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Title 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER C—DRUGS

PART 130—NEW DRUGS

Procedures for Classification of Over-the-Counter Drugs

A notice of proposed rule making regarding these regulations was published in the FEDERAL REGISTER of January 5, 1972 (37 F.R. 85). Interested persons were invited to submit comments on the proposal within 60 days. Forty-three comments were received. The comments concerned almost every part of the proposal and its accompanying preamble.

GENERAL COMMENTS

1. The preamble to the proposal stated that the review of prescription drugs was being completed and that it was now appropriate to conduct a similar review of OTC drugs. Most of the comments agreed that OTC drugs must be safe and effective and properly labeled so that the consuming public is protected. In addition, most comments supported the class approach to the review of OTC drugs provided such a review is scientifically sound. The Food and Drug Administration believes that the therapeutic category approach to OTC drugs is appropriate, since there are only an estimated 200 active ingredients in the thousands of OTC drugs now marketed; therefore, this approach is adopted in the final regulations.

2. One comment stated that the Food and Drug Administration has required compliance with the Federal Food, Drug, and Cosmetic Act for OTC drugs for 30 years, and for that reason the wholesale review contemplated by these regulations is needless. It was also stated that, by the promulgation of regulations (21 CFR Part 131—Interpretive statements Re: Warnings on Drugs * * * For Over-The-Counter Sale) governing OTC drug labeling, the Food and Drug Administration has given official status to a large number of OTC drugs. Both of these comments failed to recognize that the Food and Drug Administration has not determined the efficacy of OTC drugs marketed prior to 1962 and that it has never stated which OTC drugs are generally recognized as safe and effective and not misbranded so that manufacturers will be aware of which OTC drugs do not need NDA's prior to marketing.

3. The statement in the proposal that self-medication is essential to the nation's health care system was questioned. The comment argued that the OTC drug monographs are designed merely as a public relations gimmick to build unwarranted consumer confidence in OTC drugs and that the American public is involved in recreational pharmacology. The comment concluded that there should be a program to remove OTC drugs from the market. The Commissioner has no authority under the act, however, to remove safe, effective, and properly labeled OTC drugs from the market. Congress has specifically provided for OTC drugs, and only Congress has the power to change the law.

4. One comment suggested that the Food and Drug Administration review its entire position in this matter to make sure that it does not remove any OTC drug from the market. This comment argued that there is a lack of adequate medical personnel within our Nation to treat the ills of all people, especially the aged, the infirmed, and low income families who have limited resources to meet the cost of medical care. The Food and Drug Administration has no desire to reduce the OTC drugs available to the consumer. However, the agency's overriding purpose is to assure everyone who purchases OTC medication that he is receiving a drug which is safe and effective for its labeled purpose and that, upon reading the label, he will be able to determine the uses for the drug, any warning against use, and any other pertinent information which will allow him to use the drug adequately.

5. It was also suggested in one comment that the Food and Drug Administration had not gone far enough in its OTC drug review, because it has failed to include OTC veterinary medication. It is undoubtedly true that OTC veterinary drugs should be reviewed in the same way as OTC human drugs. Because of limited resources, however, it is impractical at this time to review OTC veterinary drugs, and a higher priority must be given to a review of OTC human drugs.

6. In the third paragraph in the preamble to the proposal, it was stated that a broadly representative group of the whole range of OTC drugs (consisting of 420 OTC drugs) was reviewed as part of the National Academy of Science-National Research Council (NAS-NRC) Drug Efficacy Study, and that only 25 percent were classified as effective. There was comment that the Food and Drug Administration was seeking to obscure facts and create a biased situation against the OTC drug market in that it reported that only about 25 percent were classified as effective, when in fact the panels used more than one characterization for effectiveness. It is true that some of the 75 percent were classified as possibly or probably effective, or "effective but." Nevertheless, only 25 percent of the drugs reviewed were found effective, and thus over 300 of the drugs were either misbranded or ineffective for one or more of their intended uses. This fact is not intended to create a bias against OTC medication. There can be no question, however, that the Food and Drug Administration is obligated to review all

OTC drugs to assure that all those found in the marketplace are safe and effective and not misbranded.

7. There was comment that the Food and Drug Administration is delaying for no good reason the implementation of the NAS–NRC review of the 420 OTC drugs and that removal of those that are ineffective should be accomplished immediately, without additional review by the OTC drug panels. Since the Food and Drug Administration is adopting the approach in the OTC drug review of creating monographs for categories of drugs which are generally recognized as safe and effective and not misbranded, it would be highly unfair and anticompetitive to move against the 420 drugs reviewed by the NAS–NRC. First, this would penalize these drugs and enhance the competitive position of other drugs that are no safer or no more effective. Second, the NAS–NRC review of OTC drugs was limited, and thus additional evidence or data may be submitted which will justify a different conclusion. Finally, there is also the possibility that the manufacturer need only reformulate or relabel after the final monograph is published to bring the drug into compliance. Thus, the agency's resources are better used in expediting the OTC drug review, which will establish those drugs that are generally recognized as safe and effective and not misbranded, rather than in implementing the limited NAS–NRC conclusions.

8. Another comment suggested that any drug product which was reviewed by the NAS–NRC drug review and found to be effective be exempted from the OTC drug review unless the manufacturer at his option wishes to resubmit the drug formulation for an OTC review to enlarge or change the labeling, claims, or dosage formulation. The Commissioner is publishing the NAS–NRC review reports for the 420 OTC drugs. These reports are proposed to be handled pursuant to the principles set forth in the FEDERAL REGISTER for April 20, 1972 (37 F.R. 7807). Since the Commissioner is taking no immediate action on most of the NAS–NRC recommendations, there is no final Food and Drug Administration adjudication in those situations. To allow those OTC drugs which were effective under the NAS–NRC review to escape the OTC review and monograph would be to defeat the very purpose for which the monograph system is being created. The NAS–NRC review did not consider all the issues the OTC review panels will consider, and therefore it would be inappropriate for the NAS–NRC report to preempt the OTC drug review. The OTC drug monographs prepared by the panels are to cover all OTC drugs, and the only way to approach this problem is to have the OTC review panels review all OTC drugs.

9. The Commissioner, in the preamble to the proposal, set forth seven paragraphs indicating the reasons why the agency proposed to adopt the OTC therapeutic category review approach. A number of comments argued that the Food and Drug Administration's justifications for this approach (lack of funds, lack of manpower, and competitive unfairness between drugs if a drug-by-drug approach was adopted) were insufficient justifications. It was stated that the lack of manpower and funds were not sufficient justifications because they could be cured by seeking additional appropriations and that the idea of competitive unfairness between manufacturers makes a shambles of the law. The Food and Drug Administration believes that its resources of manpower and funds are properly considered in deciding how best to approach its consumer protection activities. Based on present resources it would not be possible to adopt a drug-by-drug approach even if it were a better method. The Commissioner has also concluded that a drug-by-drug approach is not the best method of proceeding, since it would be so cumbersome, time consuming, and confusing. By adopting these regulations there will be no question as to which drugs are generally recognized as safe and effective and not misbranded, and what labeling is permitted. Competitive unfairness alone would not sway the Food and Drug Administration from acting on a drug-by-drug basis where necessary to protect the public, but, if the Food and Drug Administration were to proceed against one product and remove it from the market, a competitive product that is no safer or no more effective would still be available to the consumer. Under these circumstances, selective enforcement serves no useful public purpose, and agency resources are more efficiently spent doing the complete job rather than a small part of it.

10. Some comments have contended that the Food and Drug Administration does not have the authority to regulate drugs by therapeutic class, because the authority to do so has not been given by Congress. They cite as legal authority for their proposition the insulin (21 U.S.C. 356) and antibotics (21 U.S.C. 357) sections of the act, which give the Food and Drug Administration specific authority to regulate classes of products, and contend that such an approach is permissible only where specifically authorized. These comments also argue that the category reviews are not legally proper, since it is a subversion of the NDA procedures (21 U.S.C. 355), which call for a drug-by-drug review. The regulations however do not state that the OTC drugs reviewed are new drugs which have been approved, but instead provide for monographs which will include those drugs that do not require an NDA. Nothing in the act prohibits the use of the therapeutic category approach to defining those OTC drugs that are generally recognized as safe and effective and not misbranded.

11. Some comments argued that a therapeutic category approach is not reasonable, because each OTC drug and drug combination is unique in that it has a different dosage, manufacturing technique, reproductibility, and reliability of use. The manufacturer of a unique drug and any interested person has an opportunity to present to the panel under the OTC drug review all information pertinent to the safety and effectiveness of the drug. There are numerous opportunities after the panel makes its report to the Commissioner to review and amend any judgments that a pa may have made. The review system t tablished is sufficiently flexible to accommodate inclusion of unique drugs.

12. A number of comments asked how the reviewing panel would be determined for a drug formulation with claims in more than one therapeutic category. A panel will review every OTC drug with a claim in its therapeutic category. This same panel will then decide whether a drug combination may safely and effectively be used at the same time for another claim outside of that therapeutic category. Then the panel(s) responsible for the other therapeutic category(s) must decide whether the active ingredient(s) that falls within its scope is also generally recognized as safe and effective and not misbranded. For example, if a drug is a combination of an analgesic and antacid, the antacid panel would review the safety and effectiveness of the antacid component and determine whether an antacid may rationally be combined with an analgesic. Once that determination is made, the analgesic panel would determine whether the analgesic component is safe and effective and whether it may rationally be combined with an antacid.

13. Numerous comments stated that they intended to submit data but wished to have more than the 30 days that were allowed for submitting data for the antacid panel. In the future 60 days will be allowed for submission. Additional time has been allowed for submiss of data for the first two panels. Sin the proposal indicating that the Food and Drug Administration is going to review OTC drugs by therapeutic classes was published in January, there is no justification for further delays in the submission of data in the future. All interested parties are now on notice and have been for some months that at least 26 categories of drugs are going to be reviewed. Review of available data should begin immediately if it has not already begun. Since data published after 1950 may not be required to be submitted, and since other forms of abbreviated submissions may be permitted for particular ingredients, interested persons may wish to delay compilation of the final submission until the FEDERAL REGISTER notice requesting the data is published. In no event should a submission be made prior to the applicable FEDERAL REGISTER notice.

14. A number of comments would delete the words "generally recognized" before the words "safe" and "effective". Under the law, however, a drug that is safe and effective but not generally recognized as such would require an NDA unless it is grandfathered. If it is grandfathered it may not be misbranded or adulterated. Thus, only those drugs that are generally recognized as safe and effective and that are not misbranded or adulterated may be lawfully marke without an NDA.

15. The Food and Drug Administration in its policy statement (21 CFR .39) published in the FEDERAL REGISTER of May 28, 1968 (33 F.R. 7758), revoked all previous opinions that an article was not a new drug. One comment noted that paragraph (d) stated that in essentially all cases for newly marketed drug products an NDA would be required, and asked how this policy statement agrees with the OTC drug review procedure. The purpose of the OTC review is to set forth which drugs are generally recognized as safe and effective and thus, in accordance with the 1968 policy statement, do not require an NDA. Since the policy statement and the regulations are not in conflict, there is no reason to change either.

16. There was comment that some of the drugs reviewed by the OTC panel appear in the "United States Pharmacopeia" and "National Formulary," which are official compendia recognized in the Federal Food, Drug, and Cosmetic Act. It was argued that if a drug met the compendium packaging and labeling requirement and yet was not approved by the panel, it would be in violation of the regulation but not of the act. The fact that a drug appears in an official compendium does not mean that it complies with all requirements of the act. The compendia use only minimum packaging and labeling requirements. The monograph will undoubtedly require additional labeling beyond that presently required by the official compendia. Since the act recognizes the official compendia only with respect to standards of strength, quality, and purity and not with respect to safety, effectiveness, and misbranding, there is no conflict.

17. One comment asked that the Commissioner make it clear that a trademark would not be lost if a drug or combination were reformulated to meet a monograph. Any drug product which is on the market and which is reformulated and/or relabeled within the limits of the final monograph will not lose its trademark as long as its continued use is not misleading. Transitional labeling may be required where close questions arise.

18. There was comment that the agency should not request data and views until the final order has been published because submissions prepared prior to the final order could be prejudicial. Now that the final order is published, any interested person may submit any additional unsubmitted data on the first two drug categories within the next 20 days. Any person may, of course, also request an opportunity to present oral views to the panel. In the future, panels may be unwilling to review data which is submitted after the time requested unless proper justification for a late submission is made.

19. There was comment that the panel should review only those drugs posing a genuine question of safety and efficacy and that submissions by interested persons should be requested only in such cases. While this approach may be acceptable for some ingredients (such as aspirin) whose safety and effectiveness is well documented and beyond question, it would appear to be the exception rather than the rule. It is therefore concluded that the format set forth in the regulations, as revised in the final order, should apply to all drugs except those explicitly exempted by the notice calling for submission of data for a particular category.

20. There was comment that the Food and Drug Administration should solicit data and views by other means in addition to publication in the FEDERAL REGISTER. There have already been press releases concerning the OTC review and press conferences have been held. The Commissioner and others have met with consumer groups, industry groups, and professional organizations. All of these meetings and press material are an attempt to keep the public informed of what the Food and Drug Administration is doing. Any specific suggestion as to how to give wider dissemination of information concerning the OTC review will be considered.

21. One comment stated that time limits should be placed on each panel's deliberation and due dates should be set for reports so that there would be a definite time in which the reviews must be completed. Because of problems of scheduling and of providing adequate time for review of the data submitted, it is unreasonable to set arbitrary limits. The amount of data submitted may vary by drug category. It is therefore inappropriate to set down a time limit within which the review must be completed. For this reason no time limit will be set even though the Food and Drug Administration wishes to expedite the panels' consideration as much as possible.

22. There was comment that the evaluation by the panel cannot be performed according to testing standards set by the Food and Drug Administration within the past few years, because such OTC drugs have been on the market for a number of years, little public data exist, and few studies have been performed according to the standards that are presently being used. The regulations do not adopt rigid or absolute standards. The regulations indicate what the Commissioner has concluded to be appropriate evidence to prove safety and efficacy and direct that the panels ordinarily base their recommendations on such evidence. Exceptions are permitted where they can be justified.

23. Many comments stated that the proposed regulations would extend the new drug requirements of the 1962 Amendments to include those OTC drugs that were grandfathered under the 1962 and 1938 acts. This is not the situation. The Commissioner seeks to determine which nongrandfathered OTC drugs are generally recognized as safe and effective and which grandfathered OTC drugs are not misbranded. The grandfather clauses exempt those drugs to which they are applicable from the new drug provisions of the act but not from the misbranding provisions.

24. One comment questioned whether the agency intends to require manufacturers of OTC products that were covered by an NDA to submit the NDA data for review by the OTC panels. The Food and Drug Administration intends that the review will cover all OTC drugs, including those with approved NDA's since 1962. NDA files will therefore be a part of the information included in the review. If a final monograph includes an OTC drug which is covered by an NDA as generally recognized as safe and effective, the drug will be removed from NDA status. A finding by a panel that an OTC drug covered by an NDA is not generally recognized as safe and effective may or may not affect the NDA, depending upon the applicability of the basis for the decision. If such action does affect an NDA, it will be handled through the usual new drug procedures.

25. The American Institute of Homeopathy requested that homeopathic medicines be excluded from the OTC review. Because of the uniqueness of homeopathic medicine, the Commissioner has decided to exclude homeopathic drugs from this OTC drug review and to review them as a separate category at a later time after the present OTC drug review is complete.

COMMENTS RELATING TO SPECIFIC PROVISIONS OF PROPOSED § 130.301 (21 CFR 130.301)

I. PARAGRAPH (a)(1) ADVISORY REVIEW PANELS

26. There were numerous comments that the advisory panels should have "expertise" in OTC drugs. The Commissioner in his appointments is choosing as panel members individuals recommended by organizations representing professional, consumer, and industry interests, in addition to those recommended by his own staff. The individuals selected for panel membership are leading experts in the therapeutic category that the panel is reviewing. It has also been suggested that the panel include a general practitioner as one of the members so that the panels are not made up completely of individuals from teaching institutions. There is no exclusion of the general practitioner since any qualified person can be a panel member, and an attempt will be made to have such practitioners represented on as many panels as possible. Many of the panel members will no doubt have a private practice, and whether or not a panel member is a general practitioner will have no bearing on whether or not he is qualified. The only two conditions for panel membership are that the individual have expertise in the therapeutic category under consideration and that he not have a conflict of interest.

27. There was specific comment that there should be no conflict of interest for panel members. All prospective panel members will be questioned, in accordance with the usual Department of Health, Education, and Welfare procedures, to assure that they have no financial or other similar interest in any therapeutic category they are considering and to be sure that they can make an independent and unbiased evaluation.

28. There was also a comment that to insure impartiality the Commissioner should appoint the first three panel members, one from each of three interest groups (consumers, professionals, and industry), and then let those three choose the remaining panel members. The Commissioner is ultimately responsible for the work of the panel and thus for the selection of each member. The Commissioner has therefore concluded that he should select all panel members, utilizing the lists supplied by interested organizations as well as by his own staff.

29. There was also a similar comment that the panel should be made up of individuals evenly divided between the lists submitted by the three interest groups. While an attempt will be made to have all points of view represented on a panel, this cannot be done in a purely mechanical way.

30. There was a request that the lists from which panel members were selected be made known. This would constitute an invasion of privacy and would add nothing to the work of the panels or to the public understanding of the OTC drug review.

31. There was a suggestion that at least one member of the panel be a behaviorist, since the panel was reviewing labeling which must be viewed in the eyes of the user. Such a person may not be qualified to determine whether a drug is safe and effective. The consumer liaison will serve a similar function. The suggestion of obtaining a behaviorist's view on labeling may well have merit in specific cases, and the panels may wish to consult with such an individual prior to its final report. Under paragraph (a)(3), the panel may consult with any individual or group it wishes. This could include a behaviorist, a marketing expert, a qualified scientist or physician, a representative of industry, or consumers. This broad consulting scope is intended to provide the panel with as much information as it needs to make its recommendations. Similarly, the FDA may consult with anyone in reviewing the report and proposing monographs for OTC drugs.

32. There was a request that the panel members' names and curriculum vitae be published in the FEDERAL REGISTER. The names of the panel members will be made public upon selection and their curriculum vitae will be made available upon request. There is no need under the circumstances for publishing such information in the FEDERAL REGISTER.

33. It was requested that the function and presence of the nonvoting industry and consumer liaison members be set forth in the regulations. Since their participation is a matter of discretion, and they have no duties, specific mention is unnecessary and would only serve to limit the possibility of other nonvoting liaison members in the future, should that prove to be desirable.

34. There was a request that nonvoting liaison members be entitled to review all confidential material submitted. Such a request must be rejected. Nonvoting representatives are not agency employees covered by 18 U.S.C. 1905, which provides for criminal penalty for disclosure of confidential information. The panel members are Food and Drug Administration consultants and therefore subject to that statute.

35. A request was made that the industry liaison representative be a voting member. To allow the industry liaison member to vote and not the consumer liaison member or the FDA liaison member would be clearly unfair and unwarranted. Nor is there any guarantee that the industry or consumer or FDA liaison member would have the required expertise to qualify for panel membership.

36. There were numerous requests that the panel's summary minutes reflect both majority and minority views on issues or that the minutes reflect the differing views of the individual panel members. The summary minutes are necessary so that the progress of the panel can be determined but the length, detail, and discussion of minority and/or majority views should be matters that are best left to the panel's discretion. The panel may conclude that detailed minutes are useful or it may conclude that until its position is clear only general minutes are appropriate. Thus, there should be no requirement regarding the length or detail of the summary minutes.

37. There was a request that panel meetings be open, that a full record of each panel meeting be made, and that a copy of the record be made available to the public to increase the public's confidence in the proceeding. Opening the meetings to the public would not be conducive to efficient and effective deliberation of scientific and medical issues by panel experts. Nor is there any reason for a verbatim transcript, because the panel only reports recommendations to the Commissioner and the Commissioner alone issues the proposals and final orders. There is ample opportunity for any interested party to request an oral presentation before the panel, to review the report and the data on which it was based, to comment on the proposal, to request an oral hearing before the Commissioner, and to appeal the final order to the courts. Consumers and industry have designated liaison members to attend all panel meetings except executive sessions, and summary minutes will be kept and made public. In view of the extensive procedural safeguards, opening all meetings to the public and a verbatim transcript are unnecessary.

II. PARAGRAPH (a)(2) REQUEST FOR DATA AND VIEWS

38. One of the main requests was that the Food and Drug Administration not require the interested persons who submit data to justify their request for confidentiality. The proposal stated that, while data submitted in confidence is being reviewed by the panel, FDA would protect the data's confidentiality if it is entitled to such treatment under the provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j). However, the data would be made available to the public 30 days after publication of the proposed monograph unless the person submitting the data can demonstrate that it is in fact entitled to such confidentiality. Such action protects both the confidential[ity] of true trade secrets and the publ[ic] right to understand the basis for governmental decision that vitally affect it. In keeping with the congressional intent of the Freedom of Information Act (5 U.S.C. 552), the Food and Drug Administration is making available to the public as much of the OTC drug review data and information as is permissible under the law.

39. One comment suggested that anything the panels review should be in the public domain. Since all information is voluntarily submitted, however, and since the law clearly protects the confidentiality of trade secrets and other confidential information, the regulations provide an opportunity for such information to be held in confidence upon an adequate justification.

40. One comment proposed to have all data for which confidentiality is requested reviewed by the Office of General Counsel and then by the Commissioner for a determination of confidentiality. Such a procedure would be too cumbersome and is therefore rejected.

41. There were comments suggesting that the request for data to be reviewed should include a request for all other helpful data, including in vitro studies. All pertinent data should be available to the panels, but the data submitted must have some relevance to proving the safety and effectiveness of the drug. Because of the mass of data that could [be] submitted, the regulations establi[sh] reasonable criteria for pertinent data. Since in vitro studies are not significant in determining the safety and effectiveness of OTC drugs and since a statement requesting "other helpful data" is such an open ended request, the request for data excludes these categories.

A. Paragraph (a)(2), Item II Complete Quantitative Composition of the Drug

42. Comments stated that the Food and Drug Administration's request for the complete quantitative composition of the drug was not necessary because the review covered only the safety and efficacy of active ingredients. The Commissioner agrees with this comment and the regulations have been changed to require submission only of a quantitative statement of the active ingredients.

B. Paragraph (a)(2), Item V Efficacy

43. A number of comments suggested that the efficacy data to be submitted for review include pertinent marketing experience that may influence a determination as to the effectiveness of the individual active component or finished drug product. The Commissioner has concluded that, while marketing experience alone is insufficient to show effectiveness of drugs, it may be pertinent. The regulations have therefore been changed so that the efficacy data requested will include pertinent marketing data.

C. Paragraph (a)(2), Item VI Summa[ry]

44. This subsection provides that the interested person who submits data is to

write a summary of his data and views setting forth the medical rationale and purpose of the drug or, where such rationale or purpose is lacking, a statement to that effect. There were comments that the lack of rationale or purpose need not be discussed because the panel's report should cover only drugs that are safe and effective. Such a narrow approach would, however, ignore two facts. Some individual active ingredients may lack a rationale or purpose for every claim for a combination drug and yet be part of rational concurrent therapy. In addition, some interested persons may wish to submit data not to prove the safety and efficacy of a drug but to disapprove it by pointing out the lack of rationale and purpose in a drug. The summary should be scientifically complete and not an argumentative position paper which totally ignores any deficiencies in a drug.

45. Comments objected to the request that any interested person explain in his summary why controlled studies are not necessary, if in fact there are none. There may well be more than adequate justification for the lack of controlled studies for a particular drug, and the views of the interested person who is submitting the summary on this matter can be important. The panel will undoubtedly note the lack of controlled studies in a submission, because a controlled study is the predominant method used today to evaluate drugs. Although the panel will expect the best proof of safety and efficacy (which would be adequate and well controlled clinical studies) such studies may not be available and in fact may not be necessary to prove a drug safe and effective. If that is the case then the interested person should point out the absence of controlled studies and explain why they are unnecessary in the summary.

46. There was also comment that the request for data was limited to manufacturers of marketed OTC drugs and should be expanded to request information from a much broader class of interested persons. The request clearly states, however, that any "interested person" should submit data or views, and this extends to anyone whether he be a manufacturer, seller, user, researcher, consumer, or other individual or organization. The only limitation on submitting data is that it be pertinent and in the proper format. A person need not submit data for each subsection but must submit it in the requested format so that it can be easily identified and properly considered.

47. It was suggested that the format be wholly optional at the discretion of the submitter. Such an approach would severely hamper the panel's ability to review the data.

48. One comment stated that the request for data and views under this section would result in submission of a vast quantity of duplicative material at great expense and that this would result in a major screening and sorting effort by the Food and Drug Administration or the panels. The comment suggested that interested parties submit copies of the labeling and quantitative formulations that they wished reviewed and that the panel then prepare a preliminary monograph identifying formulations which are generally recognized as safe and effective and not misbranded and the labeling that would be acceptable for such formulations. At the same time the panel would prepare a statement concerning those formulations which had been considered but for which more data were needed in order to conclude that the particular formulation was safe and effective and not misbranded. The comment stated that such an approach would reduce the amount of material submitted. This approach is still under consideration by the Food and Drug Administration and may be used for some categories where it is particularly appropriate. The Food and Drug Administration is also considering conducting or contracting for a limited research of literature (probably since 1950) for ingredients in the individual OTC categories. The bibliography from this literature search would be made available at the time the proposed OTC category review is announced in the FEDERAL REGISTER and would be a master list made available to any interested party. All publications listed on the bibliography would be available to the panel members, so that interested persons would need to submit only pertinent data which were not found in the bibliography. The Food and Drug Administration may adopt either of the two above approaches or different approaches depending upon the category and ingredients involved and the resources available. Each published request for data pertinent to a drug category will use the basic format outlined in the regulation, and any variation in the request for data will be published in the request for the particular review category involved. The regulations have been revised to reflect this required flexibility in approach.

III. PARAGRAPH (a)(3) DELIBERATION OF AN ADVISORY REVIEW PANEL

49. There was comment that this section indicates that the panel would only review data which were submitted to it by interested persons and that there seemed to be no provision allowing the panel to do independent literary research. The Food and Drug Administration agrees that the panel should be able to do independent literary research and evaluation, and the regulations do not preclude this. Because the amount of data being supplied by interested persons is significant and because an independent review of the literature by each panel member is not feasible, however, substantial reliance must be placed upon the submitted data. When the Commissioner chooses a panel member, he chooses experts in the particular category, because they have the basic background to evaluate the validity of the data submitted by interested persons. If a panel or any of its members has a question as to certain data submitted, that particular question may be resolved by independent research or by a request of the Food and Drug Administration staff or executive secretary or the consumer or industry liaison.

50. A number of comments concerned the provision that any interested person may request an opportunity to present his views orally to the panel. There were those who thought the oral presentation made to the panel should not be based on whether the panel wished to hear such a presentation, but that such presentation should be a matter of right. The panel must, however, reserve the right to grant or deny a request to make an oral presentation on the basis of the merits of the request and the amount of time available. At the other extreme were those who stated that the oral presentation should be eliminated entirely, because it would be duplicative if any interested person may then request an oral hearing before the Commissioner and because it raises a legal question of whether the panel is making a rule based on the presentation. This subparagraph provides the panel discretion to grant or deny a request for an oral presentation, and the panel will undoubtedly not waste its time on requests where the information offered is duplicative, unnecessary, or uninformative. This oral presentation is not intended to allow an interested person simply to present orally information which he has already presented in written form. The discretion to allow the oral presentations has been left with the panel, since they alone know whether the presentation requested may present data, information, or views in which they are interested. Since the panel report is advisory in nature to the Commissioner, the oral presentation in no way raises a legal question or duplicates the later oral hearing before the Commissioner.

IV. PARAGRAPH (a)(4) STANDARDS FOR SAFETY, EFFECTIVENESS, AND LABELING

A. Paragraph (a)(4), subdivision (i) Safety

51. There was comment that the language should be changed to remove the statement about a low potentiality for harm. The effect would be that an OTC drug would be allowed on the market even though it had high potential for abuse as long as there was no evidence of such abuse. Clearly, any drug that has a high potential for harm should not be available without a prescription.

52. In the second sentence, the proposal stated that proof of safety shall consist of adequate tests by all methods reasonably applicable that show the drug is safe. There were comments that the word "all" should be deleted from the sentence. The requirement intended to be adopted is that safety be proven by adequate tests. To avoid the unwarranted interpretation that every conceivable test is required, the word "all" has been deleted from the final order.

53. There was also comment that there was no indication of what adequate tests

were and that the regulations should provide for scientifically adequate tests including tests for carcinogenicity and reproductive studies. The panel definitely should consider which tests are adequate to prove the safety of a particular drug and should advise the Commissioner accordingly. If it is decided that carcinogenicity and reproductive studies are necessary for a particular drug, then that fact will be reflected in the panel recommendations. There is no reason to request studies which the panel of experts may feel are unnecessary, and the regulations should not prejudge this issue by laying down requirements that more properly are handled on a category-by-category basis.

54. In the last sentence of this subdivision it is stated that the general recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data. There were numerous comments that this particular sentence be changed. There was comment that the word "ordinarily" be deleted and that general recognition be based only on published studies. There was a statement that the language of this section came from the new-drug provisions of the act (21 U.S.C. 355) and therefore was not appropriate. There was also comment that the panel's conclusion that a drug was generally recognized as safe and effective should be based on published and unpublished studies and any other data. The Food and Drug Administration believes that the panel's evaluation of a drug should be based on the best scientific evidence available. In most cases, this consists of published studies which are available for peer review and criticism. Even where published studies are available for review and criticism, there is no reason to exclude unpublished work that may represent a more recent study. Thus, although "ordinarily" the panel will use published studies as its basis, the panel may also consider unpublished studies and other data and may base its decision on such data where appropriate.

B. Paragraph (a)(4), Subdivision (ii) Effectiveness

55. There was comment that the requirement for effectiveness under the regulation should not be by reasonable expectation but should be substantial evidence as required under section 505(d) of the act for new drugs. The comment stated that the requirement is weak and should be more stringent. In fact, proof of effectiveness is required by controlled clinical investigations except where this requirement is waived. This requirement has been adopted, not because it is contained in section 505 of the act, but rather because it represents what medical science today generally regards as adequate proof of effectiveness. The proof necessary to show effectiveness for a particular drug will be determined by the panel utilizing their own expertise and based on the data submitted to them.

56. There was comment that the term "clinically significant" should be deleted from this subdivision, because it is imprecise and does not consider the judgment of the patients who are taking the medication. It was suggested that the term "clinically significant" should be used only in the review of prescription drugs where the conditions are not self-limiting and as easily recognizable as they are with OTC drugs. The patient's subjective judgment, however, is not a proper standard for determining effectiveness. Without adequate scientific evidence that the drug in question provides clinical relief, there is no basis on which to evaluate the drug as effective.

57. There was comment that the required proof of effectiveness, consisting of controlled clinical investigations as defined by 21 CFR 130.12(a)(5)(ii) unless waived, should be replaced by the new-drug standard of adequate and well controlled clinical studies that appears in section 505 of the act. In fact, 21 CFR 130.12(a)(5) is the section defining "substantial evidence consisting of adequate and well-controlled investigations." Thus, appropriate scientific evidence will be required for proof of effectiveness which will consist of controlled studies except where this is waived as unnecessary or inappropriate.

58. There was also comment that the required proof of effectiveness is far too rigorous and in effect adopts for OTC drugs a standard that should apply only to prescription drugs. It was urged that OTC drugs do not require the same sophistication in research and analysis as prescription drugs to prove their effectiveness and that the Food and Drug Administration should recognize that the majority of OTC drugs which are used are based on treating both the physiological and subjective needs of the patient. There can be no question, however, that the best possible data would consist of adequate and well controlled clinical studies of the drug as described in 21 CFR 130.12(a)(5)(ii), and in any event the regulation allows for a waiver where there is a showing that such studies are unnecessary or inappropriate. The applicability of the waiver and the adequacy of other forms of proof of effectiveness will in the first instance be determined by the panel and will then be subject to review by the Commissioner both before and after public comment and by appeal to the courts.

59. It was suggested in comments that effectiveness can properly be demonstrated by any of the following: Objective or subjective clinical studies; biotavailability of ingredients; documented clinical experience or uncontrolled clinical studies; market research studies; animal studies; general medical and scientific literature, published and unpublished; long use by the professional and the consumer; and common medical knowledge. The format for submission of data and views in paragraph (a)(2) permits inclusion of all of the above-listed material in one form or another. Such unscientific evidence as unsubstantiated opinion and marketing experience cannot, however, be regarded as sufficient to constitute adequate proof of effectiveness. Unless scientifically valid data are available or are shown not to be necessary or appropriate, only inadequate proof would exist. Other data and information may, of course, corroborate the scientific evidence.

60. Some comments criticized the statement that general recognition of effectiveness shall ordinarily be based upon published studies, which may be corroborated by unpublished studies and other data. The Commissioner has concluded that "ordinarily" general recognition shall be based upon published studies because they have been subject to public scrutiny and peer review and thus present the best evidence. In addition, general recognition inherently implies general availability of the basis of the judgment. The panel may, nevertheless, base its evaluation on unpublished data if in its expert opinion there is a sound scientific basis for such a decision which is sufficiently widespread to establish general recognition. This evaluation is, of course, subject to review by the Commissioner, public comment, and court appeal.

C. Paragraph (a)(4), Subdivision (iii) Benefit-To-Risk Ratio

61. Some comments stated that it is necessary to evaluate the benefit-to-risk ratio for OTC drugs but that such a statement should appear in the definitions of safety and effectiveness. Such a change is unnecessary because the subdivision clearly states that the benefit-to-risk ratio is to be considered in determining the safety and effectiveness of a drug.

62. Other comments argued that benefit-to-risk ratio should not be applied to OTC products. Such a position is, however, untenable. Any drug which claims to be effective must have some pharmacological action whether it is beneficial, aggravates an already existing condition, or results in an adverse reaction or side effect. In every instance the panel must evaluate whether, balancing the benefits against the risks, the target population will experience a beneficial rather than a detrimental effect. Where little or no benefit is obtainable, of course, little or no risk is acceptable.

D. Paragraph (a)(4), Subdivision (iv) Combination Drugs

63. Some comments suggested that the term "rational concurrent therapy" is without meaning and should be deleted, but no alternative term was offered. Another comment found it an acceptable standard under which to review combination products. Most of the comments indicated that the standard for safety and effectiveness for combination products should be less stringent than that proposed. Any lesser standards, however, would represent an irrational approach to OTC combination drugs. There is no sound medical or scientific reason to have an active ingredient in a combination unless it makes a contribution to the claimed effect. Nor should an active ingredient be included if it decreases the effectiveness or safety of another. [illegible] active ingredients in combinations sh[illegible]

have the effect they are claimed to have, and they should provide relief for the persons who use them, i.e., rational concurrent therapy for the target population whom they are directed. There is no medical justification for an OTC combination which is effective only for a very small number of the people to whom the labeling is directed. The combination need not be effective for the majority of the people taking it as long as it is effective for a significant portion of the population taking it based on its labeling. This is a flexible standard that will be applied initially by the panel using its expert judgment, subject to review by the Commissioner, public comment, and court appeal.

64. There was comment that the OTC combination policy is essentially the same one that was used for the prescription drugs. It is irrelevant whether the policy is the same, similar, or different. The important question is whether the policy, when applied to OTC drugs, will assure the consuming public of the safety and effectiveness of OTC drug combinations.

65. Another comment stated that it is virtually impossible to meet the combination policy as it is set forth using currently available scientific methodology for testing the safety and effectiveness of drugs. Persuasive grounds to support this contention were not given. When controlled studies are unnecessary or inappropriate they will not be required; when they are necessary and appropriate it would be unlawful to permit that a product be marketed without them.

66. One comment stated that the combination policy is deficient in that it fails to require that the combination enhance the safety and efficacy of the drug or that the combination represent an advantage for all the conditions listed in the labeling. As long as there is no decrease in safety, however, there is no sound basis for requiring increased effectiveness or any other advantage for the combination.

E. Paragraph (a)(4), Subdivision (v) Labeling

67. Almost all comments objected to the requirement that labeling be understood by "individuals of low comprehension," on the grounds that the law only requires labeling that the ordinary person can understand and that there is no standard or frame of reference by which to decide how labeling should be written for individuals of low comprehension. One comment, however, did recognize that the Food and Drug Administration is seeking to overcome the problem that OTC drugs may be used to a great extent by individuals who are poor and with lower comprehension and, thus, that an attempt must be made to develop labeling that will be understood by them. The Federal Food, Drug, and Cosmetic Act is for the protection of all citizens and does not distinguish between persons of different comprehension. This requirement does not demand an absolute and does not mean that every individual of low comprehension must be able to read and understand the labeling. The panels, the Food and Drug Administration, and the manufacturers should, however, make every attempt to write labeling in clear, concise, and easily readable statements that can be understood by individuals with low comprehension. The net result should be that people who take OTC drugs take them for the conditions which appear on the label, for which the drugs are safe and from which people would most likely derive relief.

F. Paragraph (a)(4), Subdivision (vi) OTC or Prescription Status

68. It was pointed out that the proposal did not contain the words found in section 503(b)(1) of the act indicating which drugs are prescription drugs, and this language in the regulations has been changed to reflect the language of the act. It was also suggested that the whole paragraph be deleted, since it is repetitious of section 503(b)(1), but it has been retained as a handy reference to the standard for determining the distinction between prescription and OTC drugs.

V. PARAGRAPH (a)(5) ADVISORY REVIEW PANEL REPORT TO THE COMMISSIONER

69. There was comment that a statement should be added to this section requiring the panel to submit in its report to the Commissioner a comprehensive statement of the basis on which it reached its conclusions and recommendations. Such a request is unnecessary since summary minutes of all meetings will be available, and the conclusions and recommendations will also necessarily convey at least a summary of their basis. To require a comprehensive report on how the panel reached their conclusions and recommendations would be an unjustified burden that would severely hinder their efficiency. It is not intended that the panel prepare a detailed medical summary or rationale for the therapeutic category they are reviewing as long as their conclusions and recommendations are clear and the reasons for them are discernible.

70. Comments argued that section 503(b) of the act determines prescription status and that this is not a question that should be asked of a panel. This issue is fundamentally no different, however, from the other issues being considered by the panels. Each panel is being asked for its views on the safety and effectiveness of OTC drugs, and it may well be that they will decide that a drug is generally recognized as safe and effective but that because of adverse reaction or side effects it is not safe and effective for OTC use. The panel's recommendation on this matter should be given to the Commissioner so that he can properly determine whether he concurs that the drug should be placed on prescription status.

71. It was also noted in comments that the panel's recommendation may result in moving a drug which is on prescription status to OTC status. Although the data submitted by interested parties are to relate only to OTC drugs, the panel is charged with making recommendations with respect to all drugs that should be on OTC status. Any interested person may, of course, submit data and views suggesting that a prescription drug be moved to OTC status.

72. There were comments that subdivisions (ii) and (iii) should be deleted in their entirety because the panel should be concerned only with the safety, effectiveness, and proper labeling of OTC drug products and should not be concerned with active ingredients, labeling claims, or other statements which should be excluded from monographs. It is impossible to determine what should be included in a monograph, however, without also determining what should be excluded. Interested persons and the public are entitled to know which drug, active ingredients, labeling claims, and other statements or conditions the panel reviewed and concluded were not generally recognized as safe and effective and not misbranded for OTC drugs. An interested person would otherwise not know whether a particular drug or claim be submitted was reviewed by the panel and what type of determination was made. This review is intended not only to give a stamp of approval for those drugs that are safe and effective but also to indicate what drugs are not safe and effective and what drugs require further testing before a determination of safety and effectiveness may be made.

73. There was also comment concerning the reference to manufacturing procedures which appeared in subdivision (iii) of the proposal. The panels are made up of experts for the review of the safety and effectivenes of OTC drugs. It would be inappropriate for them to review manufacturing procedures, since that it is not an area within their field of expertise. For this reason, "manufacturing procedures" has been deleted from subdivision (iii) in the regulation.

VI. PARAGRAPH (a)(6) PROPOSED MONOGRAPH

74. There was comment that this subparagraph should state that the Commissioner is not bound by the panel's monograph. There is no reason to add such language since there can be no question from the regulations that the Commissioner is not bound by the panel's proposed monograph. Only the Commissioner has the power to promulgate a proposal or a final order.

75. One comment suggested that subdivisions (ii) and (iii) of this subparagraph should be deleted, because they ask for a statement of the conditions excluded from the monograph on the grounds that they lack general recognition as to safety and effectiveness or would result in misbranding. For the reasons already related in paragraph 72 of this preamble, this comment is rejected.

76. Another comment objects to the statement in this subparagraph that the proposed monograph would specify a reasonable period of time within which drugs falling within subdivision (iii) could be marketed while the data necessary to evaluate the drug is being obtained for evaluation by the Food and Drug Administration. The comment suggests that any drug which is not found

generally recognized as safe and effective and not misbranded according to subdivision (i) continue to be marketed while interested persons obtain data to support their positions. There can be no justification to allow the continued marketing of a drug when the Commissioner finds it to be ineffective. On the other hand there is justification as provided in subdivision (iii) for allowing an interested party time to prove a drug safe and effective, if the evidence is insufficient for the Commissioner to make a proper determination. The panel will advise the Commissioner as to what time is reasonable for completing the collection of data; the Commissioner will decide upon the time element. This need not, however, represent a rigid time limitation. It is intended that reasonable time will be provided as long as testing is in progress that is adequate to resolve the medical issues raised by the panel and the Commissioner. It should also be noted that a drug classified as ineffective by the panel and by the Commissioner is not foreclosed forever from the marketplace. Any interested person can prove that the drug or combination is safe and effective and can then obtain an approved new drug application under the new drug procedures. In the interim, however, it cannot be marketed.

VII. PARAGRAPH (a)(7) TENTATIVE FINAL MONOGRAPH

77. One comment stated that this subparagraph should be removed because it provides an unjustified delay and is not necessary for due process. The procedures provided in the regulations are designed to assure that all interested persons have an opportunity to have their comments reviewed by the Commissioner prior to the publication of the final monograph. The Commissioner recognizes that this review vitally affects the interests of the public and of manufacturers and that procedural fairness is essential to guaranteeing substantive fairness. Accordingly, even though this procedural step is unnecessary, it is retained in order to provide an opportunity for final objections and an oral hearing before the final monograph is issued.

VIII. PARAGRAPH (a)(8) ORAL HEARINGS BEFORE THE COMMISSIONER

78. The proposal provided for an oral hearing before the Commissioner, if the Commissioner found reasonable grounds for such a request. The hearing was to be limited to 3 hours. Numerous comments stated that the 3-hour limitation on the hearing was inappropriate and that the time period should be left for an independent determination by the Commissioner at such time as a request is made. Since a reasonable time period for one monograph may not be reasonable for another the regulations have been changed to remove the 3-hour time limit. Thus, the Commissioner may set the length of the oral hearing at whatever time he feels appropriate on the basis of the request made to him.

79. There was also comment that the entire subparagraph should be deleted since it will only create an unnecessary delay and is not necessary to satisfy due process of law. For the reasons set forth in paragraph 76 of this preamble, this comment is rejected.

80. Another comment suggested that the hearing should be not only for those who are interested in changing the monograph, but also to allow those who are satisfied with it to present their point of view. Nothing in this subparagraph specifies who may appear at the oral hearing. The Commissioner may permit any interested person to present views, whether in support of or in opposition to the tentative final monograph.

IX. PARAGRAPH (a)(9) FINAL MONOGRAPH

81. Comment suggested that this section be amended to allow a manufacturer a reasonable time after the final monograph is published to bring a drug into compliance with the monograph. The last sentence of the section clearly states that the monograph shall become effective as specified in the order. This allows the Commissioner to vary the time for compliance depending upon the amount of time needed to bring drugs into compliance. When an individual monograph is completed the time period to bring affected drugs into compliance will be considered on the basis of that monograph. It would be inappropriate at this time to set a rigid rule as to the length of time a manufacturer will be allowed to bring a drug into compliance.

X. Paragraph (a)(10) Court Appeal

82. A number of comments stated that the statutory authority for appeal should be cited so that the interested persons may ascertain to which court an appeal can be taken. It was also argued that there is no provision for judicial review under section 701(a) of the act. Some comments also requested that the Commissioner indicate what the record for appeal would be and who the appropriate officer responsible for preparing it will be. The authority for the monograph is section 701(a) of the act, which gives authority to promulgate regulations for the efficient enforcement of the act. Once a final monograph is published, it constitutes final agency action that is subject to appeal under the Administrative Procedure Act, 5 U.S.C. 701–706. A declaratory judgment would also lie to determine the validity of a final monograph. The record for any court appeal will include all pertinent documentation of the proceeding, including the panel report(s), summary minutes, proposed monograph, tentative final monograph, transcript of oral hearing, final monograph, all comments or objections filed with the Hearing Clerk on the proposed and tentative final monographs, and all data and information received by the panel and made publicly available through the Hearing Clerk. The record for appeal will be compiled by the Office of General Counsel. There is no need to specify these details in the regulations.

83. Some comments suggested that, unless a basic question of safety is raised in the monograph, the final monograph should automatically be stayed pending a final court adjudication. Whether a stay of the effective date for all or part of a monograph should be allowed is within the discretion of the Commissioner, is subject to court review, and will be made on the basis of the facts presented to him.

XI. PARAGRAPH (a)(11) AMENDMENT OF MONOGRAPH

84. Comments suggested that, if the Commissioner denies a petition to amend a monograph, he should be required to specify his reasons in detail and that the interested person who sought an amendment to the monograph should be able to request the convening of a review panel which would review the Commissioner's denial of the petition. The Administrative Procedure Act already requires that the Commissioner's reasons be adequately articulated. An amendment ordinarily would not justify convening a review panel, but in the event of a complex medical issue the Commissioner may in his discretion convene an ad hoc expert panel to advise him. There is no need to spell out such a special procedure in these regulations. Since such a panel could legally do no more than make recommendations to the Commissioner, it should not be available as a matter of right. Any action on an amendment request will, of course, be appealable to the courts.

XII. PARAGRAPH (b) LEGAL STATUS OF MONOGRAPH

85. Almost every comment contended that the Food and Drug Administration lacks legal authority under the act to promulgate OTC drug monographs that constitute binding substantive rules and that the agency's authority is limited to issuing interpretive guidelines. Section 701(a) of the act expressly grants "the authority to promulgate regulations for the efficient enforcement of this Act." Numerous Supreme Court cases, interpreting comparable legislative authorization in other regulatory statutes, have upheld the right to proceed by substantive rule making rather than on a case-by-case basis, to particularize general statutory standards. (See e.g., Federal Power Commission v. Texaco, 377 U.S. 33 (1964); United States v. Storer Broadcasting Co., 351 U.S. 192 (1956); Securities & Exchange Commission v. Chenery, 332 U.S. 194 (1946).) In Abbott Laboratories v. Gardner, 387 U.S. 136, 151–152 (1967), the Supreme Court stated that regulations issued under section 701(a) of the act, if within the Commissioner's authority, "have the status of law and violation of these carry heavy criminal and civil sanction." More recently, in Ciba-Geigy v. Richardson, 446 F. 2d 466, 468 (2d Cir. 1971), the Court stated that:

> * * * the Commissioner has the power to issue binding interpretive regulations, e.g., Abbott Laboratories v. Gardner, 387 U.S. 136, 87 s. ct. 1507, 18 L. Ed. 2d 681 (1967). Indeed the particularization of a statute by rule-making is not only acceptable in lieu of protracted litigation, e.g., Thorpe v. Housing Authority, 393 U.S. 268, 89 s. ct. 518, 21 Ed. 2d 474 (1969); NLRB v. Wyman-Gordon Co., 394 U.S. 759, 89 s. ct. 1426, 22 L. Ed.

2d 709 (1969), but it is the preferred procedure, e.g., Elman, A Note On Administrative Adjudication, 74 Yale L. J. 652, 654–55 (1965). generally, Shapiro, The Choice of Rule-making or Adjudication in the Development of Administrative Policy, 78 Harv. L. Rev. 921 (1965).

It is thus within the discretion of the Commissioner, subject to court review, to decide whether the circumstances warrant proceeding to enforce the act through interpretive guidelines that can be collaterally attacked in enforcement litigation or through substantive rules that are binding upon court appeal.

86. Some comments stated that, even if there were authority to issue substantive regulations, the proposed OTC drug procedures fail to meet Constitutional requirements, because they do not provide for an evidentiary hearing or cross-examination and there is no written record available for review. The regulations promulgated in this order governing the OTC review meet all the requirements of the Administrative Procedure Act and of due process of law. Neither the Administrative Procedure Act nor due process of law requires an evidentiary hearing. 5 U.S.C. 553 provides for a notice of proposed rule making, reference to the legal authority, and disclosure of the substance of the proposed rule. The agency must then give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments, with or without an opportunity for oral presentation. An evidentiary hearing is required der the Administrative Procedure Act ly when it is required by other statutes. In the OTC drug review procedures, far greater procedural rights are granted than are required under the Administrative Procedure Act. Instead of a simple notice of proposed rule making giving the substance of the proposed rule, all interested persons have an opportunity, prior to any court review, to submit the data on which the proposed rule will be based and to request an oral hearing before the panel, to provide written comments and objections to the Commissioner, and to request an oral hearing before the Commissioner. In addition, interested organizations have an opportunity to recommend lists of experts to serve on the panels themselves. As noted in some comments, these procedural safeguards substantially exceed due process requirements. It is precisely because of the importance of the rules being developed, both to the public and to the industry, that the Commissioner has provided these extra precautions against promulgation of unwise, unfair, or unscientific monographs.

87. The comments argued that, even if the Food and Drug Administration had the authority to determine by rule making which drugs are generally recognized as safe and effective, there is no authority to set a standard to determine which drugs are misbranded, because the statute specifically provides for court adidication of this issue. The legal aority to utilize a rule making rather than a case-by-case adjudication approach with respect to misbranding stands on no different footing than the legal authority to exercise rule making with respect to new drug status. Both instances involve explication, particularization, and definition of general statutory requirements as they apply to large numbers of products now on the market. Although the sheer magnitude and indeed impossibility of approaching this matter through case-by-case litigation (as demonstrated by the preamble to the proposal) is insufficient in itself to provide rule making authority if none already existed, the courts have long recognized that these factors are properly considered by an administrative agency in determining when existing rule making authority should be utilized.

88. One comment suggested that, since the monographs are being developed by panels, they can be no more than guidelines. The reports of the panels must, however, be based upon adequate scientific evidence which will be subject to scrutiny by the Commissioner, the public through comments, and court appeal. Accordingly, the fact that panels are developing the initial recommendations in no way detracts from their reliability, and indeed the scientific expertise of the panel members enhances medical credibility of the recommendations.

89. Similarly, most comments argued that, even if the agency has the authority to establish binding substantive rules, the 1938 and 1962 grandfather clauses preclude review of OTC drugs protected by them. The grandfather clauses apply only to the new drug provisions of the act, however, and not to the adulteration or misbranding provisions. The review contained in these regulations is designed to particularize not just the new drug provisions of the act, but also the misbranding provisions. Accordingly, the grandfather clauses in no way preclude the agency from reviewing, through a rule making procedure, the thousands of OTC drugs now on the market that are properly the subject of grandfather protection from the new drug provisions in order to make certain that they comply with the misbranding provisions of the act.

90. Some comments stated that it is inappropriate to particularize the misbranding provisions of the act through rule making, because every individual drug label must be reviewed in totality before a judgment can be made. Based upon long experience, however, the Food and Drug Administration has determined that OTC drugs can be grouped together by therapeutic categories for purposes of reviewing the sufficiency of labeling claims, directions for use, warning statements, and other labeling requirements. The task of establishing the parameters of misbranding is fundamentally the same as the task of establishing the parameters of general recognition of safety and effectiveness, and indeed it would be a gross waste of resources to attempt to separate these two aspects of what must be essentially one review of the scientific and medical basis for OTC drug products.

91. Finally, some comments have noted that paragraph (b) is gratuitous, since it merely states the legal enforcement position that the Food and Drug Administration intends to adopt in the event of subsequent regulatory action, and therefore should be deleted. It has been pointed out that there is no comparable statement of legal enforcement position in similar agency regulations. The Commissioner finds this comment persuasive, and accordingly has deleted all of paragraph (b). The parts of former paragraph (b) which related to taking regulatory action on nonconforming products and to new drug applications justifying deviation from a final monograph have been added as new subparagraphs (12) and (13) under paragraph (a). The comments have pointed out that the regulations will be substantially followed by industry. Accordingly, it may become unnecessary to institute a substantial amount of regulatory action to enforce final monographs. Development of a specific enforcement policy can await promulgation of final monographs after which the industry response will be apparent. The Commissioner at that time may adopt whatever enforcement policy is best suited to guarantee full compliance by all OTC drugs with the provisions of the act.

XIII (C) MONOGRAPHS PROMULGATED

92. The 26 proposed categories listed in the proposal were based on therapeutic categories of drugs to be reviewed. There were comments that the therapeutic categories for the panels should not use a therapeutic indication as their basis but should be grounded on disease indications. Since many, if not most, of the conditions which the OTC drugs seek to relieve are symptomatic in nature and may not be disease related, any category approach grounded on disease indications would cause at least as many if not more problems than the therapeutic category approach proposed by the Commissioner. Because the disease category approach is less reasonable than the therapeutic, it has been rejected.

93. There was also a request that the Commissioner designate the order in which each therapeutic category will be reviewed so that an interested person may prepare those submissions which are going to be reviewed next and not spend time on collecting data for those which are going to be reviewed later. This comment has merit, but the Commissioner is unable at this time to give the order in which these categories will be reviewed. This information will be made public as soon as it is available. It will, however, also be necessary to keep some flexibility in the system in the event that circumstances later require rearranging the tentative schedule.

94. Numerous comments concerned the "vitamin-mineral products" category, which appeared as subparagraph (11) in the proposal. Most comments stated that vitamin-mineral products are foods for special dietary purposes within the meaning of section 304(j) of the act and that it would be impossible to limit the

vitamin-mineral category to therapeutic products alone because such a term is difficult to define. It was also urged that, since vitamin-mineral products have been under Food and Drug Administration review as a result of the special dietary food hearings which lasted almost 2 years, to review OTC vitamin-mineral drug products before the results of those hearings were published would be to nullify all the time and effort spent by interested persons at the hearings. There is no intent by the Food and Drug Administration to review all vitamin-mineral products under these regulations. The special dietary food hearings covered foods, and this review will cover OTC drugs. Thus, the panel in this category will be concerned only with vitamin-mineral products which are drugs. The difficulty in drawing a line between vitamin-mineral products that are foods and those that are drugs only emphasizes the need for such a review.

95. In addition to the vitamin-mineral products, there were objections to a number of other therapeutic categories which appear in the proposal. It was stated that mouthwash products, hematenics, and dentifrices and dental products should not be reviewed since they are not drugs. All of these categories include some products for which drug claims are made and which therefore must be reviewed. Any product for which only cosmetic claims are made and which is therefore not a drug will not be reviewed.

96. It was suggested by some comments that a dermatological panel should be added to the 26 therapeutic categories to be reviewed. This comment has been accepted and the regulations changed to add a dermatological product category.

97. Because the Food and Drug Administration felt that menstrual products, which appeared as subparagraph (24) in the proposal, were adequately covered by other categories, that particular category had been deleted. To clarify the therapeutic name, some category names have been changed, i.e. antiinfective to antimicrobial, mouthwash to oral hygiene aids, and antihistamine to allergy treatment products. The category of oral hygiene aids will cover a much wider range than just mouthwash products while the substitution of allergy treatment products for antithistamines will reduce the category in that particular area. The reason for removing antihistamines is that antihistamines appear in a number of other categories listed, such as sleep aids and cold remedies. The Food and Drug Administration is requesting that each of these panels consider antihistamines as they are used in that therapeutic category, and the agency believes that allergy treatment products constitute a separate category. The category list which appears in the final order does not in fact mean that a separate panel will be convened to consider each individual category. There may be some areas in which a panel can consider more than one category. It is hoped that the number of panels can be reduced, but such a reduction will occur only if it will not affect the consideration given to each therapeutic category. It also may be necessary to convene more than one panel to cover those drugs in the miscellaneous category.

98. There was also comment that interested persons may hesitate to submit data and views on a particular therapeutic category or to appear before the panel or the Commissioner because such a submission might be construed as a waiver of the right later to raise appropriate legal or other objections to the monograph. For that reason the Commissioner has recognized that voluntary submissions of data pursuant to any request or any other form of cooperation with the Food and Drug Administration with respect to the OTC drug review does not constitute agreement with the legality of the procedure or the resulting monograph. Any person submitting data or information or otherwise cooperating with the review retains the right to challenge at any time any aspect of the procedure or monograph on any legal ground. The full cooperation and participation of all interested persons is requested in order to make this review as successful as possible.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1050–53 as amended, 1055–56 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 321, 352, 355, 371) and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended; 5 U.S.C. 553, 702, 703, 704) and under authority delegated to the Commissioner (21 CFR 2.120), Part 130 is amended by adding a new Subpart D consisting at this time of one section, as follows:

Subpart D—Over-the-Counter Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded

§ 130.301 Over-the-counter (OTC) drugs for human use; procedures for rule making for the classification of OTC drugs as generally recognized as safe and effective and not misbranded under prescribed, recommended, or suggested conditions of use.

For purposes of classifying over-the-counter (OTC) drugs as drugs generally recognized among qualified experts as safe and effective for use and as not misbranded drugs, the following regulations shall apply:

(a) *Procedure for establishing OTC drug monographs*—(1) *Advisory review panels.* The Commissioner shall appoint advisory review panels of qualified experts to evaluate the safety and effectiveness of OTC drugs, to review OTC drug labeling, and to advise him on the promulgation of monographs establishing conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. A single advisory review panel shall be established for each designated category of OTC drugs and every OTC drug category will be considered by a panel. The members of a panel shall be qualified experts (appointed by the Commissioner) and may include persons from lists submitted by organizations representing professional consumer, and industry interests. The Commissioner shall designate the chairman of each panel. Summary minutes of all meetings shall be made.

(2) *Request for data and views.* The Commissioner will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of OTC drugs. Data and information submitted pursuant to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the advisory review panel and the Food and Drug Administration as confidential until publication of a proposed monograph and the full report(s) of the panel. Thirty days thereafter such data and information shall be made publicly available and may be viewed at the Office of the Hearing Clerk of the Food and Drug Administration, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of one or more of those statutes. To be considered, eight copies of the data and/or views on any marketed drug within the class must be submitted, preferably bound, indexed, and on standard sized paper (approximately 8½ x 11 inches). When requested, abbreviated submissions should be sent All submissions must be in the following format:

OTC DRUG REVIEW INFORMATION

I. Label(s) and all labeling (preferably mounted and filed with the other data—facsimile labeling is acceptable in lieu of actual container labeling).

II. A statement setting forth the quantities of active ingredients of the drug.

III. Animal safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

IV. Human safety data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiances that may influence a determination as to the safety of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination as to the safety of the finished drug product.

5. Pertinent medical and scientific literature.

V. Efficacy data.

A. Individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component.

5. Pertinent medical and scientific literature.

B. Combinations of the individual active components.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of combinations of the individual active components.

5. Pertinent medical and scientific literature.

C. Finished drug product.

1. Controlled studies.

2. Partially controlled or uncontrolled studies.

3. Documented case reports.

4. Pertinent marketing experiences that may influence a determination on the efficacy of the finished drug product.

5. Pertinent medical and scientific literature.

A summary of the data and views set forth the medical rationale and purpose (or lack thereof) for the drug and its ingredients and the scientific basis (or lack thereof) for the conclusion that the drug and its ingredients have been proven safe and effective for the intended use. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary must be included.

(3) *Deliberations of an advisory review panel.* An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner with respect to the safety and effectiveness of the drugs in a designated category of OTC drugs. A panel may consult any individual or group. Any interested person may request an opportunity to present oral views to the panel; such request may be granted or denied by the panel. Such requests for oral presentations should be in written form including a summarization of the data to be presented to the panel. Any interested person may present written data and views which shall be considered by the panel. This information shall be presented to the panel in the format set forth in subparagraph (2) of this paragraph and within the time period established for the drug category in the notice for review by a panel.

(4) *Standards for safety, effectiveness, labeling.* The advisory review panel, reviewing the data submitted to it and preparing its conclusions and recommendations, and the Commissioner, in reviewing the conclusions and recommendations of the panel and the published proposed, tentative, and final monographs, shall apply the following standards to determine general recognition that a category of OTC drugs is safe and effective and not misbranded:

(i) Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(ii) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 130.12(a)(5)(ii), unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(iii) The benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness.

(iv) An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

(v) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.

(vi) A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs.

(5) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner a report containing its conclusions and recommendations with respect to the conditions under which OTC drugs falling within the category covered by the panel are generally recognized as safe and effective and not misbranded. Included within this report shall be:

(i) A recommended monograph or monographs covering the category of OTC drugs and establishing conditions under which the drugs involved are generally recognized as safe and effective and not misbranded. This monograph may include any conditions relating to active ingredients, labeling indications, warnings and adequate directions for use, prescription or OTC status, and any other conditions necessary and appropriate for the safety and effectiveness of drugs covered by the monograph.

(ii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding.

(iii) A statement of all active ingredients, labeling claims or other statements, or other conditions reviewed and excluded from the monograph on the basis of the panel's determination that the available data are insufficient to classify such condition under either subdivision (i) or (ii) of this subparagraph and for which further testing is therefore required. The report may recommend the type of further testing required and the time period within which it might reasonably be concluded.

(6) *Proposed monograph.* After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner shall publish in the FEDERAL REGISTER a proposed order containing:

(i) A monograph or monographs establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded.

(ii) A statement of the conditions excluded from the monograph on the basis of the Commissioner's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding.

(iii) A statement of the conditions excluded from the monograph on the

*(Correction published in Federal Register of May 20, 1972; 37 F.R. 10358)

basis of the Commissioner's determination that the available data are insufficient to classify such conditions under either subdivision (i) or (ii) of this subparagraph.

(iv) The full report(s) of the panel to the Commissioner.

The proposed order shall specify a reasonable period of time within which conditions falling within subdivision (iii) of this subparagraph may be continued in marketed products while the data necessary to support them are being obtained for evaluation by the Food and Drug Administration. The summary minutes of the panel meetings shall be made available to interested persons upon request. Any interested person may, within 60 days after publication of the proposed order in the FEDERAL REGISTER, file with the Hearing Clerk of the Food and Drug Administration written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Hearing Clerk during regular working hours, Monday through Friday. Within 30 days after the final day for submission of comments, reply comments may be filed with the Hearing Clerk; these comments shall be utilized to reply to comments made by other interested persons and not to reiterate a position.

(7) *Tentative final monograph.* After reviewing all comments and reply comments, the Commissioner shall publish in the FEDERAL REGISTER a tentative order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. Within 30 days, any interested party may file with the Hearing Clerk of the Food and Drug Administration written objections specifying with particularity the omissions or additions requested. These objections are to be supported by a brief statement of the grounds therefor. A request for an oral hearing may accompany such objections.

(8) *Oral hearing before the Commissioner.* After reviewing objections filed in response to the tentative final monograph, the Commissioner, if he finds reasonable grounds in support thereof, shall by notice in the FEDERAL REGISTER schedule an oral hearing. The notice scheduling an oral hearing shall specify the length of the hearing and how the time shall be divided among the parties requesting the hearing. The hearing shall be conducted by the Commissioner and may not be delegated.

(9) *Final monograph.* After reviewing the objections and considering the arguments made at any oral hearing, the Commissioner shall publish in the FEDERAL REGISTER a final order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. The monograph shall become effective as specified in the order.

(10) *Court appeal.* The monograph contained in the final order constitutes final agency action from which appeal lies to the courts. The Food and Drug Administration will request consolidation of all appeals in a single court. Upon court appeal, the Commissioner may, at his discretion, stay the effective date for part or all of the monograph pending appeal and final court adjudication.

(11) *Amendment of monographs.* The Commissioner may propose on his own initiative to amend or repeal any monograph established pursuant to this section. Any interested person may petition the Commissioner for such proposal. A petition shall set forth the action requested and a detailed statement of the grounds in support of such action. After review of a petition, the Commissioner may deny the petition if he finds a lack of safety or effectiveness employing the standards in subparagraph (4) of this paragraph (in which case the appeal provisions of subparagraph (10) of this paragraph shall apply) or he may publish a proposed amendment or repeal in the FEDERAL REGISTER if he finds general recognition of safety and effectiveness employing the standards in subparagraph (4) of this paragraph (in which case the provisions of subparagraphs (6), (7), (8), and (9) of this paragraph shall apply). A new-drug application may be submitted in lieu of or in addition to a petition under this paragraph.

(12) *Regulatory action.* Any product which fails to conform to an applicable monograph after its effective date is liable to regulatory action.

(13) *NDA deviations from applicable monographs.* A new-drug application requesting approval of an OTC drug deviating in any respect from a monograph that has become final shall be in the form required by § 130.4(a)(2) but shall include a statement that the product meets all conditions of the applicable monograph except for the deviation for which approval is requested and may omit all information except that pertinent to the deviation.

(b) Monographs promulgated pursuant to the provisions of this section shall be established in this Subpart D and shall cover the following designated categories:

(1) Antacids.
(2) Laxatives.
(3) Antidiarrheal products.
(4) Emetics.
(5) Antiemetics.
(6) Antiperspirants.
(7) Sunburn prevention and treatment products.
(8) Vitamin-mineral products.
(9) Antimicrobial products.
(10) Dandruff products.
(11) Oral hygiene aids.
(12) Hemorrhoidal products.
(13) Hematinics.
(14) Bronchodilator and antiasthamatic products.
(15) Analgesics.
(16) Sedatives and sleep aids.
(17) Stimulants.
(18) Antitussives.
(19) Allergy treatment products.
(20) Cold remedies.
(21) Antirheumatic products.
(22) Ophthalmic products.
(23) Contraceptive products.
(24) Miscellaneous dermatologic products.
(25) Dentifrices and dental products such as analgesics, antiseptics, etc.
(26) Miscellaneous (all other OTC drugs not falling within one of the above therapeutic categories).

Any person who will be adversely affected by the foregoing order may at any time within 30 days after its date of publication in the FEDERAL REGISTER file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Md. 20852, written objections thereto. Objections shall show wherein the person filing will be adversely affected by the order and specify with particularity the provisions of the order deemed objectionable and the grounds for the objections. If a hearing is requested, the objections must state the issues for the hearing and such objections must be supported by grou legally sufficient to justify the reli sought. Objections may be accompanied by a memorandum or brief in support thereof. All documents shall be filed in six copies. Received objections may be seen in the above office during working hours, Monday through Friday.

* *Effective date.* This order shall be effective upon signature by the Commissioner of Food and Drugs. It would be contrary to the public interest to delay the effective date because:

(1) The review and classification of OTC drugs as generally recognized as safe and effective and not misbranded under prescribed, recommended, or suggested conditions of use cannot be conducted until these regulations are placed into effect; and

(2) Delay in the effective date would serve no useful purpose since interested persons were provided 60 days for the submission of comments on the proposal published in the FEDERAL REGISTER of January 5, 1972 (37 F.R. 85), and all comments have been considered in detail and discussed in the preamble to this order. *

Dated: May 8, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.