This part shall become effective 30 days after publication in final form in the FEDERAL REGISTER.

Dated: February 12, 1971.

[SEAL] WILLIAM B. CAMP,
*Comptroller of the Currency.*

[FR Doc.71-2254 Filed 2-17-71;8:52 am]

## [12 CFR Part 14]

## CHANGES IN CAPITAL STRUCTURE

### Notice of Proposed Rule Making

Notice is hereby given that the Comptroller of the Currency, pursuant to the authority contained in the national banking laws, 12 U.S.C. 1, 12 U.S.C. 57, has under consideration a proposed revision of § 14.2 dealing with the conditions under which national banks may have authorized but unissued stock. To aid in his consideration of this matter, interested persons are invited to submit relevant data, views, or comments. Such material should be submitted in writing to Robert Bloom, Chief Counsel, Comptroller of the Currency, Treasury Department, Washington, D.C. 20220, to be received not later than 30 days after the date of this notice.

Part 14, Chapter I, Title 12 of the Code of Federal Regulations, would be amended by revising § 14.2 to read as follows:

**§ 14.2 Authorized but unissued stock.**

(a) Any national banking association, with the approval of the Comptroller and by vote of stockholders owning two-thirds of the stock of the bank entitled to vote, may authorize an increase in the common stock of the bank in the category of authorized but unissued stock, except that the approval of the Comptroller shall not be required where the resulting amount of common stock in the category of authorized but unissued stock will satisfy either of the following criteria:

(1) Where the resulting total amount of authorized but unissued stock will be free of preemptive rights of shareholders and will not exceed 25 percent of the currently issued and outstanding stock. The 25 percent limitation may be calculated without regard to authorized but unissued stock which is specifically designated as being reserved for issuance in connection with employee stock option plans, employee stock purchase plans, employee bonus plans, or other similar programs, provided that such plan has been approved by the Comptroller of the Currency, and shares held for the purpose of satisfying the requirements of convertible capital notes or convertible preferred stock subject to the Comptroller's approval of the convertible capital note or preferred stock issue as required by this Part 14, or

(2) Where the resulting total amount of authorized but unissued stock, exclusive of that amount specifically reserved for issuance in connection with employee compensation programs and for satisfying requirements of the convertible securities of the banking association as referred to in the preceding subparagraph (1) of this paragraph, will be subject to preemptive rights of shareholders and will not exceed 50 percent of the currently issued and outstanding stock.

(b) Authorized but unissued stock may be issued from time to time as stock dividends or for such other purposes and considerations as may be approved by the board of directors of the bank, and by the Comptroller. Any request for approval of the Comptroller for such issuance should be in writing and submitted to the appropriate Regional Administrator of National Banks.

(c) Authorized but unissued stock may also be issued from time to time to employees of the bank pursuant to a stock option or stock purchase plan adopted in accordance with Part 13 of this chapter, or in exchange for convertible preferred stock or convertible capital notes or debentures in accordance with the terms and provisions of such securities.

(d) Nothing contained herein shall be construed as relieving any bank of the obligation to file, with the Comptroller, pursuant to 12 U.S.C. 21a, a certified copy of every amendment to the Articles of Association adopted by the shareholders. The original certificate shall be forwarded to the Comptroller at the Washington office and a copy shall be sent to the appropriate Regional Administrator of National Banks.

Dated: February 11, 1971.

[SEAL] JUSTIN T. WATSON,
*Acting Comptroller of the Currency.*

[FR Doc.71-2220 Filed 2-17-71;8:49 am]

## [12 CFR Part 20]

## INTERNATIONAL OPERATIONS

### Notice of Proposed Rule Making

Notice is hereby given that in connection with a periodic review and revision of the "Comptroller's Manual for National Banks," it is proposed to rewrite in its entirety Part 20, International Operations, to reduce the total number of reports to be filed and to increase the utility of the remaining reports. The rewritten regulation will become effective 30 days after final publication in the FEDERAL REGISTER. Persons desiring to comment on the proposed revision may do so no later than March 18, 1971. Comments should be directed to Robert A. Mullin, Director of International Operations, Comptroller of the Currency, Treasury Department, Washington, D.C. 20220.

Part 20, Chapter I, Title 12 of the Code of Federal Regulations is hereby amended to read as follows:

Sec.
20.1 Authority and policy.
20.2 Definitions and terms.
20.3 Prior notification of international activities.
20.4 Reporting of international activities.

**§ 20.1 Authority and policy.**

(a) *Authority.* This part is issued under the authority of the national banking laws, 12 U.S.C. 1 et seq.

(b) *Policy.* (1) Prior notification will be required of the intention of a national bank to establish a branch in a foreign country or to directly or indirectly acquire an interest in an Edge Act corporation, agreement corporation or foreign bank.

(2) Reports on certain other international activities must be reported to the Comptroller within 30 days of the event. The required notifications and reports will provide the basis, where needed, for special examinations by this office, and for the issuance of appropriate instructions.

**§ 20.2 Definitions and terms.**

For the purpose of this part:

(a) "Edge Act corporation" means a corporation organized under the provisions of 12 U.S.C. 611–632.

(b) "Agreement corporation" means a corporation which has entered into an agreement or undertaking in accordance with the provisions of 12 U.S.C. 603.

(c) "Foreign bank" means a corporation or other association organized under the laws of a foreign country, or of a dependency or insular possession of the United States or a foreign country, which is principally engaged in a commercial banking business.

(d) "Control" of a bank or corporation by a national bank or by an Edge Act corporation or an agreement corporation shall be presumed where a national bank, an Edge Act corporation or an agreement corporation has acquired 25 percent or more of the voting shares of the bank or corporation.

**§ 20.3 Prior notification of international activities.**

(a) *Prior notification.* Before a national bank may engage in any of the following international activities, notification to the Comptroller of the Currency is required as stipulated below:

(1) Upon application to the Board of Governors of the Federal Reserve System to establish the initial branch of a national bank in any foreign country, or in any dependency or insular possession of the United States or a foreign county; and 30 days prior to the establishment of any additional branches in a foreign country, or dependency or insular possession of the United States or foreign country.

(2) Upon application to the Board of Governors of the Federal Reserve System by a national bank to directly or indirectly acquire a controlling interest in an Edge Act corporation, agreement corporation or foreign bank.

(3) At least 30 days prior to the direct or indirect acquisition of less than a controlling interest in any Edge Act corporation, agreement corporation or foreign bank, if the cost of such acquisition exceeds $1 million.

(b) *Forms.* Prior notification shall be made on forms provided by the Comptroller of the Currency.

**§ 20.4 Reporting of international activities.**

(a) *Reports.* A report shall be made to the Comptroller of the Currency within 30 days of the occurrence of any of the following international activities:

(1) The relocation of a branch of a national bank in a foreign country, or in a dependency or insular possession of the United States or a foreign country.

(2) The disposition by a national bank of any interest in an Edge Act corporation, agreement corporation or foreign bank.

(3) The suspension of operations or final closing of any branch of a national bank in a foreign country, or in a dependency or insular possession of the United States or a foreign country; or the suspension of operations or final closing of any foreign bank in which a national bank holds an interest.

(b) *Forms.* Reports shall be made on forms provided by the Comptroller of the Currency.

Dated: February 12, 1971.

[SEAL] WILLIAM B. CAMP,
*Comptroller of the Currency.*

[FR Doc.71-2256 Filed 2-17-71;8:52 am]

# DEPARTMENT OF AGRICULTURE

## Consumer and Marketing Service

## [ 9 CFR Parts 317, 320 ]

## MEAT INSPECTION

### Procedure for Obtaining Approval of Labeling, Marking Devices, and Containers, and Authorization To Manufacture Devices Bearing Official Marks of Inspection; Extension of Time for Filing Comments

On December 17, 1970, there was published in the FEDERAL REGISTER (35 F.R. 19118-19121), a notice that the Department is considering proposals to amend Parts 317 and 320 of the Federal meat inspection regulations (35 F.R. 15552) under the Federal Meat Inspection Act (21 U.S.C. 601 et seq.). The notice included proposed new §§ 317.3, 317.4, 317.15, and 320.1(c) pertaining to approval of labeling, marking devices, and containers for meat products subject to the Act, and authorizations to make devices bearing official marks, and related matters. A 60-day period was provided for interested persons to file comments concerning the proposed regulations.

The Department has received petitions for an extension of the period of time stipulated for the submission of comments on the proposal. The nature of the comments received to date indicates that the proposal will require more extensive evaluation by the affected persons than had been contemplated by the Department.

These circumstances are considered as sufficient justification for an extension of the time originally allotted for filing comments. Therefore, notice is hereby given that any person who wishes to submit written data, views, or arguments concerning matters in the aforesaid December 17, 1970, proposal may do so by filing them in duplicate with the Hearing Clerk, U.S. Department of Agriculture, Washington, D.C. 20250, within 30 days after the date of publication of this notice in the FEDERAL REGISTER. All written submissions made pursuant to this notice will be made available for public inspection at the Office of the Hearing Clerk during regular business hours in a manner convenient to public business (7 CFR 1.27(b)). Comments on the proposal should bear a reference to the date and page number of the December 17, 1970, issue of the FEDERAL REGISTER.

Done at Washington, D.C., on February 16, 1971.

KENNETH M. MCENROE,
*Deputy Administrator, Meat and Poultry Inspection Programs.*

[FR Doc.71-2285 Filed 2-16-71;11:30 am]

# DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

## Food and Drug Administration

## [ 21 CFR Part 3 ]

## COMBINATION DRUGS FOR HUMAN USE

### Proposed Statement Amplifying Policy on Drugs in Fixed Combinations

The Commissioner of Food and Drugs after considering a number of reports from panels of the NAS-NRC Drug Efficacy Study, the large numbers of combination drugs available, and those proposed for marketing, is of the opinion that criteria for rational combination drugs should be published for the guidance of the regulated industry. This statement is intended as amplification of the requirement that a new drug or antibiotic drug application for a combination drug may be refused unless there is substantial evidence that each ingredient designated as active makes a contribution to the total effect which the drug combination is represented to have and purports to possess.

The problem of fixed combinations has been discussed with a number of experts; it is the subject of extensive discussion by experts in the medical literature. It is the consensus of these informed experts that a fixed dose combination drug must have an advantage to the patient over and above that obtained when one of the individual ingredients is used in the usual safe and effective dose. No drug should be present in a fixed combination unless its inclusion clearly enhances safety or efficacy and the fixed ratio of doses is safe and effective for all indications and for patients requiring such concurrent therapy. There are marketed combination drugs which meet these criteria. Many do not. Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended, 507, 59 Stat. 463, as amended, sec. 701 (a), 52 Stat. 1055; 21 U.S.C. 352, 355, 357, 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes that Part 3 be amended by adding thereto the following new section:

**§ 3.____ Drugs for human use in fixed combinations.**

(a) In implementing the provision of the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug, and Cosmetic Act, which requires that a new drug and an antibiotic drug be shown effective for its labeled indications through adequate and well controlled clinical investigations by qualified experts, the Food and Drug Administration has found the unique problems presented by fixed combinations to require a more clearly defined position on such drugs.

(b) Fixed combinations represent a significant proportion of all marketed drugs. A 1969 survey indicated that of the 200 most widely used prescription drugs, approximately 40 percent were fixed combination dosage forms. Over-the-counter drugs are for the most part combination drugs.

(c) The Council on Drugs of the American Medical Association has consistently expressed the need for a sound medical rationale for using drugs in fixed combinations and has recently reaffirmed its longstanding position that the use of fixed-ratio combination drugs, antibiotics included, is with few exceptions neither a sound nor judicious practice. The United States Pharmacopeia has long had a policy against inclusion of combination drugs.

(d) The National Academy of Sciences-National Research Council in its reevaluation of all drugs marketed through the new-drug prcoedures between 1938 and 1962 to determine if the products were effective for all their labeled indications has clearly indicated the limitations in medical practice of fixed combination drugs. As a result of their recommendations, a number of widely used fixed antibiotic combinations have been removed from the market.

(e) The complexities of the problems were apparent to the Food and Drug Administration in evaluating several hundred fixed combination drugs in the Drug Efficacy Study; through the review of pending new drug applications and Notices of Claimed Exemption for Investigational Drugs, and in reviewing the labeling of other marketed drugs. Policies resulting from consideration of these problems would have significant impact on the pattern of medical practice. As a result, an Ad Hoc Committee was convened, consisting of outstanding experts representative of a cross section of medical disciplines, to assist in formulating the most scientifically sound guidelines for general application to determine when a fixed combination drug is rational. In addition, an Ad Hoc Committee consisting of members of the American Society of Pharmacology and Experimental Therapeutics prepared

recommendations on this problem at the request of the Food and Drug Administration.

(f) It is recognized that fixed combination drugs have or may have certain advantages, in addition to enhanced safety or efficacy, over use of the individual ingredients. These include:

(1) Better adherence to a therapeutic regimen, greater patient convenience, and greater economy than if each of the ingredients were given separately but concurrently.

(2) Availability of information on biopharmaceutic compatibility or unanticipated drug interactions.

(g) However, fixed combination drugs also present disadvantages to their use. The most common objections to these products are:

(1) Lack of flexibility to adjust the dosage of each component to the individual patient's needs.

(2) Exposure of patients to unnecessary drugs when one drug component alone would be effective.

(3) Increased possibility of adverse reactions without increased efficacy.

(h) Based on the above considerations, and in line with the recommendations of expert advisors and sound principles of medical practice, the Food and Drug Administration concludes:

(1) The concomitant administration of two or more medicinal agents may be indicated in the treatment of a patient. However, the effects of drugs are intrinsically so complex that it is generally advisable to administer therapeutic agents separately in order that the dosage and frequency of administration of the individual drugs may be varied in accordance with the patient's requirements.

(2) A combination of drugs in one product suggests and implies an added usefulness over one component alone. The implied or suggested usefulness, as well as the claims in the labeling of a drug, must be considered by the Food and Drug Administration in its evaluation of the validity of labeling claims.

(3) Fixed combinations of drugs may be approved where there is evidence of safety and substantial evidence of effectiveness showing that each active component contributes to the effect claimed for the product in the following circumstances:

(i) Where components are combined to:

(a) Enhance efficacy (increase potency, prolong duration of effect, etc.), or

(b) Enhance safety (decrease the incidence or severity of adverse reactions), or

(c) Prevent abuse or misuse.

(ii) Or where components would be given concurrently and the dosage (amount and interval of administration) of each component is such that the fixed combination is safe and effective for patients requiring such concurrent therapy. The advantage of the combination must obtain for all conditions for which it is labeled, for the various dose schedules recommended, for the duration of dosage suggested, and for most patients for which the produce is recommended.

(iii) And studies demonstrate that the pharmaceutical compounding of the fixed combination does not interfere with the bioavailability of each of the ingredients as compared with administration of the individual ingredients separately but concurrently.

(iv) In the event that a combination, presently the subject of an approved NDA or antibiotic monograph, has not been recognized as effective by the Commissioner based on his evaluation of the appropriate NAS/NRC panel report, or for which substantial evidence of effectiveness has not otherwise been presented, formulation, labeling or dosage changes may be proposed and any resulting combination may meet the appropriate criteria listed above.

Interested persons may, within 30 days after publication hereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–62, 5600 Fishers Lane, Rockville, Md. 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof.

Dated: February 16, 1971.

CHARLES C. EDWARDS,
*Commissioner of Food and Drugs.*

[FR Doc.71-2283 Filed 2-17-71;8:52 am]

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## [ 21 CFR Part 130 ]

## ADMINISTRATIVE REVIEW OF DECISIONS ON PROBABLY AND POSSIBLY EFFECTIVE INDICATIONS FOR DRUGS

### Notice of Proposed Rule Making

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 701(a), 52 Stat. 1052–53, as amended, 1055; 21 U.S.C. 355, 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes that a new section be added to the new-drug regulations, Part 130, as follows:

§ 130.____ **Administrative review of decisions on probably and possibly effective indications for drugs.**

(a) The Food and Drug Administration is publishing announcements setting forth its conclusions as to the effectiveness of drugs in implementing the drug efficacy study participated in by the National Academy of Sciences—National Research Council. Some drugs for which there is a lack of substantial evidence of effectiveness have been classified as "possibly" or "probably" effective. Applicants are being allowed 6 months and 12 months respectively to obtain and submit data to provide the required substantial evidence for the indications so classified. Planning, executing, and evaluating these studies require time, the expertise of appropriate investigators, adequate physical facilities, and a suitable patient population. The Food and Drug Administration encourages applicants to discuss the protocols of their proposed studies on a timely basis with officials of the Bureau of Drugs to assure that any studies undertaken to develop data establishing the effectiveness of the drug are adequately planned and executed. The decisions made by the Bureau of Drugs which affect the plan and the course of study of a drug may have a significant impact on the continued availability of a number of drugs.

(b) Based on the above considerations, the Commissioner of Food and Drugs concludes that to assure a fair analysis and adequate administrative review of unfavorable decisions made during the 6 to 12 months allowed, or at the end of these periods, administrative review procedures are appropriate on the following issues:

(1) The acceptability of protocols designed to obtain evidence of effectiveness.

(2) The granting of additional time to complete studies or to analyze results of ongoing studies.

(3) The adequacy of the final results of a study undertaken to establish effectiveness of the drug.

(c) Extensions of time may be justified under the following circumstances:

(1) There is reason to believe the drug may be effective and useful and preliminary study results are encouraging in regard to establishing the effectiveness of the drug; and

(2) A practical protocol can be devised for the studies to satisfy the requirements of an adequate and well-controlled study as described in § 130.12 (a review of the proposed protocol by the appropriate Division of the Bureau of Drugs is desirable prior to initiation of the study and is required prior to granting an extension of time beyond the initial 6 or 12 months period); and

(3) It is likely that the study can be completed within a reasonable time frame; and

(4) The applicant has proceeded expeditiously in planning and conducting the studies to obtain the required data; and

(5) If the drug is a fixed combination it complies with the agency guidelines for combination drugs.

The availability of alternative drugs will be a consideration in making such a decision.

(d) Procedures for obtaining a review of adverse decisions not to accept a protocol, not to grant additional time, or not to accept the applicant's data as substantial evidence of effectiveness are as follows:

(1) After the applicant has been advised of a Bureau decision on any of the above issues, he may request (orally or in writing) a conference with appropriate experts in the Bureau or with outside consultants to the Bureau within 10 days after notification of such decision.

(2) He will be notified of the date of the scheduled conference and must submit a written well-organized statement setting forth the issues, summarizing the