testing of laboratories that do not participate in approved proficiency testing programs.
- Issuing laboratories a certification of compliance or, after the final rule is published establishing the CLIA '88 standards, a certificate of compliance or a certification of waiver from Federal regulation;
- Providing proficiency testing results to the general public upon request;
- Developing and making available to physicians and the general public an annual report listing the laboratories whose certificates have been revoked, suspended or limited as well as those laboratories which have been subjects of intermediate sanctions, Medicare terminations, injunctions or withdrawal of accreditation, including the reasons for these actions;
- Conducting studies, research, and evaluations directed toward assessing and improving the regulatory process;
- Preparing annual reports to Congress on the monitoring and evaluation of proficiency testing and accreditation programs; and
- Performing enforcement activities to assure compliance with program requirements.

Various aspects of the above activities would be performed by three different entities: State survey agencies, Federal agencies, and HHS contractors. In § 493.649, we propose to establish fee amounts fixed to the schedule in which the laboratory falls, which is related to the average hourly rates established for these three entities and to the average number of hours required to perform the activities. As we gain experience using the schedules, with regard to actual hours and resources required to perform compliance determination activities for each laboratory, we will consider appropriate adjustments to the methodology for assessing fees to ensure that each laboratory is charged the fee amount related to the time and resources needed to determine the laboratory's compliance with the requirements. We may (or could) alter the use of schedules for minimum fees and use State by State schedules based on local hourly rates for all activities at that time. We propose to include the following costs in establishing the average hourly rate.

1. State Survey Agencies

The State survey agency would evaluate personnel qualifications, monitor each laboratory's participation in an approved proficiency testing program, conduct onsite surveys, evaluate plans to correct deficiencies cited as a result of onsite surveys, and conduct followup surveys, if appropriate. An hourly rate would be determined for each calendar year based on the most recent hourly rate negotiated between the Federal government and each State survey agency. The negotiated hourly rate would encompass salary costs (as determined by each State's civil service pay scales) and fringe benefit costs for the required number of State inspectors, management, and direct support staff. Necessary travel costs would be included that would comply with each State's administrative requirements. The hourly rate would include other direct costs, such as equipment, printing and supplies, that would be established based on actual historical State requirements. Also included in the hourly rate would be the indirect costs which would be negotiated by HHS's Division of Cost Allocation.

2. Federal Agencies

The cost of Federal administration of the CLIA '88 provisions would include the establishment and evaluation of Federal health and safety standards, including cytology requirements, to implement CLIA '88; conducting surveyor training; performance monitoring of State agencies, and other contractors; approving and monitoring accrediting organizations and State licensure programs; imposing intermediate sanctions; revoking, suspending, or limiting certificates; holding and attending ALJ hearings (including the costs of ALJs and attorney representation); and other program operation functions such as compilation of information for physicians and the general public to evaluate the performance of laboratories. Also included would be: the cost to develop proficiency testing standards to encompass tests not currently subject to proficiency testing standards; the cost to evaluate, for approval, and monitor, on a ongoing basis, State and private nonprofit professional organizations' proficiency testing programs; the cost to conduct full scale studies including those mandated by CLIA '88; the cost of

research and evaluation directed toward assessing and improving the regulatory program; and the cost of PHS technical and scientific support to resolve technical issues concerning tests for waiver, the complexity model, new technology, and the effectiveness of the CLIA '88 regulatory process. We propose that the average hourly rate for Federal administrative activities be the most current average hourly cost to HCFA to staff and support a full time equivalent employee. Included in this rate would be the salary and fringe benefit costs, necessary administrative costs such as printing, training, postage, express mail, supplies, equipment, ADP computer usage and building service charges associated with support services provided by organizational components such as a computer center and any other oversight activities necessary to support the program.

3. Contractors

We propose that the hourly rate for activities performed by HHS contractors would be the average hourly rate established for contractor assistance based on an independent government cost estimate for the required workload. This rate would include the cost of contractor support to provide proficiency testing programs to laboratories that do not participate in an approved proficiency testing program, provide specialized assistance in the evaluation of laboratories' performance in an approved proficiency testing program, bill and collect fees, issue certificates, provisional certificates, certificates of waiver, and accreditation certificates, establish accounting, monitoring and reporting systems, and assist with necessary surveyor training.

We propose that the number of hours used to determine the overall fee in each of the schedules initially would be HCFA's estimate of the average time needed by each entity to perform the activities for which it is responsible. For survey activities, HCFA's estimate is based on the historical data (time records for State surveyors for actual surveys). Administrative activities would be performed by both Federal contractors (for example, processing applications; billing; establishing accounting, monitoring, and reporting systems) and Federal agencies (for example, establishing standards, approving and monitoring accreditation organizations and State licensure programs, information collection). In arriving at our estimates of the amount of Federal contractor administrative time, we relied on the advice of independent contractors that have had experience performing these types of activities for other organizations. Since administering the CLIA '88 laboratory certification program is a new Federal agency function, we do not have directly applicable historical information. We based our estimate of the time necessary on our analysis of the processes involved in performing these administrative functions and our experience in performing similar activities. As additional experience is gained and/or new requirements are mandated, appropriate adjustments would be made to the required time to conduct activities.

We ask for comments from all laboratories on the methodology proposed for establishing the fee amounts for determination of compliance because we propose to use the same methodology to determine fees for laboratories that are not subject to CLIA '67 but will be subject to CLIA '88 determinations of compliance.

On the basis of this methodology, the fee assessed to issue a provisional certificate, or certificate of accreditation [1], or certificate to a laboratory in fiscal year 1991 would be as follows:

[1] Certificate of accreditation fee would not be assessed until criteria are published in a final rule for recognition of accreditation and State programs.

Functions or Tasks	Hours	Hourly Rate	User Fee
Federal administration	3	*$51	$153
Contractor administration	2	54	108
Total			261

*The hourly rate of $51 for Federal administration includes approximately $31 for salaries and fringe benefits, and the remaining $20 is for overhead costs, including the support of a nationwide satellite training network.

If a laboratory is issued a revised certificate, an additional certificate fee as specified above would be assessed.

A certificate of waiver fee [2] would be assessed as follows:

[2] Certificate of waiver fee would not be assessed until rulemaking is published in final establishing the standards for waivered laboratories.

Functions or tasks	Hours	Hourly rate	User fee
Federal administration	2	*$51	$102
Contractor administration	1	54	54
Total			156

*The hourly rate of $51 for Federal administration includes approximately $31 for salaries and fringe benefits, and the remaining $20 is for overhead costs, including the support of a nationwide satellite training network.

Under the proposed methodology, the time and cost required to determine compliance during fiscal year 199I would be as follows:

	Hours	Average Hourly Rate [1]	Biennial User Fee
Schedule A Laboratories:			
Biennial inspection [2]	24	$35	$840
Followup visit or complaint investigation	15	35	525
Sanctions/hearings	8	35	280
Schedule B Laboratories:			
Biennial inspection [2]	32	35	1,120
Followup visit or complaint investigation	17	35	595
Sanctions/hearings	9	35	315
Schedule C Laboratories:			
Biennial inspection [2]	40	35	1,400
Followup visit or complaint investigation	19	35	665
Sanctions/hearings	10	35	350
Schedule D Laboratories:			
Biennial inspection [2]	47	35	1,645
Followup visit or complaint investigation	21	35	735
Sanctions/hearings	11	35	385
Schedule E Laboratories:			
Biennial inspection [2]	54	35	1,890
Followup visit or complaint investigation	24	35	840
Sanctions/hearings	12	35	420
Schedule F Laboratories:			
Biennial inspection [2]	61	35	2,135
Followup visit or complaint investigation	26	35	910
Sanctions/hearings	13	35	455
Schedule G Laboratories:			
Biennial inspection [2]	68	35	2,380
Followup visit or complaint investigation	28	35	980
Sanctions/hearings	14	35	490
Schedule H Laboratories:			
Biennial inspection [2]	75	35	2,625
Followup visit or complaint investigation	30	35	1,050
Sanctions/hearings	15	35	525
Schedule I Laboratories:			
Biennial inspection [2]	82	35	2,870
Followup visit or complaint investigation	32	35	1,120
Sanctions/hearings	16	35	560
Schedule J Laboratories:			
Biennial inspection [2]: The sum of 82 hours plus 7 hours for each additional 500,000 tests or portion thereof multiplied by a $35 hourly rate. [3]			
Followup visit or complaint investigation: The sum of 32 plus 2 hours for each additional 500,000 tests or portion thereof multiplied by a $35 hourly rate.			
Sanctions/hearings: The sum of 16 hours plus 1 hour for each additional 500,000 tests or portion thereof multiplied by a $35 hourly rate.			

[1] Average hourly rates and user fees are shown since individual contracts are negotiated with 53 State survey agencies. The actual user fee for determining compliance would depend upon the State in which the laboratory is located. The $35 hourly rate is based on total surveyor time, which includes the time surveyors are not involved in activities directly related to determinations of compliance. The unit cost budget methodology is based on actual surveyor time to conduct compliance evaluations, which is about $27 per hour. We add an adjustment of $8 per hour to cover surveyor costs for holidays, vacation, sick leave, and attendance at training courses. Therefore, the cost of these other work-related activities has been included in the user fee methodology.

[2] Includes evaluating qualifications of personnel; monitoring proficiency testing; conducting onsite surveys; developing deficiency statements; and evaluating laboratories plans to correct deficiencies.

Under the proposed methodology, the fee that a laboratory issued a certificate of accreditation would pay [4] in fiscal year 1991 to share the cost of the 5 percent random inspections discussed earlier would be:

Schedule A Laboratories; $42.
Schedule B Laboratories; $56.
Schedule C Laboratories; $70.
Schedule D Laboratories; $82.
Schedule E Laboratories; $95.
Schedule F Laboratories; $107.
Schedule G Laboratories; $119.
Schedule H Laboratories; $131.
Schedule I Laboratories; $144.
Schedule J Laboratories; Schedule I base fee plus $12 for each additional 500,000 tests or portion thereof.

Under the proposed methodology, the fee that a laboratory issued a certificate of accreditation would pay, if it is necessary to perform the following activities in the case of that particular laboratory during fiscal year 1991, would be:

Follow-up visits or complaint investigations:

Schedule A Laboratories; $525.
Schedule B Laboratories; $595.
Schedule C Laboratories; $665.
Schedule D Laboratories; $735.
Schedule E Laboratories; $840.
Schedule F Laboratories; $910.
Schedule G Laboratories; $980.
Schedule H Laboratories; $1,050.
Schedule I Laboratories; $1,120.
Schedule J Laboratories; Schedule I base fee plus $70 for each additional 500,000 tests or portion thereof.

Sanctions/Hearing:

Schedule A Laboratories; $280.
Schedule B Laboratories; $315.
Schedule C Laboratories; $350.
Schedule D Laboratories; $385.
Schedule E Laboratories; $420.
Schedule F Laboratories; $455.
Schedule G Laboratories; $490.
Schedule H Laboratories; $525.
Schedule I Laboratories; $560.
Schedule J Laboratories; Schedule I base fee plus $35 for each additional 500,000 tests or portion thereof.

The minimum fee that a laboratory would be required to pay for determination of program compliance would be the amount representing the biennial inspection costs in the aforementioned schedules. If the laboratory requires additional survey time as a result of followup visit(s), certificate revisions, complaint investigation(s) that are substantiated, intermediate sanctions, appeals or hearings, an additional assessment will be made for such activities.

If a complaint investigation results in a complaint being unsubstantiated or if an HHS adverse action is overturned at

[4] Includes evaluating qualifications of personnel; monitoring proficiency testing; conducting onsite surveys; developing deficiency statements; and evaluating laboratories' plans to correct deficiencies.

the conclusion of the administrative appeals process, the costs of these activities would not be imposed upon the laboratory. The intermediate sanction provisions of CLIA '88 will be addressed in a separate rulemaking. These provisions include separate payments for onsite monitoring and civil monetary penalties which would be imposed on those laboratories failing to comply with CLIA '88 requirements.

We plan that future certificate and program compliance fees be based on our actual experience with regard to hours required to conduct the workload, and we may modify the schedules described here. Separate rulemaking to change the methodology will be initiated when appropriate. The Federal data on laboratories that are currently regulated were used to provide us with the average time to perform the various tasks.

In order to assess laboratory performance in proficiency testing, HCFA will initially conduct sample onsite proficiency testing to evaluate laboratory performance. As more information becomes available on these costs, it may become necessary to update these fees to accommodate the requirements for proficiency testing.

Based on our actual survey experience with CLIA '67 laboratories, we divided laboratories into the ten schedules previously discussed. In setting up these groups, we looked in depth at the experience of one State to determine if there were a way to coalesce laboratories into broad categories of size that would correlate directly with the amount of time (and, therefore, cost) that would be necessary to determine compliance. We looked at the State's workload information to determine the amount of time and resources needed to determine laboratory compliance and arrayed all of the laboratories by listing the number of individuals and resources that were applied to compliance determinations. While certainly many choices might be made, we would opt for a system that groups laboratories into the ten categories that, on the average, reflect a reasonably uniform use of resources for a range of scope and volume of laboratory services and which are more sensitive to cost variations as a function of scope and volume, thereby distributing the costs more equitably between large and small laboratories. We are interested in comments presenting information on existing inspection experience that would be useful in assessing this question, or otherwise suggesting improvements in this aspect of the methodology.

The following are examples of how we set three of the schedules. We are proposing to base all of the schedules on a similar analysis.

A Schedule A laboratory requires one surveyor approximately 4 hours to travel to and from the laboratory with an additional 14 hours for the following activities: evaluate the laboratory's history file prior to on site inspection; assess proficiency testing performance four times per year for each specialty and subspecialty of services performed; evaluate qualifications, including education and experience of laboratory employees; develop statements of deficiencies; and evaluate the laboratory's plan to correct the deficiencies cited. Supervisory review/administration and clerical support require approximately 6 additional hours.

A Schedule D laboratory requires one surveyor approximately 4 hours of round trip travel time, with an additional 43 hours for the following activities: evaluate the laboratory's history file prior to onsite inspection; assess proficiency testing performance four times per year for each specialty and subspecialty of services performed; evaluate qualifications and experience of laboratory employees; develop statements of deficiencies; and evaluate the laboratory's plan to correct the deficiencies cited. In this size laboratory we would hope to employ two surveyors to conduct the compliance determination. In such a case, the total hours expended per person would be reduced but the resources employed would be doubled. Therefore, the estimates are based on one surveyor. Supervisory review/administration and clerical support require approximately 9 additional hours.

A Schedule I laboratory requires one surveyor approximately 4 hours of round trip travel time, with an additional 78 hours for the following activities: evaluate the laboratory's history file prior to onsite inspection; assess proficiency testing performance four times per year for each specialty and subspecialty of services performed; evaluate qualifications and experience of laboratory employees; develop statements of deficiencies; and evaluate the laboratory's plan to correct the deficiencies cited. As stated above, in this size laboratory we would hope to employ at least two surveyors to determine compliance. Even though having a larger survey team would reduce the number of hours per person per inspection, the amount of resources increases. Thus, these figures are based on the total hours for one surveyor.

IV. Regulatory Impact Analysis

A. Introduction

Executive Order 12291 (E. O. 12291) requires us to prepare and publish regulatory impact analysis for any proposed regulation that meets one of the E. O. 12291 criteria for a "major rule"; that is, that will be likely to result in—

- An annual effect on the economy of $100 million or more;
- A major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or
- Significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign based enterprises in domestic or export markets.

In addition, we generally prepare a regulatory flexibility analysis that is consistent with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 through 612), unless the Secretary certifies that a regulation will not have a significant economic impact on a substantial number of small entities. For purposes of the RFA, we consider all laboratories as small entities. Individuals and States are not included in the definition of a small entity.

In addition, section 1102(b) of the Act requires the Secretary to prepare a regulatory impact analysis for any proposed rule that may have a significant impact on the operations of a substantial number of small rural hospitals. Such an analysis must conform to the provisions of section 603 of the RFA. For purposes of section 1102(b) of the Act, we define a small rural hospital as a hospital which is located outside of a metropolitan statistical area and has fewer than 50 beds.

This rule, in combination with the proposed rule "Regulations Implementing the Clinical Laboratory Improvement Amendments of 1988" (55 FR 20896) would constitute a major rule as defined by E.O. 12291. While the law authorizes inspections and specifies that inspections be conducted on a biennial basis or a frequency established by HHS, it does not otherwise mandate any particular frequency or intensity of inspections. Nor does the law specify the specific details of the requirements that inspections examine, or the depth with which compliance is probed. Thus, subject to the statutory requirement that fees charged cover the total cost of administering the program and to the unavoidable reality that any inspection

system would be costly, HHS has latitude to implement cost-effective alternatives. We request comments on the option discussed in this preamble, on any other options that are likely to be less costly and equally effective. We also call attention to the opportunity to comment on any standards significantly affecting inspection costs included in the proposed "Regulations Implementing the Clinical Laboratory Improvement Amendments of 1988".

B. Anticipated Impact

1. Affected Entities

There are approximately 12,000 Federally regulated laboratories located in hospitals and independent settings according to HCFA. These facilities range from large medical centers and corporate-operated independent laboratories to small, independent laboratories and physicians' office laboratories. However, CLIA '88 requires all laboratories to pay fees to cover the costs of implementing the provisions of the statute. We estimate that there may be anywhere from 300,000–600,000 laboratories altogether that could potentially come under these provisions.

We expect that the fees we have proposed to conduct inspections would not have a significant economic effect on many physician office laboratories. We believe most of these laboratories probably will qualify for a certificate of waiver and would not be required to meet Federal inspection standards and would thus avoid compliance fees. They would pay only a nominal fee as required by the law. However, we believe that most remaining laboratories will fall into 1 of the 10 schedules that would require compliance fees.

Although not small entities, we expect some States may experience some additional administrative burden because they may have to adapt or establish a methodology for assessing inspection requirements and for ensuring compliance with these proposed requirements. States may have to make more recommendations for termination of Medicare approval if these inspection requirements are not met.

We expect that several accrediting bodies, some of which currently provide compliance reviews, will continue and expand their roles in the monitoring of laboratories for their various organizations. Other accrediting bodies are expected to seek approval under CLIA.

2. Costs/Savings

We do not expect certification and inspection fees to cause any undue hardship on the majority of laboratories although some laboratories may have to incur costs to meet the required standards for certification and inspections. These costs will be examined in the regulatory impact analysis of the final rule "Regulations Implementing the Clinical Laboratory Improvement Amendments of 1988."

Currently we are unable to determine with any high degree of accuracy, due to the lack of data, the universe of laboratories that would be compelled to meet the requirements of these provisions. This observation is further complicated by the number of laboratories that would qualify for each type of certificate and its average fee. A facility's certification category is dependent on final decisions both on the standards regulation (for example, waiver criteria) and on where the boundaries between the schedules are set. Average fees would be determined by the level of enforcement and costs as a result of these provisions. In light of these uncertainties we have projected a potential range of costs at various fee levels as indicated in the table below:

POTENTIAL RANGE OF GROSS COSTS AT VARIOUS FEE LEVELS AND ESTIMATES OF NUMBER OF LABORATORIES REGULATED

Type	Fee	Number by type		Biennial cost (in thousands)	
		Lower	Higher	Lower	Higher
Assuming Relatively Few Waivers					
Waiver	$156	10000	30000	$1,560	$4,680
Schedule A	840	60000	180000	50,400	151,200
Schedule D (B through F)	1,645	50000	80000	82,250	131,600
Schedule I (G through J)	2,870	20000	30000	57,400	86,100
Total		140000	320000	191,610	373,580
Assuming Many Waivers					
Waiver	156	40000	100000	6,240	15,600
Schedule A	840	60000	150000	50,400	126,200
Schedule D (B through F)	1,645	20000	40000	32,900	65,800
Schedule I (G through J)	2,870	20000	30000	57,400	86,100
Total		140000	320000	146,940	293,700

Note: Lower estimate is based on an Office of Inspector General Study of physician office laboratories, plus interstate and hospital laboratories, plus 20,000 others. Higher estimate assumes that total number of laboratories is over 300,000, based on HCFA projections. None of these data include a deduction for costs currently incurred. Because the lack of data makes an accurate breakdown of the number of laboratories that would fall into the individual schedules difficult, we have based our estimates on the number of laboratories within a range of schedules (B through F and G through J). We then used representative fee amounts (the amounts for laboratories in schedules D and I) for the range of schedules to calculate total biennial costs.

3. Effect on Patients

Although laboratories conducting only waiver tests would not be subject routinely to determination of compliance, we do not believe this would affect patients since waiver tests are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result. We intend to evaluate whether improved quality of care results from inspection of laboratories under these schedules. We believe that these inspections would encourage more responsible testing, that heretofore has been questionable by some sources.

The number of false negatives may be reduced, resulting in more detection of illness in the primary stages. Because later stages generally require more costly treatments, savings could result. Also, more false positives may be eliminated thus saving the costs of unnecessary treatments. Further, the House Committee on Energy and

Commerce, which authorized CLIA '88, noted in committee language that although "consumers bear the ultimate costs of regulation," the proper performance of laboratory tests "not only protects patients from undergoing unnecessary and dangerous treatment, but ultimately saves money."

4. Alternatives

We believe we have proposed the most effective methodology for reaching the desired patient outcomes at a minimal cost to laboratories. For example, we believe that by proposing inspections on a biennial basis as opposed to an annual basis we have limited laboratory costs without minimizing the quality of care.

Another approach could be to develop inspection criteria so that a basic inspection could be conducted to determine if a laboratory meets critical compliance requirements. If they do, then they would be certified as in compliance. If they do not meet the minimum requirements, a more intensive inspection would be required. This approach would benefit those laboratories that are generally in compliance with the inspection requirements by reducing inspection costs and penalize those facilities not in compliance by increasing their costs.

We believe this methodology would have the potential to encourage laboratories to achieve compliance and, thus, decrease costs. However, there is the possibility of overlooking some unqualified laboratories, which could result in adverse effects on beneficiaries in terms of cost and quality of care. This approach may require a change in the law, since the statute makes no reference to an inspection scheme that would involve less than a full inspection of compliance with all requirements concerning the issuance of certificates. Regardless, throughout this preamble and in the standards analyzed in the proposed "Regulations Implementing the Clinical Laboratory Improvement Amendments of 1988" (55 FR 20896), we have identified a number of alternatives that have varying ability to reduce costs to laboratories. For example, our proposed approach to handling waivers, together with the far lower fee charged for waivered laboratories, would greatly reduce, if not totally eliminate, the number of small physician office laboratories exposed to more substantial fees.

5. Conclusion

Initially, the only laboratories that would have to pay a fee for determination of compliance would be those laboratories licensed under section 353 of the PHSA on December 31, 1988. Also we expect many laboratories to choose an approved accreditation program and thereby not be subject to Federal compliance fees and only be subject to a certificate fee and a small portion of the cost to validate the accreditation program standards.

After establishment of the CLIA '88 standards, laboratories that were not formerly regulated under CLIA '67 would be subject to determination of compliance fees if they do not qualify for a certificate of waiver or accreditation certificate. Our determination of compliance fees reflected in the schedules is based on our estimate of time to conduct the activities related to evaluation of compliance. These fee schedules for determination of compliance may be adjusted periodically as we gain experience in determining the true costs for evaluating individual laboratories' compliance with the requirements.

However, since our analysis is not conclusive, we encourage comments and submission of any applicable data concerning these provisions, particularly if there is a perception that they may result in significant increased costs.

In combination with the proposed rule "Regulations Implementing the Clinical Laboratory Improvement Amendments of 1988," this proposed rule would constitute a major rule and would have a significant impact on some laboratories, including laboratories in small rural hospitals. Consequently, we are soliciting comments on the benefits and costs of these rules, and we will conduct the analysis prior to issuing a final rule. To the extent that the analysis in this proposed rule does not constitute a complete preliminary Regulatory Impact Analysis, the Office of Management and Budget has waived the requirement, under section 6(a)(4) of E.O. 12291.

V. Collection of Information Requirements

Proposed regulations at §§ 493.614, 493.618, 493.633(a)(1), and 493.634 contain information collection requirement that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1980 (44 U.S.C. 3501 *et seq.*). A notice will be published in the **Federal Register** after approval is obtained. The information collection requirements concern information that must be provided on a laboratory's application for a provisional certificate, certificate of waiver, certification of accreditation, or certificate and subsequent notification of any changes in the information provided on the application. All laboratories would be required to provide the information.

Public reporting burden for this collection of information is estimated to be approximately 3 hours per application. Organizations and individuals desiring to submit comments on the information collection and recordkeeping requirements should direct them to HCFA and the OMB official whose name appears in the **ADDRESSES** section of this preamble.

VI. Response to Comments

Because of the large number of items of correspondence we normally receive on proposed rules, we are not able to acknowledge or respond to them individually. However, we will consider all comments that we receive by the date and time specified in the "**DATES**" section of this preamble, and, if we proceed with a final rule, we will respond to the comments in the preamble of that rule.

List of Subjects in 42 CFR Part 493

Laboratories, Medicare, Medicaid, Health facilities, Reporting and recordkeeping requirements.

For the reasons set forth in the preamble, 42 CFR part 493 would be amended as follows:

PART 493—[AMENDED]

1. The authority citation for part 493 should be revised to read as follows:

Authority: Sec. 353 of the Public Health Service Act, secs. 1102, 1861(e), the sentence following sec. 1861(s)(11), 1861(s) (12) and (13) of the Social Security Act (42 U.S.C. 263a, 1302, the sentence following sec. 1395x(s)(11), and sec. 1395x(s) (12) and (13).)

2. A new subpart F is added to part 493 to read as follows:

PART 493—LABORATORY REQUIREMENTS

Subpart F—General Administration

Sec.

493.602 Scope of subpart.
493.606 Applicability of subpart.
493.610 Provisional certificate or certificate required for laboratories.
493.614 Application procedures.
493.618 Additional application requirements.
493.622 Opportunity for hearing.
493.626 Provisional certificate.
493.630 Certificate.
493.631 Certificate of waiver.
493.632 Certificate of accreditation.
493.633 Applicability of certificate, certificate of waiver, and certificate of accreditation.
493.634 Notification of changes.

Sec.
493.636 Provisional certificate and certificate fees.
493.639 Fee for revised certificate.
493.643 Fee for determination of program compliance.
493.645 Additional fee(s) for accredited laboratories.
493.646 Payment of fees.
493.649 Methodology for determining fee amount.

Subpart F—General Administration

§ 493.602 Scope of subpart.

This subpart sets forth requirements all laboratories must meet in order to apply for and be issued a provisional certificate, certificate of waiver, certificate of accreditation, or certificate under section 353 of the Public Health Service Act (42 U.S.C. 263a). It also sets forth the methodology for determining the amount of the fees for issuing provisional certificates, certificates of waiver, certificates of accreditation, or certificates and for determining compliance with the applicable standards of the Public Health Service Act (the PHSA).

§ 493.606 Applicability of subpart.

This subpart applies to all entities that perform laboratory testing as defined in section 353(a) of the PHSA. These rules do not apply to any component or function of a laboratory that has been certified by the National Institute on Drug Abuse (NIDA) for the purpose of performing forensic urine drug testing under the Mandatory Guidelines for Federal Workplace Drug Testing Programs published on April 11, 1988 (53 FR 11970) or research laboratories that test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of, the health of individual patient(s). This includes any component or function of any laboratory whose forensic functions have been certified by NIDA under authority of Executive Order 12564 and section 503 of Public Law 100–71, regulations adopted by the Nuclear Regulatory Commission (10 CFR part 26) and the Department of Transportation (49 CFR part 40, effective January 2, 1990), and other Federal law requiring performance of forensic urine drug testing under NIDA certification. Any laboratory, or any component or function of a laboratory, that performs clinical urine drug testing or forensic urine drug testing without NIDA certification remains subject to these rules.

§ 493.610 Provisional certificate or certificate required for laboratories.

No person may solicit or accept materials derived from the human body for laboratory examination or other procedure unless there is in effect for the laboratory a provisional certificate issued by HHS or a certificate, a certificate of waiver, or a certificate of accreditation issued by HHS that is applicable to the specialty or subspecialties of services offered by the laboratory.

§ 493.614 Application procedures.

(a) Laboratories not licensed under the Clinical Laboratories Improvement Act of 1967 (CLIA '67) or Medicare/Medicaid approved must contact HHS or its designee to receive initial application forms. HHS or its designee automatically sends applications to laboratories licensed under CLIA '67 and to those laboratories that were exempt under CLIA '67 (New York State-approved, College of American Pathologists-accredited and low-volume exempt laboratories) and Medicare/Medicaid approved laboratories.

(b) A separate application must be filed for each laboratory location.

(c) An application for the issuance of a provisional certificate or a certificate of waiver or for a certificate of accreditation or certificate applicable to one or more laboratory test procedures or examinations included in the specialties or subspecialties listed in § 493.643(d)(3) must be made to HHS or its designee on a form or forms prescribed by HHS and must be signed by the owner, operator or authorized representative of the laboratory.

(d) The application must include information that describes the characteristics of the laboratory operation and the examinations and other test procedures performed by the laboratory including—

(1) The names of the test procedures and examinations performed and the total number of test procedures and examinations performed annually;

(2) The methodologies for test procedures and examinations performed; and

(3) The qualifications (educational background, training, and experience) of the personnel directing and supervising the laboratory and performing the laboratory test procedures and examinations.

§ 493.618 Additional application requirements.

In submitting an application for a provisional certificate, a certificate of waiver, certificate of accreditation, or a certificate, a laboratory must agree to the following:

(a) To make records available and submit reports to HHS as HHS may require.

(b) To permit inspections by HHS as specified in subpart N of this part, except that the effective date of this requirement for laboratories not licensed under section 353 of the PHSA as of December 31, 1988 is July 1, 1991. (Certificate of waiver laboratories are not subject to routine inspections.)

(c) To treat proficiency testing samples in the same manner as it treats materials derived from the human body referred to it for laboratory examinations or other procedures in the ordinary course of business. (This requirement does not apply to certificate of waiver laboratories.)

(d) To provide HHS with satisfactory assurances, through an attestation statement, signed by the laboratory owner, operator, or authorized representative that the laboratory will be operated in accordance with the requirements established by the Secretary under section 353 of the PHSA.

§ 493.622 Opportunity for hearing.

(a) If HHS denies a laboratory's application for a provisional certificate, certificate of waiver, certificate of accreditation, or certificate or limits the laboratory's applicable certificate, HHS gives the laboratory a statement of the grounds on which the denial or limitation is based and an opportunity for a hearing, in accordance with the procedures set forth in Part 498 of this chapter.

(b) If a laboratory that is seeking an initial certificate of any form has its application denied or its certificate limited, it cannot operate as a laboratory under the PHSA (or, in the case of a limitation, in the areas covered by the limitation) unless the denial or limitation is overturned at the conclusion of the administrative appeals process provided by Part 498 of this chapter. (In addition, the laboratory is not eligible for payment under the Medicare or Medicaid programs.)

§ 493.626 Provisional certificate.

(a) HHS or its designee initially issues a provisional certificate or, if the laboratory meets the requirements, a certificate of waiver to each laboratory that was not licensed under section 353 of the PHSA as of December 31, 1988, provided that the laboratory meets the application requirements of § 493.614 and § 493.618 and pays the applicable fee as specified in § 493.636. A

provisional certificate issued under this section is not renewable and is valid for a period of not more than 2 years or until such time as an inspection to determine program compliance can be conducted or the laboratory demonstrates that it qualifies to receive a certificate of waiver or a certificate of accreditation, whichever is shorter. HHS reissues a provisional certificate to any laboratory for which HHS or its designee has not had an opportunity to determine compliance.

(b) Prior to expiration of the provisional certificate, HHS notifies the laboratory of the applicable requirements to obtain a certificate of waiver, a certificate of accreditation, or a certificate and of the amounts of the fees for issuing these certificates and, if applicable, the amount of the fee for determination of compliance. HHS initiates revocation or limitation of a laboratory's provisional certificate for failure to comply with the applicable requirements as set forth in the notification by HHS and denies the laboratory's application for the applicable certificate. In such an event, HHS provides the laboratory with a statement of the grounds on which the revocation or limitation and denial is based and with an opportunity for a hearing. If the laboratory requests a hearing, the expiration date of the provisional certificate is extended until a hearing decision by an Administrative Law Judge (ALJ) is issued, unless HHS finds that conditions at the laboratory pose an imminent and serious risk to human health.

(c) In the event of a non-compliance determination resulting in denial of a laboratory's application for a certificate of waiver, certificate of accreditation, or certificate, HHS also initiates revocation or limitation of the laboratory's provisional certificate. HHS provides the laboratory with a statement of the grounds on which the revocation or limitation of the provisional certificate and application denial are based and with an opportunity for a hearing. If the laboratory requests a hearing, the expiration date of the provisional certificate is extended until a hearing decision is issued by an ALJ, unless HHS finds that conditions at the laboratory pose an imminent and serious risk to human health. (In addition, for laboratories participating in Medicare, payments are suspended or denied on the effective date specified in the notice to the laboratory of the denial of the application for the applicable certificate, even if there has been no hearing decision issued.)

§ 493.630 Certificate.

(a) HHS or its designee issues a certificate to each laboratory that was licensed under section 353 of the PHSA as of December 31, 1988, provided the laboratory meets the application requirements of § 493.614 and § 493.618, pays the applicable fee as specified in § 493.638, and meets all other applicable requirements of this part.

(b) HHS or its designee issues a certificate to each laboratory that was not licensed under section 353 of the PHSA as of December 31, 1988, provided the laboratory has a provisional certificate and meets the application requirements of § 493.614 and § 493.618, pays the applicable fee as specified in § 493.638, and meets all other applicable requirements of this part.

§ 493.631 Certificate of waiver.

HHS or its designee issues a certificate of waiver to a laboratory if it performs only waiver tests, provided the laboratory meets the application requirements of § 493.614 and § 493.618, pays the applicable fee as specified in § 493.638, and meets all other applicable requirements of this part.

§ 493.632 Certificate of accreditation.

HHS or its designee issues a certificate to a laboratory accredited by an HHS approved accreditation program or licensed in an HHS approved State program, provided the laboratory has a provisional certificate and meets the application requirements of § 493.614 and § 493.618, pays the applicable fee as specified in § 493.638, and meets all other applicable requirements of this part.

§ 493.633 Applicability of the certificate, certificate of waiver, and certificate of accreditation.

(a) The certificate, certificate of waiver, or certificate of accreditation issued under this part is applicable to those specialties and subspecialties of service that include the test procedures and examinations that the laboratory has indicated on its application that it performs.

(1) The laboratory may not perform any examination or procedure within a specialty or subspecialty that is not included on the laboratory's certificate, certificate of waiver, or certificate of accreditation until it has requested and been issued a revised certificate that covers the examination or procedure.

(2) The laboratory must notify HHS or its designee within 6 months of any deletions and/or changes in methodologies for any test procedure or examination for which the laboratory has been issued a certificate, certificate of waiver, or certificate of accreditation.

(b) HHS initiates revocation of a laboratory's certificate, certificate of waiver, or certificate of accreditation, in whole or in part for failure to comply with the applicable requirements of this part. In such an event, HHS provides the laboratory with a statement of grounds on which the revocation is based and an opportunity for a hearing, in accordance with the procedures set forth in part 498 of this chapter. (In addition, for laboratories participating in Medicare or Medicaid, payments are suspended or denied for failure to comply with the requirements of this part.)

§ 493.634 Notification of changes.

A laboratory must notify HHS or its designee within 30 days if changes occur in—

(a) Ownership;
(b) Name;
(c) Location;
(d) Director (not applicable for provisional certificates); or
(e) Supervisor (not applicable for provisional certificates).

§ 493.638 Provisional certificate and certificate fees.

(a) *Basic rule.* Laboratories must pay a fee for the issuance of a provisional certificate, certificate of waiver, certificate of accreditation, or a certificate, as applicable. Laboratories must also pay a fee for the renewal of a certificate of waiver, certificate of accreditation, or a certificate. The total of fees collected by HHS under the laboratory program must be sufficient to cover the general costs of administering the laboratory certification program under section 353 of the PHSA. For provisional certificates and certificates, this includes evaluating and monitoring proficiency testing programs and accreditation bodies and implementing, monitoring, and enforcing compliance with section 353 of the PHSA and collection of fees and issuing provisional certificates and certificates. For a certificate of waiver, this includes the cost of issuing the certificate of waiver, collection of fees and the administrative costs associated with evaluating tests to determine if a certificate of waiver should be issued. For a certificate of accreditation this includes the cost of issuing the certificate of accreditation, collection of fees and the administrative costs associated with evaluating programs of accrediting organizations and the costs to conduct sample validation surveys of accredited laboratories.

(b) *Fee amount.* The fee amount is set annually by HHS on a calendar year

basis and is based on schedules, or ranges, of laboratory test volume and scope of specialties tested, with the amounts of the inspection fees in each schedule a function of the average hourly rates for the required activities and the average length of time required for the activity. This fee is assessed and payable biennially. The methodology used to determine the amount of the fee is found in § 493.649. The amount of the fee applicable to the issuance of the provisional certificate or the issuance or renewal of the certificate of waiver, certificate of accreditation, or certificate is the amount in effect at the time the application is received. Upon receipt of an application for a provisional certificate, certificate of waiver, certificate of accreditation, or certificate, HHS or its designee notifies the laboratory of the amount of the required fee.

§ 493.639 Fee for revised certificate.

If after a certificate, certificate of accreditation, or certificate of waiver is issued a laboratory wishes to add services and requests that its certificate or certificate of accreditation be upgraded or that its certificate of waiver be changed or eliminated, the laboratory must pay a fee to cover the cost of issuing a revised certificate. (An additional fee is also required under § 493.643(e) if it is necessary to determine compliance with additional requirements.) The fee for issuing an appropriate revised certificate is based on the actual cost to issue the revised certificate to the laboratory.

§ 493.643 Fee for determination of program compliance.

(a) *Laboratories licensed under section 353 of the PHSA on December 31, 1988.* In addition to the fee required under § 493.638, a laboratory whose license under section 353 of the PHSA was in effect on December 31, 1988 must pay a fee to cover the cost of determining program compliance, unless it is issued a certificate of waiver or a certificate of accreditation.

(b) *Other laboratories.* Effective July 1, 1991, laboratories not licensed under section 353 of the PHSA as of December 31, 1988 and that do not meet the requirements for a certificate of waiver or certificate of accreditation must pay a fee to cover the cost of determining program compliance.

(c) *Costs included in fee.* Included in the fee for determining program compliance is the cost of evaluating qualifications of personnel; monitoring proficiency testing; conducting onsite surveys; documenting deficiencies; and evaluating laboratories' plans to correct deficiencies. If additional expenses are incurred to conduct followup visits to verify correction of deficiencies, to impose sanctions, and/or for surveyor preparation for and attendance at ALJ hearings, HHS assesses an additional fee to include these costs. HHS sets the fee amounts annually on a calendar year basis. Laboratories are inspected biennially; therefore, fees are assessed and payable biennially.

(d) *Classification of laboratories that require inspection for purpose of determining amount of fee.* (1) There are ten classifications of laboratories for the purpose of determining the fee amount a laboratory is assessed. Each laboratory is placed into one of the ten following schedules based on the laboratory's scope and volume of testing.

(i) *Schedule A.* The laboratory performs tests in no more than 3 specialties of service with a total annual volume of not more than 10,000 laboratory tests.

(ii) *Schedule B.* The laboratory performs tests in at least 4 specialties of service with a total annual volume of not more than 10,000 laboratory tests.

(iii) *Schedule C.* The laboratory performs tests in no more than 3 specialties of service with a total annual volume of more than 10,000 but not more than 25,000 laboratory tests.

(iv) *Schedule D.* The laboratory performs tests in at least 4 specialties with a total annual volume of more than 10,000 but not more than 25,000 laboratory tests.

(v) *Schedule E.* The laboratory performs tests in at least 1 specialty with a total annual volume of more than 25,000 but not more than 50,000 laboratory tests.

(vi) *Schedule F.* The laboratory performs tests in at least 1 specialty with a total annual volume of more than 50,000 but not more than 75,000 laboratory tests.

(vii) *Schedule G.* The laboratory performs tests in at least 1 specialty with a total annual volume of more than 75,000 but not more than 100,000 laboratory tests.

(viii) *Schedule H.* The laboratory performs tests in at least 1 specialty with a total annual volume of more than 100,000 but not more than 500,000 laboratory tests.

(ix) *Schedule I.* The laboratory performs tests in at least 1 specialty with a total annual volume of more than 500,000 but not more than 1,000,000 laboratory tests.

(x) *Schedule J.* The laboratory performs tests in at least 1 specialty with a total annual volume of more than 1,000,000 laboratory tests.

(2) For purposes of determining a laboratory's classification under this section, a test is a procedure or examination for a single analyte. Each profile (that is, group of tests) is counted as the number of separate procedures or examinations; for example, a chemistry profile consisting of 18 tests is counted as 18 separate procedures or tests.

(3) For purposes of determining a laboratory's classification under this section, the specialties and subspecialties of service for inclusion are:

(i) The specialty of Microbiology, which includes one or more of the following subspecialties:

(A) Bacteriology.
(B) Mycobacteriology.
(C) Mycology.
(D) Parasitology.
(E) Virology.

(ii) The specialty of Serology, which includes one or more of the following subspecialties:

(A) Syphilis serology.
(B) General immunology.

(iii) The specialty of Chemistry, which includes one or more of the following subspecialties:

(A) Routine chemistry.
(B) Endocrinology.
(C) Toxicology.
(D) Urinalysis.

(iv) The specialty of Hematology.

(v) The specialty of Immunohematology, which includes one or more of the following subspecialties:

(A) ABO grouping and Rh typing.
(B) Unexpected antibody detection.
(C) Compatibility testing.
(D) Unexpected antibody identification.

(vi) The specialty of Pathology, which includes the following subspecialties:

(A) Cytology.
(B) Histopathology.
(C) Oral Pathology.

(vii) The specialty of Radiobioassay.

(viii) The specialty of Histocompatibility.

(ix) The specialty of Cytogenetics.

(e) *Additional fee.* If after a certificate, certificate of waiver, or certificate of accreditation is issued a laboratory adds services and requests that its certificate be upgraded, the laboratory must pay an additional fee if, in order to determine compliance with additional requirements, it is necessary to conduct an inspection, evaluate personnel, or monitor proficiency testing performance. The additional fee is based on the actual resources and time necessary to perform the activities.

§ 493.645 Additional fee(s) for accredited laboratories.

(a) In addition to the certificate fee, a laboratory that is issued a certificate of accreditation is also assessed a fee to cover the cost of evaluating individual laboratories to determine overall whether an accreditation program's standards and inspection policies are equivalent to the Federal program. An annual random sample of 5 percent of all accredited laboratories is inspected in order to compare inspection findings of HCFA or its agents with the findings of the accreditation organizations. All accredited laboratories share in the cost of these inspections. These costs are the same as those that are incurred when inspecting nonaccredited laboratories.

(b) If, in the case of a laboratory that has been issued a certificate of accreditation, it is necessary to conduct a complaint investigation, impose sanctions or conduct a hearing, HHS assesses that laboratory a fee to cover the cost of these activities. If a complaint investigation results in a complaint being unsubstantiated, or if an HHS adverse action is overturned at the conclusion of the administrative appeals process, the cost of these activities are not imposed upon the laboratory. Costs for these activities are not assessed until after a laboratory concedes the existence of deficiencies or an ALJ rules in favor of HHS. If, in the case of a laboratory subject to an inspection under paragraph (a) of this section, followup visits are necessary because of identified deficiencies, HHS assesses the laboratory a fee to cover the cost of these visits.

§ 493.646 Payment of fees.

HHS or its designee notifies laboratories by mail of the appropriate fee(s) and instructions for submitting the fee(s), including the due date for payment and the United States Department of Treasury designated commercial bank to which payment must be made. Provisional certificates, certificates of waiver, certificates of accreditation, or certificates are not issued until the applicable fees have been paid.

§ 493.649 Methodology for determining fee amount.

(a) *General rule.* The amount of the fee in each schedule is based on the average hourly rate to perform the required activities multiplied by the average number of hours required, or if activities are performed by more than one of the entities listed in paragraph (b) of this section, the sum of the products of the applicable hourly rates multiplied by the average number of hours required by the entity to perform the activity.

(b) *Determining average hourly rates used in fee schedules.* Three different entities perform activities related to the issuance or renewal of certificates of waiver, certificates of accreditation, or certificates and determining program compliance. HHS determines the average hourly rates for the activities of each of these entities.

(1) *State survey agencies.* The following costs are included in determining an average hourly rate for the activities performed by State survey agencies:

(i) The costs incurred by the State survey agencies in evaluating personnel qualifications and monitoring each laboratory's participation in an approved proficiency testing program. The cost of onsite inspections and monitoring activities is the hourly rate derived as a result of an annual budget negotiation process with each State. The hourly rate encompasses salary costs (as determined by each State's civil service pay scale) and fringe benefit costs to support the required number of State inspectors, management and direct support staff.

(ii) Travel costs necessary to comply with each State's administrative requirements and other direct costs such as equipment, printing and supplies. These costs are established based on historical State requirements.

(iii) Indirect costs as negotiated by HHS.

(2) *Federal agencies.* The hourly rate for activities performed by Federal agencies is the most recent average hourly cost to HCFA to staff and support a full time equivalent employee. Included in this cost are salary and fringe benefit costs, necessary administrative costs, such as printing, training, postage, express mail, supplies, equipment, ADP computer usage and building service charges associated with support services provided by organizational components such as a computer center and any other oversight activities necessary to support the program.

(3) *HHS contractors.* The hourly rate for activities performed by HHS contractors is the average hourly rate established for contractor assistance based on an independent government cost estimate for the required workload. This rate includes the cost of contractor support to provide proficiency testing programs to laboratories that do not participate in an approved proficiency testing program, provide specialized assistance in the evaluation of laboratory performance in an approved proficiency testing program, perform assessments of cytology testing laboratories, conduct special studies, bill and collect fees, issue certificates, establish accounting, monitoring and reporting systems, and assist with necessary surveyor training.

(c) *Determining number of hours.* The average number of hours used to determine the overall fee in each schedule is HCFA's estimate, based on historical experience, of the average time needed by each entity to perform the activities for which it is responsible.

(Catalog of Federal Domestic Assistance Program No. 13.714, Medical Assistance Program; No. 13.773, Medicare—Hospital Insurance; and No. 13.774, Medicare—Supplementary Medical Insurance)

Dated: April 13, 1990.

Gail R. Wilensky,

Administrator, Health Care Financing Administrator.

Approved: July 9, 1990.

Louis W. Sullivan,

Secretary.

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Friday
August 3, 1990

Part VI

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 310, 346, and 369

Anorectal Drug Products for Over-the-Counter Human Use; Final Monograph; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 346, and 369

[Docket No. 80N-0050]

RIN 0905-AA06

Anorectal Drug Products for Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) anorectal drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on anorectal drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: August 5, 1991.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the Federal Register of May 27, 1980 (45 FR 35576), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC anorectal drug products, together with the recommendations of the Advisory Review Panel on OTC Hemorrhoidal Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by August 25, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by September 24, 1980.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC anorectal drug products was published in the Federal Register of August 15, 1988 (53 FR 30756). Interested persons were invited to file by December 13, 1988, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by December 13, 1988. New data could have been submitted until August 15, 1989, and comments on the new data until October 15, 1989.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC anorectal drug products (53 FR 30756 at 30757), the agency advises that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the Federal Register. Therefore, on or after August 5, 1991, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule on OTC anorectal drug products, three manufacturers submitted comments. A request for an oral hearing before the Commissioner was also received. Copies of the comments and the hearing request received are on public display in the Dockets Management Branch (address above). Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

One comment, which was submitted at the very end of the period for the submission of new data, contained the results of two new clinical studies conducted to demonstrate the effectiveness of live yeast cell derivative in the relief of hemorrhoidal symptoms. These studies are currently being evaluated by the agency. The status of this ingredient does not directly relate to the other portions of the final monograph. Accordingly, in order to complete the publication of the final monograph for OTC anorectal drug products without undue delay, the agency is not addressing the data submitted on live yeast cell derivative in this document. The data will be addressed as soon as the agency's review is completed. If the data establish the effectiveness of live yeast cell derivative, the monograph will be amended accordingly. In the interim, products containing live yeast cell derivative may remain in the marketplace and are not subject to this final monograph.

The hearing request concerned the ingredient hydrocortisone. The requester asked that: (1) the definition section (§ 346.3) of the monograph be amended to provide for a drug that has anti-inflammatory properties, such as hydrocortisone; (2) hydrocortisone be allowed to be combined with other appropriate OTC ingredients at OTC strengths, including a typical anesthetic such as pramoxine; and (3) a combination of hydrocortisone and pramoxine, which is presently a prescription drug at 0.5 percent hydrocortisone and 1 percent pramoxine, be switched to OTC use and be generally recognized as safe and effective. The comment stated that general recognition of the safety and effectiveness of hydrocortisone-pramoxine combination OTC drug products exists in the published literature and cited a number of supporting references (Ref. 1). The requester also noted that the issues it raised directly relate to, and are virtually identical to, the issues in

another FDA proceeding, "In the matter of Pramoxine Hydrochloride and Hydrocortisone Acetate Drug Products," Docket No. 88N–0242, published in the **Federal Register** of July 1, 1988 (53 FR 25013).

The agency is currently reviewing the cited references and considering the request for a hearing. The agency did not include hydrocortisone in the tentative final monograph for OTC anorectal drug products (53 FR 30756 at 30766) because a claim for hydrocortisone and hydrocortisone acetate for the temporary relief of anal itching is already included in the OTC external analgesic tentative final monograph. The external analgesic tentative final monograph (48 FR 5852; February 8, 1983) includes both hydrocortisone and hydrocortisone acetate 0.25 to 0.5 percent and pramoxine hydrochloride 0.5 to 1 percent as proposed monograph ingredients. However, neither that monograph nor any other OTC drug monograph currently provides for any OTC combination drug products containing hydrocortisone and any other ingredient. Accordingly, such combination drug products are not currently legally marketed as OTC drug products. Resolution of the above issues related to hydrocortisone does not directly relate to the other conditions proposed in the tentative final monograph for OTC anorectal drug products. Accordingly, in order to complete this rulemaking with regard to the other conditions proposed in the tentative final monograph for OTC anorectal drug products without undue delay, the agency is not addressing the hearing request at this time. Resolution of the related issues in the other FDA proceeding (Docket No. 88N–0242—see above), which is currently pending the completion of studies by the interested parties, may have a bearing on the hearing request. If, after reviewing the information presented, the agency determines that a hearing should be held, it will issue a notice to that effect in a subsequent issue of the **Federal Register**.

The agency will publish its final decision on the issues related to hydrocortisone and live yeast cell derivative in OTC anorectal drug products in a future issue of the **Federal Register**. Final agency action on the remainder of the OTC anorectal drug products rulemaking occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC anorectal drug products.

Reference

(1) Comment No. HER00001, pages 61 to 65, Docket No. 80N–0050, Dockets Management Branch.

I. The Agency's Conclusions on the Comments

1. One comment suggested that § 346.14(a)(3) be revised to read: "Glycerin in solution (provided that the minimum absolute amount of glycerin is not less than 10%)." The comment contended that the language in that section as now worded (i.e., "The following active ingredients may be used as the sole protectant active ingredient in a product if the ingredient as identified constitutes 50 percent or more by weight of the final product * * *. Glycerin in a 20- to 45-percent (weight/weight) aqueous solution.") is unclear as to what is the acceptable minimum absolute amount of glycerin needed to qualify as a protectant active ingredient. The comment maintained that the intent of the section is to indicate that 50 percent of a 20-percent aqueous solution of glycerin is needed to qualify as a protectant active ingredient and, that in absolute terms, this translates to 10 percent glycerin.

The agency agrees that the comment is correct about the minimum amount of glycerin needed to qualify as a sole protectant ingredient. However, the comment's suggested change in § 346.14(a)(3) does not consider the maximum amount of glycerin that may be present in a product. If the final product consisted entirely (100 percent) of a 45-percent (weight/weight) aqueous solution of glycerin, then the product could contain 45 percent glycerin (weight/weight).

The comment's proposed revision to § 346.14(c)(3) states "glycerin in solution," but does not specify an aqueous solution. Any product containing glycerin for use as an OTC anorectal protectant in accord with the monograph cannot be formulated by including only 10 to 45 percent glycerin. Water must be present in the finished product. In discussing the importance of aqueous dilutions of glycerin (45 FR 35576 at 35631), the Panel noted that undiluted glycerin absorbs water and is somewhat dehydrating and irritating to mucous membranes and particularly to inflamed skin. The Panel determined that a lower concentration of glycerin is necessary for safe use in OTC anorectal preparations, and that there are no reports of reactions with 45 percent concentrations. The Panel also noted that undiluted glycerin is not effective as a protectant, whereas a dilution of 20 to 45 percent glycerin in water when applied to skin will lose water to epidermal tissue and acts to soften the skin (45 FR 35631). The Panel also stated at 45 FR 35627 and the agency proposed in the tentative final monograph at 45 FR 30767 that any single protectant active ingredient in a product must constitute 50 percent or more by weight of the final product. Thus, if glycerin were used as the sole protectant in a 20-percent weight/weight aqueous solution, and the glycerin in aqueous solution constituted 50 percent of the weight of the final product, the product would contain 10 percent glycerin by weight. If glycerin were used as the sole protectant in a 45-percent weight/weight aqueous solution and the glycerin in aqueous solution constituted 100 percent of the weight of the final product, the product would contain 45-percent glycerin. Therefore, the minimum concentration of glycerin in a final product would be 10 percent and the maximum concentration would be 45 percent. Accordingly, to clarify this usage, the agency is revising § 346.14(a)(3) to read as follows: "Glycerin in a 20- to 45-percent (weight/weight) aqueous solution so that the final product contains not less than 10 and not more than 45 percent glycerin (weight/weight)." The agency is adding an additional statement to § 346.14(a)(3) to make it clear that any combination product containing glycerin must contain at least this minimum amount of glycerin.

2. One comment requested final authorization regarding the anorectal use of 19 grades of Witepsol (cocoa butter substitutes, hydrogenated coco-glycerides, and hydrogenated palm kernal glycerides). The comment referred to its original citizen petition and its submissions of additional data.

The citizen petition and most of the additional submissions were fully discussed in paragraph 19 of the tentative final monograph (53 FR 30756 at 30763). The remaining information was designated in the tentative final monograph as being under review and is discussed below.

Since the petition was submitted, an official monograph for "hard fat" has been included in "The National Formulary" (NF) (Ref. 2). The agency has determined that all of the 19 grades of Witepsol ingredients meet the requirements for melting range, acid value, iodine value, saponification value, hydroxyl value, and unsaponifiable matter listed in the official NF monograph for hard fat. Accordingly, the agency is including the Witepsol ingredients in the OTC final monograph under the official NF compendial designation of "hard fat." This name replaces the descriptions

previously used or proposed by the comment, i.e, cocoa butter substitutes, hydrogenated coco-glycerides, and hydrogenated palm kernel glycerides.

The agency has the following specific comments on an effectiveness study that was conducted on one hundred subjects (Ref. 1). The volar surfaces of the arms were used as test sites, with sites of 3 square centimeters randomly assigned to each test product. Control sites were also used. Twenty materials were tested: 19 grades of Witepsol and cocoa butter. Thickness of application varied from 0.007 to 0.07 millimeters on a random basis.

Trans-epidermal water loss (an acceptable means of estimating the effectiveness of anorectal protectants) was determined by a method in which the vapor pressure above the chosen area of skin is measured without use of carrier gas currents or gravimetric analysis of the contents of an unventilated chamber (Ref. 3). The results are based on the estimation of the vapor-pressure gradient immediately above the skin and are presented in the following table:

Product (Witepsol grade)	Number of subjects	Mean percent reduction in trans-epidermal water loss	Number of subjects showing no effect
E075	94	41.5	20
E076	94	43.3	18
E085	94	50.6	14
H005	91	44.3	19
H012	91	38.5	24
H015	92	38.7	15
H019	94	45.4	18
H032	93	44.8	16
H035	95	43.2	19
H037	88	51.2	16
H039	91	46.2	19
H042	94	52.5	9
HI75	93	43.1	19
HI85	94	45.5	22
W025	90	41.3	17
W031	88	40.8	19
W032	92	38.4	22
W035	83	38.3	21
W045	90	35.7	22
Cocoa butter	93	30.6	28

The data demonstrate that the Witepsol-type ingredients perform in similar fashion to cocoa butter and may be considered effective as skin protectants.

Based on the above discussion, the agency has determined that the Witepsol ingredients may be included as monograph ingredients under the designation of "hard fat" in this OTC anorectal drug products final monograph. The ingredient "hard fat" is being listed in paragraph (a) of § 346.14 of the monograph under the heading "Protectant active ingredients" and should be considered in the same manner as any other protectant active ingredient listed in that paragraph.

The agency's detailed comments and evaluations of the above data are on file in the Dockets Management Branch (Ref. 4).

References

(1) Letter from B. Pagliocca, Kay-Fries, Inc., to FDA, coded LET015, Docket No. 80N-0050, Dockets Management Branch.

(2) "The United States Pharmacopoeia XXII and The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1931, 1989.

(3) Nilsson, G.E., "Medical and Biological Engineering and Computing," 1977.

(4) Letter from W.E. Gilbertson, FDA, to T.E. Maggio, Dynamit Nobel of America, Inc., coded LET 022, Docket No. 80N-0050, Dockets Management Branch.

II. Agency Initiated Change

In the advance notice of proposed rulemaking for OTC anorectal drug products, the Panel recommended the following warning for products containing aluminum hydroxide gel (45 FR 35576 at 35629) or kaolin (45 FR 35632): "Remove petrolatum or greasy ointment before using this product because they interfere with the ability of this product to adhere properly to the skin area." That warning was included in the Panel's recommended monograph in § 346.56(c)(1) and in the tentative final monograph in § 346.50(c)(8).

Despite the above warning, § 346.22 of the Panel's recommended monograph and § 346.22(a) of the tentative final monograph provided that any of the protectant ingredients could be combined. The agency did not receive any comments on this issue following publication of the Panel's report and the tentative final monograph. The agency has determined that aluminum hydroxide gel and kaolin should not be combined with any "greasy" ingredient. The following monograph ingredients are "greasy" in nature and therefore should not be combined with aluminum hydroxide gel or kaolin: Cocoa butter, cod liver oil, hard fat, lanolin, mineral oil, petrolatum, shark liver oil, and white petrolatum. Accordingly, the agency is stating in § 346.22(a) of this final monograph that "Any two, three, or four protectants identified in § 346.14 may be combined, except aluminum hydroxide gel in § 346.14(a)(1) and kaolin in § 346.14(a)(5) may not be combined with any ingredient in § 346.14(a) (2), (4), (6), (7), (8) and (10), and (b)(2) and (3), provided that the combined percentage by weight of all protectants in the combination is at least 50 percent of the final product (e.g., 1 gram of a 2 gram dosage unit). Any protectant ingredient included in the combination must be present at a level that contributes at least 12.5 percent by weight (e.g., 0.25 gram of a 2-gram dosage unit), except cod liver oil and shark liver oil. If an ingredient in § 346.14(b) is included in the combination, it must not exceed the concentration limit specified in § 346.14(b)."

III. Summary of Changes From the Proposed Rule

1. The agency is revising the designation of the concentrations for glycerin in § 346.14(a)(3) for clarity. (See comment 1 above.)

2. The agency is adding hard fat to § 346.14(a) of the final monograph. (See comment 2 above.)

3. The agency is revising the permitted combinations of protectants in § 346.22(a) to be consistent with the warning in § 346.50(c)(8). (See Part II. "Agency Initiated Change" above.)

IV. The Agency's Final Conclusions on OTC Anorectal Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC anorectal drug products are generally recognized as safe and effective and not misbranded. The agency has determined that the following active ingredients are a monograph condition for their respective drug class: Local anesthetics—benzocaine, benzyl alcohol, dibucaine, dibucaine hydrochloride, dyclonine hydrochloride, lidocaine, pramoxine hydrochloride, tetracaine, and tetracaine hydrochloride; vasconstrictors—ephedrine sulfate, epinephrine, epinephrine hydrochloride, and phenylephrine hydrochloride; protectants—aluminum hydroxide gel, calamine, cocoa butter, cod liver oil, glycerin, hard fat, kaolin, lanolin, mineral oil, petrolatum, shark liver oil, topical starch, white petrolatum, and zinc oxide; analgesics, anesthetics, and antipruritics—camphor, juniper tar, and menthol; astringents—calamine, hamamelis water, and zinc oxide; and keratolytics—alcloxa and resorcinol. With the exception of hydrocortisone and live yeast cell derivative, all other ingredients for anorectal use whether or not considered in this rulemaking are considered nonmonograph ingredients. Ingredients considered in this rulemaking were: local anesthetics—diperodon and phenacaine hydrochloride; vasconstrictor—epinephrine undecylenate; protectants—bismuth oxide, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate,

and lanolin alcohols; counterirritants—camphor (greater than 3 to 11 percent), hydrastis, menthol (1.25 to 16 percent), and turpentine oil (rectified) (6 to 50 percent); astringents—tannic acid; wound healing agents—cholecalciferol, cod liver oil, peruvian balsam, shark liver oil, and vitamin A; antiseptics—boric acid, boroglycerin, hydrastis, phenol, resorcinol, and sodium salicylic acid phenolate; keratolytics—precipitated sulfur and sublimed sulfur; anticholinergics—atropine and belladonna extract; and miscellaneous ingredients—collinsonia extract, *Echerichia coli* vaccines, lappa extract, leptandra extract, and mullein. Any drug product marketed for use as an OTC anorectal drug product that is not in conformance with the monograph (21 CFR part 346) may be considered a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352) and may not be marketed for this use unless it is the subject of an approved application. An appropriate citizen petition to amend the monograph may also be submitted under 21 CFR 10.30.

In the Federal Register of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) The specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The final rule in this document is subject to the labeling provisions in § 330.1(c)(2).

The agency is removing the existing labeling requirements of § 310.201(a)(23)(v)(*b*) (21 CFR 310.201(a)(23)(v)(*b*)) relating to dyclonine hydrochloride upon the effective date of the final monograph for OTC anorectal drug products. In addition, the agency is revising § 369.20 (21 CFR 369.20) by removing the reference to rectal preparations from the entry for "BELLADONNA PREPARATIONS * * *" and by removing the entry for "RECTAL PREPARATIONS FOR EXTERNAL USE." These regulations are being revised because the above entries are superseded by this final monograph for OTC anorectal drug products.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (53 FR 30756 at 30780). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final rule for OTC anorectal drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96-354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC anorectal drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR part 25).

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 346

Anorectal drug products, Labeling, Over-the-counter drugs.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, subchapter D of chapter I of title 21 of the Code of Federal Regulations is amended in parts 310, 346, and 369 as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

§ 310.201 [Amended]

2. Section 310.201 Exemption for certain drugs limited by new-drug applications to prescription sale is amended by removing paragraph (a)(23)(v)(*b*) and reserving it.

3. Part 346, consisting of §§ 346.1 to 346.52 is added to read as follows:

PART 346—ANORECTAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
346.1 Scope.
346.3 Definitions.

Subpart B—Active Ingredients

346.10 Local anesthetic active ingredients.
346.12 Vasoconstrictor active ingredients.
346.14 Protectant active ingredients.
346.16 Analgesic, anesthetic, and antipruritic active ingredients.
346.18 Astringent active ingredients.
346.20 Keratolytic active ingredients.

346.22 Permitted combinations of anorectal active ingredients.

Subpart C—Labeling

346.50 Labeling of anorectal drug products.
346.52 Labeling of permitted combinations of anorectal active ingredients.

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

Subpart A—General Provisions

§ 346.1 Scope.

(a) An over-the-counter anorectal drug product in a form suitable for external (topical) or intrarectal (rectal) administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 212 unless otherwise noted.

§ 346.3 Definitions.

As used in this part:

(a) *Analgesic, anesthetic drug.* A topically (externally) applied drug that relieves pain by depressing cutaneous sensory receptors.

(b) *Anorectal drug.* A drug that is used to relieve symptoms caused by anorectal disorders in the anal canal, perianal area, and/or the lower rectal areas.

(c) *Antipruritic drug.* A topically (externally) applied drug that relieves itching by depressing cutaneous sensory receptors.

(d) *Astringent drug.* A drug that is applied topically (externally) to the skin or mucous membranes for a local and limited protein coagulant effect.

(e) *External use.* Topical application of an anorectal drug product to the skin of the perianal area and/or the skin of the anal canal.

(f) *Intrarectal use.* Topical application of an anorectal drug product to the mucous membrane of the rectum.

(g) *Keratolytic drug.* A drug that causes desquamation (loosening) and debridement or sloughing of the surface cells of the epidermis.

(h) *Local anesthetic drug.* A drug that produces local disappearance of pain, burning, itching, irritation, and/or discomfort by reversibly blocking nerve conduction when applied to nerve tissue in appropriate concentrations.

(i) *Protectant drug.* A drug that provides a physical barrier, forming a protective coating over skin or mucous membranes.

(j) *Vasoconstrictor.* A drug that causes temporary constriction of blood vessels.

Subpart B—Active Ingredients

§ 346.10 Local anesthetic active ingredients.

The active ingredient of the product consists of any of the following when used in the concentration or within the concentration range established for each ingredient:

(a) Benzocaine 5 to 20 percent.
(b) Benzyl alcohol 1 to 4 percent.
(c) Dibucaine 0.25 to 1 percent.
(d) Dibucaine hydrochloride 0.25 to 1 percent.
(e) Dyclonine hydrochloride 0.5 to 1 percent.
(f) Lidocaine 2 to 5 percent.
(g) Pramoxine hydrochloride 1 percent.
(h) Tetracaine 0.5 to 1 percent.
(i) Tetracaine hydrochloride 0.5 to 1 percent.

§ 346.12 Vasoconstrictor active ingredients.

The active ingredient of the product consists of any of the following when used in the concentration or within the concentration range established for each ingredient.

(a) Ephedrine sulfate 0.1 to 1.25 percent.
(b) Epinephrine 0.005 to 0.01 percent.
(c) Epinephrine hydrochloride 0.005 to 0.01 percent.
(d) Phenylephrine hydrochloride 0.25 percent.

§ 346.14 Protectant active ingredients.

(a) The following active ingredients may be used as the sole protectant active ingredient in a product if the ingredient as identified constitutes 50 percent or more by weight of the final product. In addition, the following active ingredients may be used in concentrations of less than 50 percent by weight only when used in combinations in accordance with § 346.22 (a), (b), or (n).

(1) Aluminum hydroxide gel.
(2) Cocoa butter.
(3) Glycerin in a 20- to 45-percent (weight/weight) aqueous solution so that the final product contains not less than 10 and not more than 45 percent glycerin (weight/weight). Any combination product containing glycerin must contain at least this minimum amount of glycerin.
(4) Hard fat.
(5) Kaolin.
(6) Lanolin.
(7) Mineral oil.
(8) Petrolatum.
(9) Topical starch.
(10) White petrolatum.

(b) The following active ingredients may not be used as a sole protectant ingredient but may be used in combination with one, two, or three other protectant active ingredients in accordance with § 346.22 (a), (b), (n), and (o) and with the following limitations:

(1) Calamine not to exceed 25 percent by weight per dosage unit (based on the zinc oxide content of calamine).

(2) Cod liver oil, provided that the product is labeled so that the amount of the product that is used in a 24-hour period represents a quantity that provides 10,000 U.S.P. units of vitamin A and 400 U.S.P. units of cholecalciferol.

(3) Shark liver oil, provided that the product is labeled so that the amount of the product that is used in a 24-hour period represents a quantity that provides 10,000 U.S.P. units of vitamin A and 400 U.S.P. units of cholecalciferol.

(4) Zinc oxide not to exceed 25 percent by weight per dosage unit.

§ 346.16 Analgesic, anesthetic, and antipruritic active ingredients.

The active ingredient of the product consists of any of the following when used within the concentration range established for each ingredient:

(a) Camphor 0.1 to 3 percent.
(b) Juniper tar 1 to 5 percent.
(c) Menthol 0.1 to 1 percent.

§ 346.18 Astringent active ingredients.

The active ingredient of the product consists of any of the following when used within the concentration range established for each ingredient:

(a) Calamine, within a concentration range of 5 to 25 percent by weight per dosage unit (based on the zinc oxide content of calamine).

(b) Hamamelis water, "The National Formulary XI," 10 to 50 percent.

(c) Zinc oxide, within a concentration range of 5 to 25 percent by weight per dosage unit.

§ 346.20 Keratolytic active ingredients.

The active ingredient of the product consists of any of the following when used within the concentration range established for each ingredient:

(a) Alcloxa 0.2 to 2 percent.
(b) Resorcinol 1 to 3 percent.

§ 346.22 Permitted combinations of anorectal active ingredients.

(a) Any two, three, or four protectants identified in (a) § 346.14 may be combined, except aluminum hydroxide gel in § 346.14(a)(1) and kaolin in § 346.14(a)(5) may not be combined with any ingredient in § 346.14(a) (2), (4), (6), (7), (8) and (10), and (b) (2) and (3), provided that the combined percentage by weight of all protectants in the combination is at least 50 percent of the

final product (*e.g.*, 1 gram of a 2-gram dosage unit). Any protectant ingredient included in the combination must be present at a level that contributes at least 12.5 percent by weight (*e.g.*, 0.25 gram of a 2-gram dosage unit), except cod liver oil and shark liver oil. If an ingredient in § 346.14(b) is included in the combination, it must not exceed the concentration limit specified in § 346.14(b).

(b) Any single anorectal ingredient identified in § 346.10, 346.12, 346.16, 346.18, or 346.20 may be combined with up to four protectants in accordance with paragraph (a) of this section.

(c) Any single local anesthetic identified in § 346.10 may be combined with any single vasoconstrictor identified in § 346.12.

(d) Any single local anesthetic identified in § 346.10 may be combined with any single astringent identified in § 346.18.

(e) Any single local anesthetic identified in § 346.10 may be combined with any single keratolytic identified in § 346.20.

(f) Any single vasoconstrictor identified in § 346.12 may be combined with any single astringent identified in § 346.18.

(g) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single astringent identified in § 346.18.

(h) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single keratolytic identified in § 346.20.

(i) Any single astringent identified in § 346.18 may be combined with any single keratolytic identified in § 346.20.

(j) Any single local anesthetic identified in § 346.10 may be combined with any single vasoconstrictor identified in § 346.12 and with any single astringent identified in § 346.18.

(k) Any single local anesthetic identified in § 346.10 may be combined with any single astringent identified in § 346.18 and with any single keratolytic identified in § 346.20.

(l) Any single vasoconstrictor identified in § 346.12 may be combined with any single analgesic, anesthetic, and antipruritic identified in § 346.16 and with any single astringent identified in § 346.18.

(m) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single astringent identified in § 346.18 and with any single keratolytic identified in § 346.20.

(n) Any combination of ingredients listed in paragraphs (c) through (m) of this section may be combined with up to four protectants in accordance with paragraph (a) of this section.

(o) Any product containing calamine for use as a protectant and/or as an astringent and/or containing zinc oxide for use as a protectant and/or as an astringent may not have a total weight of zinc oxide exceeding 25 percent by weight per dosage unit.

Subpart C—Labeling

§ 346.50 Labeling of anorectal drug products.

The labeling of the product contains the following information for anorectal ingredients identified in §§ 346.10, 346.12, 346.14, 346.16, 346.18, and 346.20, and for combinations of anorectal ingredients identified in § 346.22. Unless otherwise specified, the labeling in this subpart is applicable to anorectal drug products for both external and intrarectal use.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as "anorectal (hemorrhoidal)," "hemorrhoidal," "hemorrhoidal (anorectal) (insert dosage form, e.g., cream, lotion, or ointment)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in paragraph (b) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) ("For the temporary relief of," "Gives temporary relief of," or "Helps relieve the") (As an option, select one or both of the following: "local" or "anorectal") [select one or more of the following: "discomfort," "itching," or "itching and discomfort," followed by: "in the perianal area" or "associated with" (select one or more of the following: "hemorrhoids," "anorectal disorders," "inflamed hemorrhoidal tissues," "anorectal inflammation," "hemorrhoidal tissues," or "piles (hemorrhoids).")]

(2) *Additional indications.* Indications applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting indication is clear and understandable. In addition to the indication identified in paragraph (b)(1) of this section, the labeling of the product intended for external or intrarectal use may also contain the following indications, as appropriate.

(i) *For products for external use only containing any ingredient identified in § 346.10.* "For the temporary relief of" (select one or more of the following: "pain," "soreness," or "burning").

(ii) *For products containing epinephrine or epinephrine hydrochloride identified in § 346.12 (b) and (c) for external use only, and for products containing ephedrine sulfate or phenylephrine hydrochloride identified in § 346.12 (a) and (d).*

(A) "Temporarily reduces the swelling associated with" (select one of the following: "irritated hemorrhoidal tissue and other anorectal disorders" or "irritation in hemorrhoids and other anorectal disorders").

(B) "Temporarily shrinks hemorrhoidal tissue."

(iii) *For products for external use only containing glycerin identified in § 346.14(a)(3) and for products for external and/or intrarectal use containing any protectant identified in § 346.14(a) (2), (4), (6) through (10), and (b) (1) through (4).*

(A) "Temporarily forms a protective coating over inflamed tissues to help prevent drying of tissues."

(B) "Temporarily protects irritated areas."

(C) "Temporarily relieves burning."

(D) "Provides temporary relief from skin irritations."

(E) "Temporarily provides a coating for relief of anorectal discomforts."

(F) "Temporarily protects the inflamed, irritated anorectal surface" (select one of the following: "to help make bowel movements less painful" or "from irritation and abrasion during bowel movement").

(G) "Temporarily protects inflamed perianal skin."

(H) "Temporarily relieves the symptoms of perianal skin irritation."

(iv) *For products containing aluminum hydroxide gel identified in § 346.14(a)(1) and for products containing kaolin identified in § 346.14(a)(5).* "For the temporary relief of itching associated with moist anorectal conditions."

(v) *For products for external use only containing any analgesic, anesthetic, and antipruritic identified in § 346.16.*

(A) "For the temporary relief of" (select one or both of the following: "pain" or "burning").

(B) "Can help distract from pain."

(C) "May provide a cooling sensation."

(vi) *For products for external use only containing hamamelis water identified in § 346.18(b), and for products for external use and/or intrarectal use containing calamine or zinc oxide identified in § 346.18 (a) and (c).*

(A) "Aids in protecting irritated anorectal areas."

(B) "Temporary relief of" (select one or both of the following: "irritation" or "burning").

(vii) *For products for external use only containing any ingredient identified in § 346.20.* The indication in paragraph (b)(1) of this section applies.

(c) *Warnings.* Warnings applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting warning is clear and understandable. The labeling of the product contains the following warnings under the heading "Warnings":

(1) "If condition worsens or does not improve within 7 days, consult a doctor."

(2) "Do not exceed the recommended daily dosage unless directed by a doctor."

(3) "In case of bleeding, consult a doctor promptly."

(4) *For products for external use only.* "Do not put this product into the rectum by using fingers or any mechanical device or applicator."

(5) *For products for intrarectal use to be used with a special applicator such as a pile pipe or other mechanical device.* "Do not use this product with an applicator if the introduction of the applicator into the rectum causes additional pain. Consult a doctor promptly."

(6) *For products for external use only containing any local anesthetic identified in § 346.10, menthol identified in § 346.16(c), or resorcinol identified in § 346.20(b).* "Certain persons can develop allergic reactions to ingredients in this product. If the symptom being treated does not subside or if redness, irritation, swelling, pain, or other symptoms develop or increase, discontinue use and consult a doctor."

(7) *For products containing any vasoconstrictor identified in § 346.12.* (i) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(ii) "*Drug interaction precaution.* Do not use this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

(iii) *For products containing ephedrine sulfate identified in § 346.12(a).* "Some users of this product may experience nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your doctor."

(8) *For products containing aluminum hydroxide gel identified in § 346.14(a)(1) and for products containing kaolin identified in § 346.14(a)(5).* "Remove petrolatum or greasy ointment before using this product because they interfere with the ability of this product to adhere properly to the skin area."

(9) *For products for external use only containing resorcinol identified in § 346.20(b).* "Do not use on open wounds near the anus."

(d) *Directions.* Directions applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. The labeling of the product contains the following information under the heading "Directions":

(1) "*Adults:* When practical, cleanse the affected area" (select one or both of the following: "with mild soap and warm water and rinse thoroughly" or "by patting or blotting with an appropriate cleansing pad"). "Gently dry by patting or blotting with toilet tissue or a soft cloth before application of this product." [Other appropriate directions in this section may be inserted here.] "Children under 12 years of age: consult a doctor."

(2) *For products for external use only.* "Apply externally to the affected area" (insert appropriate time interval of administration as identified in paragraphs (d)(6), (7), (8), or (9) of this section).

(3) *For products for external use that are pads containing anorectal ingredients.* "Gently apply to the affected area by patting and then discard."

(4) *For products for intrarectal use that are wrapped suppositories.* "Remove wrapper before inserting into the rectum."

(5) *For products for intrarectal use that are to be used with a special applicator such as a pile pipe or other mechanical device.* "FOR INTRARECTAL USE: Attach applicator to tube. Lubricate applicator well, then gently insert applicator into the rectum."

(6) *For products for external use only containing any of the local anesthetics identified in § 346.10; analgesics, anesthetics, and antipruritics identified in § 346.16; or alcloxa or resorcinol identified in § 346.20.* Apply to the affected area up to 6 times daily.

(i) *For products for external use only containing dibucaine or dibucaine hydrochloride identified in § 346.10 (c) and (d).* Apply to the affected area up to 3 or 4 times daily.

(ii) *For products for external use only containing pramoxine hydrochloride identified in § 346.10(g).* Apply to the affected area up to 5 times daily.

(7) *For products containing vasoconstrictors identified in § 346.12.* Apply to the affected area up to 4 times daily.

(8) *For products for external use only containing glycerin identified in § 346.14(a)(3) or hamamelis water identified in § 346.18(b), and for products for external and/or intrarectal use containing any protectant identified in § 346.14(a)(1), (2), (4), (5), (6), (7), and (9), and (b)(1), (2), (3), and (4), or any astringent identified in § 346.18(a) and (c).* Apply to the affected area up to 6 times daily or after each bowel movement.

(9) *For products containing petrolatum or white petrolatum identified in § 346.14(a)(8) and (10).* Apply liberally to the affected area as often as necessary.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 346.52 Labeling of permitted combinations of anorectal active ingredients.

Indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity established in § 346.50(a). For a combination drug product that does not have an established name, the labeling of the product states the statement of identity established in § 346.50(a).

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of this subpart.

(c) *Warnings.* The labeling of the product states, under the heading

"Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of this subpart.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of this subpart. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

4. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.20 [Amended]

5. Section 369.20 Drugs; recommended warning and caution statements is amended by removing the statement, "See also Rectal Preparations for additional warnings," from the entry for "BELLADONNA PREPARATIONS AND PREPARATIONS OF ITS ALKALOIDS (ATROPINE, HYOSCYAMINE, AND SCOPOLAMINE (HYOSCINE)); HYOSCYAMUS, STRAMONIUM, THEIR DERIVATIVES, AND RELATED DRUG PREPARATIONS" and by removing the entry "RECTAL PREPARATIONS FOR EXTERNAL USE."

Dated: May 15, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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