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New Drug and Antibiotic Regulations; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 71, 170, 171, 180, 201, 310, 312, 314, 330, 430, 431, 433, 510, 511, 514, 570, 571, 601, 812, 1003, and 1010

[Docket No. 82N-0293]

New Drug and Antibiotic Regulations

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising its regulations governing the approval for marketing of new drugs and antibiotic drugs for human use. FDA is taking this action to speed up the availability of beneficial drugs to consumers by improving the efficiency of the agency's approval process for new drugs and antibiotic drugs, while improving the already high level of public health protection the drug approval and surveillance processes now provide. The improvements will help applicants prepare and submit higher quality applications and permit FDA to review them more efficiently and with fewer delays. This will benefit both consumers and applicants by permitting earlier availability and marketing of new drugs and antibiotics. This action is one part of a larger effort by FDA to review all facets of the agency's drug approval process.

DATES: These final regulations are effective May 23, 1985, except 21 CFR 314.80 *Postmarketing reporting of adverse drug experiences* is effective August 22, 1985. FDA will, however, accept applications until February 24, 1986 that are in the format required under either the current regulations or this final rule. For additional information concerning these effective dates see IV. "Paperwork Reduction Act of 1980" appearing in the preamble of this document.

FOR FURTHER INFORMATION CONTACT: Steve H. Unger, Center for Drugs and Biologics (HFN-362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5220.

SUPPLEMENTARY INFORMATION:

I. Introduction

This final rule completes the first phase of efforts by the Department of Health and Human Services (HHS) to revise Federal regulations governing the new drug approval process. This phase of the regulations (called the NDA Rewrite) finalizes new procedures in 21 CFR Part 314 for FDA review of new drug and antibiotic applications for marketing. This action completes the rulemaking process begun on October 19, 1982 (47 FR 46622). The second phase of these regulatory revision efforts (called the IND Rewrite) covers FDA procedures in 21 CFR Part 312 for reviewing investigational new drug applications. This second phase is nearing completion, following the publication of proposed regulations in the **Federal Register** of June 9, 1983 (48 FR 26720). A third phase of improving the drug approval process involves noncodified guidelines on application format and on fulfulling testing requirements. Together with other regulatory and administrative reforms, the IND/NDA Rewrite and related guidelines represent a major effort on the part of FDA to improve the entire process of drug approval regulation. This effort was begun by FDA through concept papers made available for public comment (44 FR 58919, October 12, 1979) and a related public meeting on November 9, 1979. It was accelerated and intensified at the request of the President's Task Force on Regulatory Relief.

The objectives of the NDA Rewrite final rule are to establish an efficient, but thorough, drug approval process in order both: (a) To facilitate the approval of drugs shown to be safe and effective; and (b) to ensure the disapproval of drugs not shown to be safe and effective. These regulations are also intended to improve FDA's surveillance of marketed drugs. Accordingly, the final regulations enable FDA to act as both a public health promoter, by facilitating the approval of important new safe and effective therapies, and as a public health protector, by keeping off or taking off the market drugs not shown to meet safety and efficacy standards.

In preparing the final rule, FDA carefully reviewed approximately 120 comments received from pharmaceutical manufacturers, trade associations, health professionals and professional societies, consumers and consumer organizations, and Congress. In addition, FDA held a series of meetings with agency employees in order to gain their views as part of the internal decisionmaking process. The agency also considered the recommendations of the Congressionally sponsored Commission on the Federal Drug Approval Process. In preparing the final rule, therefore, the agency has considered the views of virtually all persons having an interest in the drug approval process.

Like both the NDA and IND proposals, the NDA final rule has been reviewed by a special task force appointed by the Secretary of Health and Human Services, and chaired by the Commissioner of Food and Drugs, whose specific charge has been to review these regulations in accordance with Executive Order 12291 (46 FR 13193, February 19, 1981), the mandate of the President's Task Force on Regulatory Relief, and the policy objectives outlined above. Many of these issues were also reviewed by a separate FDA task force, which the Commissioner also chaired.

The NDA final rule is designed to complement the proposed IND regulations, especially in terms of fostering a continuous dialogue between FDA and applications throughout the drug development and approval process. For example, one of the major improvements over present practice suggested in the IND proposal was to allow any drug sponsor an opportunity to attend an "end-of-Phase 2" meeting with FDA officials in order to agree on a plan for Phase 3 clinical investigations. As stated in that proposal, FDA believes that such meetings can significantly shorten the period of subsequent NDA review. The IND proposal also encourages "Pre-NDA" meetings between FDA and applicants to discuss format and modes of presentation in the marketing application. These meetings will be especially necessary as applicants learn how to prepare marketing applications under the new format. As described further below, the NDA Rewrite final rule encourages such dialogue to continue throughout the NDA review period as well.

The new NDA regulations will be supplemented by a series of guidelines. These guidelines are intended to provide applicants with guidance on application format and on how to fulfill testing requirements. The format guidelines will address the overall summary and each of the different technical sections of the application. The guidelines on how to fulfill testing requirements will focus on the areas of animal toxicity testing and chemistry and manufacturing controls, as previously announced in the preamble to the IND Rewrite proposal (48 FR 26720, 26721). These guidelines are in addition to the overall 25 clinical guidelines that FDA prepared in the middle and late 1970's concerning the design of adequate and well-controlled studies on different classes of drugs. Finally, FDA plans to issue a guideline regarding the reporting of adverse drug experiences on marketed drugs, a draft of which has already been made available for public comment (48 FR 4049; January 28, 1983). FDA intends to continue to solicit public comment on

draft guidelines before they are published in final form. For example, notices announcing the availability of several draft guidelines concerning how to fulfill chemistry and manufacturing controls requirements have already been published (see the Federal Register of February 1, 1984 (49 FR 4040) and May 7, 1984 (49 FR 19412 and 19413)). FDA hopes to have all these guidelines publicly available, at least in draft form, before the new regulations become effective, although the agency does not view the existence of draft or final guidelines as being a prerequisite for implementing this final rule.

The IND/NDA Rewrites and related guidelines are part of a larger, overall effort to improve the drug development and approval process. For example, FDA will continue to recognize the high priority given to new drug and antibiotic application reviews, to increase the efficiency in the management review of applications, and to strengthen the agency's scientific base. In addition, with the passage of the Orphan Drug Act of 1983, the agency's Office of Orphan Products Development is actively involved in facilitating the development of new drug and other products intended to treat rare diseases.

Highlights of this final rule, the agency's economic analysis, and responses to general comments are contained in the following introductory sections. The remainder of this preamble is devoted to a section-by-section analysis of comments received, responses to them, and contents of the final regulations.

II. Highlights of the Final Rule

As noted above, the guiding principle in the NDA Rewrite final rule is that the drug approval process should be efficient, but thorough, in order to facilitate the approval of drugs shown to be safe and effective, and ensure the disapproval of drugs not shown to be safe and effective. The regulations are also intended to improve FDA's surveillance of marketed drugs. In response to comments and further internal deliberations, the final rule has modified certain provisions of the proposal in order to meet these objectives better. The major provisions of the final rule are summarized as follows:

1. *Application format.* The final rule incorporates the proposed revisions designed to make the application format more amenable to efficient agency review. Thus, like the proposal, the new format requires an overall summary of the entire application and separate, detailed technical sections that each contain individual summaries and analyses of the specific information needed by the particular reviewing disciplines: clinical, pharmacology, chemistry, statistics, and biopharmaceutics (as well as microbiology for anti-infective drugs). The new format will therefore permit parallel review by each of the five (or six) disciplines. In addition, detailed technical sections that synthesize the important information about the drug will greatly facilitate review by agency officials. The final rule also provides applicants the option of submitting the chemistry section (if it is complete) 90 to 120 days prior to submission of the main application in order to expedite review and permit early resolution of deficiencies.

2. *Safety update reports.* The final rule also incorporates the general requirement contained in the proposal for applicants to submit new safety information learned about a drug while an application is being reviewed by FDA. The final rule modifies the timing and frequency of these reports in order to focus FDA evaluation of them at key points in the review process. Thus, under the final rule, safety update reports will be required 4 months following the initial submission of the application, following receipt of an "approvable" letter, and at other times upon FDA request. These safety update reports will ensure that approval decisions reflect the most up-to-date safety information available.

3. *Case report forms and data tabulations.* The final rule follows the general principle enunciated in the proposal that an efficient agency review of individual patient data should be based primarily on well-organized, concise, data tabulations, and that reliance on the more lengthy case report forms should be reserved for those instances where a more detailed review is necessary. Accordingly, the final rule provides: (i) That case report forms will be routinely required where the patient dropped out or died during a clinical study (because these forms are likely to disclose the most serious safety problems); (ii) that individual patient data tabulations will be required for the remaining patients; and (iii) that additional case report forms will be requested by FDA when needed to conduct a proper review of the application. In response to comments, the final rule clarifies that FDA reviewers, with the concurrence of the division director, will have access to whatever additional case report forms are needed to conduct a proper review. The preamble explains that this may include requests for full case reports from the most critical studies, but that these reports will ordinarily be requested early in the review process so as not to cause undue delay. These data submission requirements should promote a more focused, efficient review of the application without compromising the thoroughness of that review. FDA estimates that this approach will result in a 75 percent reduction, on average, in the number of case report forms now required to be submitted to the agency in order to obtain approval.

4. *Time frames for FDA review.* The final rule incorporates the time frames contained in the proposal pertaining to the agency's review of applications. Accordingly, the final rule gives the agency 180 days from receipt of an application to issue either an "approval" letter, an "approvable" letter, or a "not approvable" letter. This time period may be extended when major amendments are received, although the extension would only be for the extra time needed to review the amendments. The final rule, like the proposal, also defines the procedure and time frame for "filing" an application within the meaning of section 505(c) of the act (21 U.S.C. 355(c)). Codification of these time frames demonstrates the agency's commitment to reviewing applications promptly in accordance with the statutory mandate.

5. *Action letters.* The final rule also incorporates provisions contained in the proposal which clarify the meaning of its three action letters: approval letters, approvable letters, and not approvable letters. Like the proposal, the final rule clarifies that only an approval letter grants permission for marketing of a drug. In addition, the final rule adopts the proposed policy that the agency will issue an approval letter, rather than an approvable letter, when the only deficiencies in the application concern editorial or other minor changes in the labeling, with approval conditioned on the deficiencies being corrected, as requested, before the drug is marketed.

6. *Foreign data.* The final rule incorporates the proposed policy that an application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved by FDA if: (i) The foreign data are applicable to the U.S. population and U.S. medical practice; (ii) the studies have been performed by clinical investigators of recognized competence; and (iii) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate

means. These criteria assure the quality of any drug products so approved, while at the same time removing the need to conduct repetitive clinical testing in this country in those instances where adequate data have been generated abroad.

7. *Communication between FDA and applicants.* The final rule greatly expands upon the proposed provision concerning communication between FDA and applicants. The final rule, with greater emphasis than the proposal, encourages dialogue between FDA and applicants about scientific and medical issues that arise during the review process. This includes notifying applicants of easily correctable deficiencies found in an application shortly after those deficiencies are discovered, providing an opportunity for an informal meeting mid-way through the review process and again after FDA's review is completed, and expressly permitting telephone calls and other informal meetings as the need may arise. This provision builds on portions of the IND Rewrite proposal that encouraged such communication during the testing phase of the drug development process.

8. *Dispute resolution.* The final provision on dispute resolution has been significantly revised in order to build upon the general principles noted above with respect to communication between FDA and applicants. For administrative and procedural issues, the final rule establishes an ombudsman whose function will be to investigate what has happened and to facilitate a timely and equitable resolution. For scientific and medical disputes, the final rule provides that applicants should seek resolution through an "end-of-review conference", with appropriate agency staff and management representatives, and at other informal meetings as the need may arise. The final rule also provides for the participation of outside experts at these informal meetings when feasible. This procedure supersedes the appeals process described in the NDA (and IND) Rewrite proposals because that process was seen as being too formal and was not effective during the pilot period.

9. *Supplements.* The final rule, like the proposal, establishes different categories of supplements to approved applications concerning manufacturing and controls changes. The rationale for the categories is that changes that could affect the safety or effectiveness of a final drug product should be preapproved by FDA, but that other changes may be implemented by a firm while notifying FDA either concurrently or in the next annual report. Although some changes have been placed in different categories than originally proposed, the final rule should still result in a 20 percent reduction in the number of manufacturing and controls supplements that require prior approval by the agency. Thus, the final rule will enable drug manufacturers to implement some kinds of manufacturing changes significantly more promptly without compromising drug safety and effectiveness.

10. *Postmarketing surveillance.* The final rule modifies the proposal in several ways in order to focus FDA review more directly on the more serious adverse drug experiences. Under the final rule, 15 working day "alert reports" will be required for all adverse drug experiences that are both serious and unexpected, and for any significant increase in frequency of an adverse drug experience that is both serious and expected (rather than only unexpected fatal and life-threatening experiences, as had been proposed). Other adverse drug experiences, as specified in the final rule, will be required to be reported at quarterly intervals in the first 3 years following approval, and annually thereafter. The quarterly reporting requirement reflects the fact that close surveillance of a new drug's side effects is especially important during the first 3 years of marketing. Although the quarterly/annual reporting of adverse drug experiences is less frequent than the proposed period of 30 working days, FDA believes that such quarterly/annual reporting is consonant with the agency's need to review reports of expected or nonserious adverse drug experiences.

III. Economic Analysis

The agency has examined the economic consequences of these regulations in accordance with Executive Order 12291 and the Regulatory Flexibility Act. A final regulatory impact analysis has been prepared and placed in file with the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

The regulations are expected to shorten the total elapsed time required to approve the average application, including resubmission, from about 27 months to 21 months—an average savings of 6 months. The average approval time for applications involving important new chemical entities is projected to improve from about 19 months to 17 months—an average savings of 2 months. The faster approval and smaller savings for new chemical entities reflect the special priority already accorded these applications. Faster approvals for applications would benefit both consumers and pharmaceutical manufacturers. Consumers would have earlier access to important new drugs that have the potential to extend life, avoid hospitalization, or provide other significant health benefits. Firms developing new drugs would realize faster return on their research investments, thereby encouraging further investment in subsequent pharmaceutical research. The regulatory impact analysis examines some measures of these various benefits, although none are amenable to simple quantification in monetary terms.

Nonetheless, these benefits are substantial. For example, a 2-month speed-up in the approval of 15 therapeutically significant applications per year would result in about 500,000 additional prescriptions for these important drugs in the first year following FDA approval. The number of persons benefiting from these additional prescriptions would probably exceed 200,000, after adjusting the total for renewal and repeat prescriptions. Some of these individuals should receive very significant medical benefits such as avoidance of surgery, cure or stabilization of a life-threatening disease, or relief of a physical handicap. Many individuals should also save money as compared to alternate treatments.

The accelerated availability of new drugs to consumers will also increase industry revenues. However, the increase will not be as great as gross sales because some of the new drugs will displace less effective or more costly drugs.

Changes in the cost of the new drug application process itself will be minor. Increases include $1.2 million annually for detailed NDA summaries, $0.5 million annually for NDA safety update reports, and $0.4 million annually for increased adverse experience reports for approved NDA's; decreases include $0.4 million for less routine paperwork for NDA's, $1.6 million for reduced supplements for approved NDA's, and $1.6 million for reduced supplements for approved ANDA's. These latter two decreases relate to applications to change postmarketing manufacturing procedures for NDA's or ANDA's in minor ways. The net decrease of $1.5 million is about $1.0 million less than the cost savings estimated in the preliminary analysis, attributable primarily to cost estimates for safety update reports and adverse experience

reports that were not calculated at the proposal stage.

The agency also concludes that these regulations will have a favorable impact on small firms because of cost savings associated with abbreviated applications, the type of application most frequently held by small firms. Due to the elimination of requirements for submitting certain postmarketing supplements, FDA estimates a savings of $540 for each abbreviated application. While this impact is favorable, it will not be a significant savings for any one firm. Therefore, the agency certifies, in accordance with the Regulatory Flexibility Act, that this rule will not have a significant economic impact on a substantial number of small entities.

IV. Paperwork Reduction Act of 1980

In accordance with the Paperwork Reduction Act of 1980 (44 U.S.C. Chapter 35), the reporting and recordkeeping requirements in §§ 314.50, 314.55, 314.70, 314.71, 314.72, 314.80, 314.81, 314.90, 314.110, 314.120, 314.126, 314.200, 314.300, and 314.420 in these regulations will be submitted for approval to the Office of Management and Budget (OMB). Interested persons desiring to submit comments on the collection of information requirements pursuant to the Paperwork Reduction Act and its implementing regulations (5 CFR Part 1320) should direct them by April 15, 1985, to the Office of Information and Regulatory Affairs, OMB, Rm. 3002, New Executive Office Bldg., Washington, DC 20503, Attn: Bruce Artim. These requirements will not be effective until FDA obtains OMB approval. FDA will publish a notice concerning OMB approval of these requirements in the Federal Register prior to May 23, 1985.

V. Comments on Proposed Rule

General Comments

1. FDA received approximately 120 comments on the proposed rule. These comments were received from pharmaceutical manufacturers, trade associations, health professionals and professional societies, consumer and consumer organizations, and Congress. A number of the proposed changes were generally supported by these diverse groups, especially those improving the application format, establishing time frames for FDA review of applications, and requiring safety update reports for pending applications. Other items considered especially beneficial by consumers included the requirement for a description of the foreign marketing history of the drug and the proposal concerning postmarketing surveillance. In addition, industry comments found especially beneficial the adoption of a single set of regulations for both antibiotics and nonantibiotic drugs, the reductions in supplements and other reports, and the clarified definitions and procedures for FDA's issuance of action letters.

2. The major concerns raised by consumers and consumer organizations was the fear that two of the proposed changes could possibly result in the marketing of drugs that are not safe or effective, as required by law. The issues of concern in this regard were the proposal to eliminate the routine submission of most case report forms, and the proposal concerning the acceptance of foreign data.

FDA shares the view that any changes made in the new drug regulations should not in any way lower the safety and effectiveness of marketed drugs, and FDA has carefully reviewed each section of the final regulations to ensure that that result does not occur. With respect to case report forms, the final rule ensures that FDA reviewers will have access to any case report forms necessary to conduct a proper review of the drug's safety and effectiveness. With respect to foreign data, FDA carefully reviewed its proposed policy, and explains in this preamble why the agency does not believe that fears about a possible lowering of drug quality are warranted. The agency intends to administer the policy with this concern in mind. Both of these issues are discussed in more detail in the section-by-section analysis.

3. Comments received from the pharmaceutical industry raised three kinds of objections. First, industry comments believed that the proposed regulations were deficient in not addressing several areas that the industry believes are important, such as granting sponsors a right to bring disputed matters to an outside advisory committee, providing an ombudsman to resolve minor procedural disputes, expanding communication between FDA and applicants, and codifying substantive provisions of the standards for safety and effectiveness.

Second, industry comments suggested that, although many of the proposed revisions represented movement in the right direction, FDA should make more dramatic changes in the drug approval process in order to achieve adequate regulatory reform. For example, some industry comments urged replacing both case report forms and detailed tabulations with briefer summaries, placing even greater reliance on foreign data and requiring many fewer supplements to approved applications.

Finally, while agreeing with the concept of strengthened postmarketing surveillance, industry comments generally stated that the specific reporting requirements proposed were excessive and did not provide a corresponding public health benefit. These comments stated that the reporting requirements should be better tailored to the relative importance of the adverse drug experiences involved.

In response to these comments, FDA has added to the final rule major sections on communication between FDA and applicants and on dispute resolution, including establishment of an ombudsman. The final rule also contains a detailed statement on the agency's use of advisory committees, although the agency has not provided, for the reasons stated in that discussion, applicants with rights to advisory committee reviews of issues. With respect to codifying substantive standards for safety and effectiveness, FDA believes that current statutory and regulatory provisions contain the necessary flexibility to administer these provisions to the wide variety of drugs subject to FDA's approval authority. The agency has, moreover, undertaken to provide further guidance with respect to the efficacy standard through the publication of guidelines for over 25 classes of drugs. Finally, in the IND Rewrite proposal, FDA stated its intent to make "end-of-Phase 2" meetings available for all IND's. These meetings provide a mechanism for agency reviewing officials and sponsors, with input from outside experts, to agree on an overall plan for Phase 3 investigations and the objectives and design of particular studies necessary to demonstrate the safety and effectiveness of the drug. (See 48 FR 26732.) FDA believes that this in-depth, case-by-case approach, will greatly facilitate the drug development process by providing sponsors with specific information about safety and effectiveness requirements in a timely manner.

Second, FDA generally disagrees with the industry comments that suggested that specific provisions in the proposal did not go far enough in providing regulatory relief. As described further below, FDA believes that case report forms and tabulations provide information, viewed as necessary, that may not be obtained through summaries alone; that further changes in the foreign data policy are not now appropriate; and that significant further changes in the area of supplements could possibly adversely affect the assurance of FDA regulation of marketed drugs.

Finally, FDA agrees that improvements in postmarketing surveillance should focus high priority reporting requirements on the more important adverse drug experiences. Accordingly, as described further below, the final rule provides for more stringent reporting requirements for adverse drug experiences that are both enexpected and serious, and less stringent requirements for the others.

4. Several comments urged FDA to adopt more specific and detailed regulations that give clear guidance to the regulated industry and to FDA personnel. According to these comments, these regulations should include detailed requirements for FDA actions, broad admonitions about normative conduct, requirements for agency documentation of decisions, and internal review mechanisms. Comments objected to FDA relying upon guidelines, internal manuals, memoranda, and other similar informal mechanisms to handle practices and procedures because they are too imprecise, subject to change, and of questionable authority. However, if FDA does decide to rely heavily on staff manual guides, one comment urged FDA to establish and codify a policy stating that such guides are binding upon the agency.

Many comments addressed further the issue of guidelines. Several comments argued that it was hard to discern the proposal's true impact without reviewing the guidelines FDA intends to use to implement the regulations and, accordingly, that FDA should reopen the administrative record once the guidelines are available. Moreover, these comments believe FDA should limit the use of guidelines to those situations where negotiation and alternative methods are clearly necessary or desirable, such as in clinical trials of different diseases. Several comments also asked FDA to provide notice and comment procedures on draft guidelines and staff and compliance manuals before final ones are prepared. Finally, some comments objected to FDA's reliance on guidelines because such documents often remain internal working documents and, according to these comments, are applied less consistently than the regulations. Finally, one comment urged that the final rule, or another proposal, should address procedural issues in the application review process, such as the designation of a primary review team early in the process, the need for meetings, concurrent review of an application by members of a review team, the finality of each part of the review once it is completed, and the importance of a tracking system to determine the history and current location and status of all submissions to FDA.

FDA believes its proposal provided adequate notice of the rights and responsibilities of both applicants and the agency in the drug approval process. FDA believes the more detailed regulations urged by these comments would add very little to the structure of the new drug approval process provided by FDA's combination of regulations, guidelines, and staff guides, while making the process more inflexible and difficult to change. The agency believes the proposal struck a proper balance between the need for regulatory requirements, the use of guidelines to help persons comply with those requirements, and the use of staff manuals to direct agency employees. FDA recognizes that the prompt issuance of clear guidelines will be most helpful to applicants and, thus, the agency is taking steps to expedite the development of guidelines and to clarify for its staff the role of guidelines in the regulatory process. Because FDA recognizes the significant contribution the industry, the medical community, and other members of the public can make to the development of scientifically sound guidelines, the agency routinely solicits comments on its guidelines either as draft or as final documents. With respect to the guidelines developed to implement this final rule, FDA intends to issue them as draft guidelines and to seek comments on them before they are made final. FDA believes it has provided adequate notice for this rulemaking proceedings and does not intend to reopen the administrative record on the regulations after the guidelines (or draft guidelines) are issued. Finally, FDA believes that administrative steps short of codification, such as staff manual guides, are appropriate for many management issues.

5. Several comments suggested that FDA implement many of its proposed procedural improvements in the new drug approval process immediately following the closing of the comment period (for example, changes in the content and format of an application, time frames for filing and reviewing an application and amendments, provisions on communications between the agency and applicants, and procedures for action letters).

Although FDA implemented several changes at the time it published the proposal (i.e., implementation of the informal appeals process; changes in the procedures for submitting samples; and the policy to notify applicants about deficiencies in chemistry, manufacturing, and controls information within 90 days of the beginning of the review of an application), the agency believes there is insufficient justification to implement other new requirements in advance of traditional effective date periods. FDA also notes that certain changes in the regulation (such as the procedures for action letters) simply codify current practice and so that immediate implementation of the final rule would not have had measurable impact.

6. One comment suggested that FDA impose user fees on industry for services FDA performs, particularly the costs of on-site inspections of domestic and foreign facilities. Another comment suggested that the agency incorporate into a final rule requirements for the evaluation of important new drugs in children before or at the time of approval of the application.

FDA believes these complex issues are sufficiently unrelated to the regulatory improvements in the new drug approval process that are implemented by the final rule that full consideration of them now would unnecessarily delay implementation of the rule. The agency is, however, exploring each of these issues separately and welcomes further discussion of them.

Effective Date

7. FDA received several comments recommending various effective dates for the final rule. Several comments suggested an effective date for the final rule of 180 days or 1 year, but also suggested that FDA accept applications up to the effective date in either the old, proposed, or new formats. A medical association suggested that FDA clarify how the regulations will apply to studies already in progress and to studies completed but not submitted before the effective date of the regulations. Finally, one comment urged that FDA not issue a final rule amending its new drug application regulations until after it has published and received comments on its proposal to revise the investigational new drug regulations.

FDA has concluded that these final regulations will become effective May 23, 1985, except § 314.80 *Postmarketing reporting of adverse drug experiences* will become effective August 22, 1985. FDA will, however, accept applications until February 24, 1986, that are in the format required under either the current regulations or this final rule. The separate effective date for the reporting of adverse drug experiences reflects the

time FDA believes applicants may need to adapt to the new regulations. As noted above, with respect to application format, FDA has followed the suggestion to permit applications to be submitted in the format prescribed by either the current regulations or this final rule (but not the proposed rule). This 1-year period also covers the submission of case report forms and data tabulations. FDA believes this 1-year period of optional formatting will facilitate a smooth transition from the old to the new regulations. Within the parameters described above, the effective dates apply to studies in progress or not yet submitted to FDA.

Although FDA will accept for 1 year applications in the format required under the current regulations, the substantive requirements of the regulations will apply to pending and approved applications on and after May 23, 1985 under this final rule. For example, the requirements and procedures for amendments, communication between FDA and applicants, dispute resolution, withdrawal by the applicant, safety update reports, supplements, records and reports, time frames for FDA action, action letters, adequate and well-controlled studies, and withdrawal of approval will apply after 90 days to all applications regardless of the format in which they appear.

Finally, in the Federal Register of June 9, 1983 (48 FR 26720), FDA proposed to revise its regulation governing the investigational use of new drugs. The comment period on the proposal closed August 8, 1983, and the agency is reviewing those comments. FDA does not believe that the IND rulemaking proceeding should further delay these final regulations because the two sets of regulations address different stages of the new drug development and approval process, and can be implemented separately in a satisfactory manner.

8. FDA has added to the final rule a new section that states the agency's intention that the regulations be applied in a manner that facilitates the approval of safe and effective new drugs, ensures that drugs not shown to be safe and effective are not marketed, and provides for an effective system for FDA's surveillance of marketed drugs.

Definitions (§ 314.3)

9. Several comments objected to the agency's proposed definition of the term "drug substance," claiming that the definition is overbroad and would wrongly subject the following to FDA regulation as new drugs: foods, vitamins, minerals, amino acids, other nutritional substances, and intermediates used in the synthesis of the drug substances.

FDA does not believe that the proposed definition of "drug substance" has the broad reach attributed to it by the comments. The proposed definition does not subject substances to FDA regulation as new drugs that do not fall within the definition of "new drug" in section 201(p) of the act (21 U.S.C. 321(p)). Moreover, the proposed definition is consistent with the definition of "drug" in section 201(g)(1) of the act and the agency's definition of "active ingredient" in § 210.3(b)(7) (21 CFR 210.3(b)(7)) of FDA's current good manufacturing practice regulations. FDA has, however, revised the definition in the final rule to make clear that it does not apply to intermediates used in the synthesis of the drug substance.

Application Form (§ 314.50(a))

10. One comment suggested that the proposed changes in the format for an application, under which a reviewer would receive only an overall summary and a technical section devoted to the reviewer's own discipline, would make it harder for a reviewer to consider relevant data that appear only in another reviewer's technical section.

The new application format should not have the result suggested by this comment. The application summary is intended to provide reviewers with adequate information about subjects outside their own review disciplines. Moreover, reviewers will also have access to other technical sections in the archival copy of the application, which will be maintained as a reference copy in the reviewing division's document room. Thus, reviewers will have access to whatever data they need for their reviews.

11. Several comments suggested that the regulations should make it clearer that the revised new drug and antibiotic application form is intended to serve essentially as a check list of basic information about the new drug and the application.

FDA agrees that the application form should serve only as a capsule listing of the contents of the application and the most basic information about the drug. This purpose will be self-evident from the revised form itself and, for that reason, no changes in this regard have been made in the regulations.

12. One comment objected to the requirement that the application form contain the established name, proprietary name, and code of the drug product. The reason for the objection was that some of the information may not yet exist when the application is filed. Two comments also sought clarification of the term "code" and asked whether it referred to the chemical name, shipping code, or marketing code.

The reason that names and codes used for the drug product must be submitted on the application form is to provide reviewers with easy identification of the product formulations to which the application refers. The term "code" would apply to any designation of a drug that would help identify it. To the extent one of the listed identifiers is not available, it would not need to be provided.

13. One comment suggested that the agency should establish procedures providing for the early submission and review of the chemistry, manufacturing, and controls section and/or the preclinical data section before submission of the clinical data and other sections. According to the comment, these early submissions would expedite ultimate approval by permitting early review and resolution of deficiencies in these technical areas.

FDA has revised the final rule (to be elaborated on by a staff manual guide) to provide for the early submission of chemistry, manufacturing, and controls information, at the option of the applicant. During the IND period, applicants will be permitted to submit information about fully developed chemistry, manufacturing, and controls procedures and specifications 90 to 120 days in advance of the submission of the main application. Chemistry, manufacturing, and controls submissions would not be accepted less than 90 days before the submission of the main application, as they would come too late to improve the speed of the review process significantly. Similarly, such submissions would not be accepted more than 120 days before submission of the main application because they would be premature and would likely not be sufficiently complete or final for review purposes. (Because review of preclinical data is not a common source of delay in the review process, the final rule does not provide for their early submission.)

The final rule expands upon past practice which had been to limit such early submissions only to drugs offering therapeutic advances. The agency notes, however, that in expanding the permissibility of such early submissions to other drugs, FDA's ability to review them early will depend upon available resources. Full applications are viewed as having higher priority, as are early submissions of chemistry, manufacturing, and controls information for drugs offering therapeutic advances.

Nevertheless, this change in the final rule provides a mechanism for speeding the review of at least some applications for which a mechanism does not presently exist.

14. One comment suggested that FDA clarify the status of its paper NDA policy in the final rule.

FDA has revised the final rule to include a description of the "paper NDA." This is an application for a duplicate of a marketed drug product which relies primarily on published literature to provide substantial evidence of effectiveness and adequate scientific evidence of safety for the claimed indications. A complete description of FDA's paper NDA policy appears in the **Federal Register** of May 19, 1981 (46 FR 27396).

Summary (§ 314.50(c))

15. Several comments endorsed the requirement for an overall summary, but urged that it should resemble more a brief summary than a lengthy treatise.

FDA agrees in part. As stated in the proposal, the summary is intended to facilitate review of the application. If a more complete summary of any specific section of the application is needed to provide the necessary information for review purposes, it should appear in the appropriate technical section. FDA also will not refuse to file an application or delay its approval if the summary is inadequate, provided the data contained in the technical sections of the application show that the drug is safe and effective. Applicants should recognize, however, that a superficial, poorly written, or incomplete summary will not serve its intended function of facilitating review and could even prolong the review process if it is confusing. The summary, therefore, should include critical details of study design, sufficient numerical data (tabular or graphic) to provide a quantitative understanding of the data, and a forthright discussion of any problem areas. Althought the preamble to the proposal suggested that a typical summary should be 50 to 200 pages long, length will likely vary according to the nature of the drug and the quantity and type of information available. Fifty pages should not be viewed as a minimum requirement, nor 200 pages a maximum; applicants should instead be guided by the circumstances surrounding the particular application at hand.

16. FDA received several comments concerning the proposed requirement that the overall summary contain a fully annotated copy of the draft labeling. One comment asked that FDA require annotations to drug labeling only for claims about safety and effectiveness. Another comment asked for clarification about how omissions from labeling should be annotated. The comment also objected to the requirement that the labeling bear annotations to the information in both the summary and the technical sections of the application, suggesting that such a requirement is redundant. A third comment suggested that the summary should contain only a brief summary of the labeling information about the drug, and that copies of the labeling itself (including labels, packages, and package inserts) should not be required. Finally, one comment found the proposal unclear about whether labeling should be included in the clinical or chemistry sections of the application, and whether reviewers would receive copies of labeling.

Assessment of the adequacy of labeling is a critical part of FDA's review of a new drug application. In determining whether the data and information in an application support the claims made in the product's labeling, it is helpful to know the precise information that the sponsor considers supportive. By providing reviewers with an annotated copy of the proposed labeling for the drug, and by directing the reviewer to both the summarized and detailed data supporting the labeling, the sponsor can assure that critical supporting data are not ignored and that confusion (with its inevitable delay) about the basis for labeling does not arise.

As indicated, FDA believes that annotations referring to both the technical sections and the overall summary will best facilitate review. The inclusion of annotations to the summary will be particularly important to the reviewers who do not receive the technical sections, and to others, such as FDA's managers and advisory committee members, who will not review all of the technical data. These reviewers also may wish to consider certain matters in detail, however, and the references to technical sections will facilitate this. By law, "specimens" of the labeling are required to be submitted, and brief summaries, as suggested by one comment, are not viewed as adequate. The agency's guideline on preparing a summary will clarify more fully the kinds of information that should appear in annotated labeling, and how omissions from the labeling should be annotated.

Finally, an annotated copy of the labeling will appear in the summary, which will be provided to each reviewer. In addition, copies of labels and other labeling pieces will be contained in the archival copy of the application where they will be available to all reviewers, as necessary.

17. One comment supported FDA's proposal to use the application summary to prepare the summary basis of approval (SBA) document that is made publicly available following approval of the application. Another comment suggested that FDA work with the applicant during the preparation of the SBA and allow the applicant to review the SBA before it is released to ensure the protection of proprietary information.

Although FDA believes applicants can play a large role in the development of the SBA through the preparation of the summary, the SBA necessarily reflects FDA's judgment, and not the applicant's, of what data and information in the application support approval of the drug product. FDA believes that an applicant's review of the SBA to identify proprietary information is unnecessary because FDA has traditionally not included such information in the SBA.

18. One comment suggested that applicants should not ordinarily be required to submit a completely revised summary with a resubmitted application, and should be permitted, to the extent possible, to submit only an addendum to the original summary.

FDA agrees that an addendum to a summary is appropriate if minor changes are made to an application. Significant submissions, however, such as providing additional data in response to a "not approvable" letter, would necessitate a revised summary that again reflects a clear and concise description of the information in the application.

19. One comment asked FDA to clarify its requirement for the "marketing history" of a drug by other persons.

This requirement is limited to the marketing of the drug outside of the United States, and it is intended that it will be met with brief information concerning where and when the drug has been marketed, for what indications, and any significant safety or effectiveness problems that developed during such foreign marketing. The agency has revised this provision to require also a list of countries in which applications for marketing are pending. This information will facilitate FDA contacts with foreign drug regulatory officials about the drug.

Chemistry, Manufacturing, and Controls Section (§ 314.50(d)(1))

20. FDA received several favorable comments concerning proposed changes in the chemistry section of the

application. For example, one comment was pleased that the proposal generally reflected the format and level of detail of manufacturing and controls data required by the European Economic Community to market a drug product. Another comment agreed with FDA's proposal to eliminate requirements for information available to the agency under its current good manufacturing practice (CGMP) regulations, stating that this change will substantially lessen the burden of preparing an application without compromising safety or effectiveness.

21. FDA received several comments regarding the agency's proposal to permit references in the chemistry technical section to compendial monographs. One comment urged FDA to go even further and not require detailed descriptions of drug substances subject to compendial monographs if the source of the substance is identified and CGMP's are followed in manufacturing it. A comment supported the proposal, believing that it reflects FDA's willingness to rely upon the compendia as authoritative sources of pharmaceutical quality standards. Two other comments suggested that the agency should also permit references to the Food Chemicals Codex, the British Pharmacopeia, and other compendia.

The agency is issuing this provision essentially as proposed, with one clarification. Although FDA believes that references to the official compendia may be relied upon under proper circumstances to provide required information, new developments in drug synthesis and advances in analytical technology may introduce new concerns about the chemistry of drug substances that are not adequately addressed by current compendial monographs. In those cases, FDA may need additional information about a drug substance to ensure that additives or byproducts of the synthetic process are properly controlled. Although a reference to official compendia will often satisfy the requirements, FDA has revised the final rule to state that FDA may require that additional information be submitted to permit the proper review of the application. This is particularly the case for tests for impurities and adulterants that might be present depending upon the source of material and the manner of processing the applicant employs. While compendial monographs are intended to assure the identity, strength, quality, and purity of the drug, they are not intended to include in each monograph a test for every impurity or adulterant. Thus, FDA concludes that additional information about drug substances subject to compendial monographs will sometimes be required.

The regulation limits the compendial sources that may be referenced to "official compendia" because a special relationship exists between FDA and the official compendia (United States Pharmacopeia/National Formulary) under the act, where FDA is authorized to enforce compendial standards (see section 502(g) of the act (21 U.S.C. 352(g)).

22. Several comments addressed the proposed requirements for documentation of raw materials and reagents used in the manufacture of the drug substance. One comment thought the requirements were ambiguous. A second comment criticized the proposal as continuing to require too much information about the method of synthesis, isolation, and purification of a drug substance. This comment suggested that either the regulations or a guideline should make it clear that an applicant need only submit such information that applies after a pivotal intermediate used to produce the drug substance is identified. Another comment asked for clarification of the requirement for the submission of specifications and analytical methods for components of a drug product (regardless of whether they appear in the finished product) and whether it includes raw materials used in the drug substance.

FDA believes that complete information about raw materials, reagents, in-process controls, and methods used in the manufacture of a drug substance are needed (particularly for a new chemical entity) to characterize fully the drug substance. The level of detail required, however, will vary according to the nature of the drug and FDA's familiarity with it. To provide flexibility, the regulation itself is general in nature, and FDA will prepare a guideline on the chemistry technical section to aid applicants in determining the appropriate level of data and information on a drug substance needed in a particular case.

23. One comment suggested that the agency should only require information about components of a drug substance that remain, in some measure, in the drug product or which could have an adverse effect on safety or effectiveness.

FDA disagrees with this comment. Information about components that do not appear in the finished drug substance or drug product is important in determining whether the specifications and analytical methods are appropriate to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of drug products made for it. This information is also important to assure batch-to-batch reproducibility of the drug substance. Although these components do not appear in the finished drug substance or drug product, they may, or changes in them may, significant affect the finished drug product.

24. Several comments suggested that the final rule should explicitly recognize current practice, under which applications may provide for alternative sources of inactive ingredients and alternative manufacturing procedures, including the following: (1) Reasonable alternatives for any material used in the synthesis of the new drug substance, (2) alternative methods or variations of methods of synthesis within reasonable limits which do not affect the characteristics of the substance, and (3) reasonable quantitative variations in the ingredients in the product.

FDA agrees with these comments, and has revised the final rule to provide for identifying such alternatives. Generally, an alternative method or variation should include a description of the circumstances under which the alternative or variation will be used. Comparable specifications and analytical data for the material produced by the alternative methods or variations must also be submitted.

25. Several comments addressed the inclusion of bioavailability-related information in the chemistry section. One comment objected to the addition of bioavailability to the statutory standards of identity, strength, quality, and purity—standards that, according to the comment, adequately cover the physical and chemical parameters affecting bioavailability. The comment also pointed out tht bioavailability is covered under its own technical section. Another comment objected to the requirement to provide specifications and analytical methods to ensure bioavailability because the methodology may not exist. A third comment suggested that references to the bioavailability of drug products made from a drug substance be deleted from the paragraph on the drug substance because it appears in the paragraph on the drug product.

FDA believes that these comments misunderstood the proposed requirements. The final rule, like the proposal, does not require the chemistry section of an application to contain information about the bioavailability of the drug product. That information is contained in the human pharmacokinetics and bioavailability section. What is required in the

chemistry section is that an applicant provide specifications and analytical methods for the drug substance and the drug product that will assure the ultimate bioavailability characteristics of the drug product. For example, if the bioavailability of the drug product depends on the crystalline form of the drug substance used in the drug product, the chemistry technical section must contain the necessary specifications and analytical methods to ensure that the substance has the necessary crystalline form. This requirement for specifications and analytical methods pertains to both the drug substance and drug product, because specifications at either or both stages could be pertinent to bioavailability, but it does not apply to intermediates and raw materials used in the manufacturing of the drug substance. If specifications and methods are unnecessary for assuring bioavailability, they need not be supplied. Although it might be argued that the standard of "quality" adequately covers the physical and chemical parameters affecting bioavailability, there is no good reason not to be explicit about the requirements for information about drug chemistry that, although they pertain to bioavailability, must be evaluated by FDA's chemistry reviewers.

26. One comment suggested that the phrase "specifications related to stability" should be deleted from the requirements for the drug substance because expiration dates on drug substances are not required.

Like the previous comments on specifications relating to bioavailability, FDA believes this comment misunderstood the proposal. Although expiration dates for drug substances are not required, establishment of a specification for stability of the drug substance may in some cases be needed to assure the quality of the drug product. If there is no such specification, it need not be supplied.

27. One comment suggested that references to process controls should not be required because they are adequately regulated under the CGMP regulations. According to this comment, requiring this information in an application and requiring agency approval before changes can be made takes away manufacturers' flexibility for establishing procedures for in-process tests and for determining the significance of testing results.

The agency disagrees with this comment. FDA believes that a review prior to marketing of in-process controls is needed to determine whether appropriate tests and limits are established (for example, for solvents and particle size) which may affect physiological or pharmacological activity.

28. One comment urged that the agency codify its current policy that methods validations will not delay approval of an application.

FDA views itself as bound by its current policy, unless changed, regardless of whether it is included in the regulations. Moreover, the policy is of a type that the agency would more likely cast as a guideline, given its length and complexity, than as a regulation. In addition, the agency memoranda on this subject, which have been made public, adequately describe the policy and, thus, FDA does not believe that codifying the policy is necessary.

Nonclinical Pharmacology and Toxicology Section (§ 314.50(d)(2))

29. Several comments objected to FDA's proposal to require a description of studies of nonclinical pharmacological actions of the drug for possible therapeutic indications for which the applicant is not seeking approval. These objections are premised on the belief that the information would be irrelevant to the drug's proposed indications, that the requirement would delay submission of an application while the applicant gathered the information, and that time and effort of reviewers would be wasted, particularly if the information were to lead them to speculate about other potential, new indications.

FDA agrees in part with these comments, but believes the purpose of this section was not well described in the proposal. Information about pharmacological effects other than the primary effect related to the proposed use is not usually critical to evaluating the effectiveness of the drug, but these pharmacologic properties are pertinent to a full understanding of the drug's effects, e.g., they may help explain side effects and drug interactions. Such information also is pertinent to investigational use of the drug, so it should be unnecessary for an applicant to perform new analyses to meet the requirement. The agency has revised the final rule to make this requirement clearer.

30. Several comments addressed the form of submission of data from animal studies. One comment requested clarification as to whether the revised regulations are intended to continue the current practice under which individual animal data are only reported in tabulations, and the "raw data" (laboratory notebook, worksheets, and other documentation relating to individual animals) are not submitted unless FDA has reason to request them in a particular case. Another comment suggested that FDA require summaries instead of tabulated individual data from long-term toxicity and carcinogenicity studies in order to reduce the size of the application.

The nonclinical pharmacology and toxicity section of the application is intended to continue current practices with respect to the submission of individual animal data. Thus, applicants are not required to submit laboratory notebooks, worksheets, and other documentation relating to individual animals (although those materials are subject to record retention requirements under the good laboratory practice (GLP) regulations (21 CFR Part 58)). Although summaries that contain tabulations and graphs are helpful for describing long-term toxicity and carcinogenicity studies, FDA believes that full tabulations of individual animal data are necessary to conduct a proper review of these important safety-oriented studies.

31. Several comments questioned the implication in the proposal that all pharmacological studies are subject to the agency's GLP regulations. These comments noted that those regulations apply only to nonclinical safety studies and not to other animal studies, such as nonclinical pharmacology studies. Other comments suggested that the regulation should require only a description of "significant" deviations from the GLP regulations, or a "statement of differences" for studies that were not in "substantial" compliance with them.

FDA agrees that the proposal might be read to imply that all pharmacological studies are subject to FDA's GLP regulations. The agency has revised the final rule to clarify that an application is only required to contain a statement regarding compliance with GLP's for a "nonclinical laboratory study" as defined in 21 CFR 58.3(d). FDA, however, has not made the other suggested change. Because the GLP regulations describe minimum standards for nonclinical laboratory studies, FDA believes that it is appropriate that the application contains a description of deviations from those requirements. The agency advises that such studies may still be relied upon, depending on the nature of the deviations.

Human Pharmacokinetics and Bioavailability Section (§ 314.50(d)(3))

32. One comment urged that this section contain a comparison analysis of human and animal pharmacokinetic data and the rationale for setting the specifications for the drug substance

and drug product based upon the results of bioavailability studies.

FDA does not agree that the final rule should require a comparison of human and animal pharmacokinetic data. Animal pharmacokinetic data are generally most relevant during the investigational phases of drug development, where they permit the establishment of parameters for the safe use of the drug in human subjects. After human pharmacokinetic data are collected, however, they alone are usually adequate for review of an application. An applicant is free, however, to provide a comparison analysis of the animal and human data if the applicant believes it results in a clearer presentation. At the same time, the agency agrees with the suggestion for inclusion of the rationale for specifications and analytical methods for the drug substance and drug product needed to assure the bioavailability, and FDA has revised the final rule to add that requirement. The rationale for establishing specifications and analytical methods, with the data and information supporting the rationale, is needed to determine whether the proposed specifications or methods will assure the bioavailability of the drug substance or drug product.

33. One comment objected to the statement in the preamble that bioavailability data are needed to assure batch-to-batch consistency and to reevaluate product reformulations or changes in manufacturing processes. The comment argued instead that simpler methods, such as in vitro dissolution, are adequate.

The ability of in vitro dissolution data to determine the bioavailability of a batch of a drug product depends, in FDA's view, on whether the data can be correlated with in vivo data. Generally in vivo bioavailability data and in vitro dissolution data are examined and, if possible, in vitro dissolution methods and specifications are set for the product. Subsequent batch-to-batch consistency is assured by testing each batch by the in vitro method and evaluating the results against the in vitro specifications. Thus, bioavailability data are often needed to establish the simpler in vitro tests.

34. One comment urged that the summarizing discussion and analysis be clearly required at the beginning of the pharmacokinetics and bioavailability section because it brings together information not necessarily present in each of the bioavailability and bioequivalence studies. This comment also suggested that this section should require that the analytical and statistical methods used in each study be described in the report of the study, and not grouped together in a separate section as the proposal suggests. Moreover, the comment believed that each study should be evaluated as an entity because that is the way reports of studies are prepared. The comment asserted that breaking reports in this section apart is likely to lead to errors.

FDA believes this comment misunderstood the proposal. The regulation is intended to describe in general terms the kinds of data and information that are required to appear in this section and the applicant is free to present it in the format that provides the clearest presentation, which may include either an opening or closing summary. Because FDA agrees that, in most instances, the analytical and statistical methods used in each study should be described in the study report, the agency has revised the regulation to suggest that use of that format is usually preferable. Again, however, FDA believes the applicant should use a format that provides the clearest presentation and permits the most efficient review.

Clinical Data Section—General (§ 314.50(d)(5))

35. One comment objected to the requirement that the results of each human clinical pharmacology study be compared with the animal pharmacology and toxicology data. The comment explained that most toxicology studies use doses higher than those used in human studies and often for longer periods of time, and that animal pharmacology studies may include disease states in animals not present in clinical studies. Thus, according to this comment, applicants should only be required to compare the results of clinical pharmacology studies with the "major findings" of animal pharmacology and toxicology studies. Another comment urged that this requirement be limited to information related to the intended use of the drug under its proposed labeling and to possible side effects to ensure that the applicant and the agency do not become sidetracked on issues related to potential new indications for the drug.

The agency does not agree that it is necessary to limit the comparison between clinical pharmacology data and animal data, as suggested by the comment. The proposal's call for "a brief comparison of the results of human [pharmacology] studies with the animal pharmacology and toxicology data" is intended to require an examination of the clues to potential usefulness or toxicology in humans provided by animal data. With respect to the second comment, virtually all of the pharmacologic properties of a drug are pertinent to the intended use of the drug, even those properties that are not the ones leading to the drug's intended use. The human results should thus be compared to all pertinent animal observations. If no human observations concerning a particular property exist, of course, no comparison can be made.

36. Noting that a controlled clinical study on a drug may not be relevant to the indications proposed in the application, one comment suggested that the final rule should only require a description and analysis of each controlled clinical study pertinent to the proposed indications for the drug and that other controlled studies should be included in the general description of other data or information relevant to an evaluation of the safety and effectiveness of the drug. This comment also suggested that the regulations require only that the applicant describe, and not analyze, data from studies that are not controlled.

FDA has revised the final rule to require description and analyses of controlled clinical studies pertinent to a proposed use of the drug. The agency notes, however, that § 314.50(d)(5)(iv) still calls for "a description and analysis of any other data or information relevant to an evaluation of the safety * * * of the drug product" not a "general description" as implied by the comment, and does require some analysis of controlled studies not pertinent to the proposed uses of the drug. FDA continues to believe that the usefulness of sources of data, such as clinical trials of drug uses other than those proposed, depends on a reasonably detailed description and analysis of the safety of those trials. The agency notes, however, that the proposal did not require analyses of uncontrolled studies, but only a description of them, which accords with the comment's suggestion. Finally, FDA has revised the final rule to include a requirement for a brief description of pertinent studies that have been discontinued or are ongoing.

37. One comment objected to a requirement for safety data from epidemiological studies of related drugs, believing that the requirement is vague and potentially subject to an overbroad application.

The agency does not believe that information about related drugs, such as epidemiologic data, can be ignored in evaluating a new drug. An applicant developing a new member of an already established drug class usually is, and should be, conscious of the experience

with other members of the class. Such information may be relevant to labeling and may help focus the evaluation of the data submitted. FDA does not believe that the requirement will be applied unreasonably.

38. On its own initiative, the agency has made two additional changes in the final rule. First, FDA has added an explicit requirement for the applicant to synthesize, in an integrated summary, the data which it believes provide substantial evidence of effectiveness of the drug for its proposed uses (§ 314.50(d)(5)(v)). FDA believes that this requirement was implicit in the proposed requirements for an overall summary to help the agency prepare the SBA document, but has determined that a specifically focused discussion in the clinical section will significantly facilitate review. Second, the final rule also requires an applicant to explain briefly why a study is not considered adequate and well-controlled. This will enable the agency reviewers to determine what conclusions can be validly drawn from those studies.

Safety Update Reports (§ 314.50(d)(5)(vi)(b))

39. FDA received several comments on the proposed "safety update reports," which are designed to advise FDA of new safety information that becomes available while the application is being reviewed by the agency. The proposal would have required such reports at 4-month intervals and upon receipt of an approvable letter. Although most of the comments addressing this issue favored the concept of safety update reports, concerns were raised that the reporting intervals were too frequent and that the data being requested were more than were necessary. Concerns were also raised that, if not properly limited, the requirement for safety update reports could delay the approval process by creating an ongoing need to review more data.

FDA believes that the basis for the proposed safety update reports, which is to ensure that drug approvals are based on the most up-to-date safety information available, is sound. FDA has, however, revised the final rule to ensure that reporting obligations are no greater than are needed, so that the requirement does not unduly delay approvals.

First, FDA has defined more precisely the type of information that needs to be reported. Whereas the proposal simply said "new safety information," the final rule specifies "new safety information * * * that may reasonably be expected to affect the statement of contraindications, warnings, precautions, and adverse reactions contained in the draft labeling." Thus, under the final rule, the only information that must be submitted in a safety update report is safety information that is different from that previously submitted and that may warrant revision in the draft labeling. It should be emphasized that (1) "new" information includes both adverse effects that were never seen before and a material change in the frequency or severity of effects that were recognized previously; and (2) case report forms for patients who die or who leave a study prematurely because of an adverse event are always required (unless the requirement is waived). Thus, for example, new safety information that suggests that an adverse effect occurs at a higher rate than previously thought would be required because it might change a precaution to a warning in the labeling.

Second, FDA has revised the reporting intervals so that safety update reports will be required (1) 4 months after the initial submission; (2) following receipt of an approval letter; and (3) at other times as requested by FDA. The first safety update report is important because it is designed to let reviewers know if any major new data are available that could affect their recommendations regarding approval of the drug. This first report covers a much longer period than 4 months because it also covers the time period between the "data lock point" and submission of the application, during which time the applicant is preparing the application for submission to the agency. The report following an approvable letter is intended to provide the agency with the most current information available immediately before approval. Moreover, it parallels the normal submission of final printed labeling so that FDA reviewers can be assured that the labeling is up-to-date. In addition, FDA may request safety update reports at other times, such as before an advisory committee meeting or before an approval letter where an unusual amount of time may have passed since issuance of the approvable letter. This may also include the situation where the agency intends to issue an approval (instead of an approvable) letter based on draft labeling, and a special request for a final safety update report will prevent undue delay. Thus, by replacing the "every 4 months" requirement with discretionary requests by the agency, the regulations allow applicants to submit interim reports only when the agency believes they are necessary for review and approval of the application.

FDA does not believe this policy will delay the approval process. As noted above, the reports themselves are tied to information pertinent to labeling, and will be in a familiar format, permitting prompt review. Moreover, FDA expects that major changes in safety information will not be common. If an applicant, however, does obtain new safety information that is so significant that it could affect the overall risk/benefit determination of the drug for one or more indications, a further extension of the review process will inevitably be necessary.

The guideline on the clinical section of the application will describe the format of both original safety reports and updates.

Samples and Labeling (§ 314.50(e))

40. Several comments suggested that requiring four samples is excessive and that FDA should request only the actual amount needed.

FDA's experience is that four samples are needed to perform necessary testing. One sample is tested by each of two FDA laboratories, for purposes of replication, and the two remaining samples are held as reserve samples for each of those laboratories in the event that additional testing is necessary. In addition, the final rule represents a significant reduction from past practice in the amount of samples applicants must submit to support approval of an application. Samples are no longer required, for example, of the finished dosage forms used in the clinical investigations, nor of the new drug substance used in manufacturing those dosage forms. FDA has revised the final rule to increase from two to three copies of the analytical methods and related descriptive information FDA needs to test the samples. One copy is needed for each of the FDA laboratories assigned to test the samples and a third copy is needed for the agency's headquarters files.

41. One comment urged that samples be required earlier in the review process, specifically either at the time the application is submitted or when the application is filed. This suggestion was aimed at ensuring that necessary testing is completed on time and does not delay approval of the application.

FDA disagrees with this comment. Under the final rule, the FDA reviewer will contact the applicant to request samples and provide laboratory assignments after a preliminary review of the analytical procedures indicates that the procedures are satisfactory. The date of filing is not appropriate because the review necessary to determine

whether an application is complete and can be filed is not as detailed as the review needed to determine whether analytical procedures are satisfactory. The procedure in the final rule will prevent the premature submission of samples and will ensure that methods validation testing is not conducted on outdated samples. The procedure should not, however, delay the review process so long as applicants make every effort to provide the samples when requested. Moreover, as noted above, it is FDA's policy not to delay approval of a drug solely because methods validation has not been completed.

42. Several comments questioned whether, by combining requirements for samples and labeling, the proposal implied that labeling should be submitted only upon request. Another comment asked FDA to clarify what it means by "related descriptive information" and noted that the proposal would not have required submission of results of the applicant's tests on samples.

FDA has revised the final rule to state that copies of the product's label and labeling should be submitted with the application, and not only upon request. The final rule also states that "related descriptive information" includes a list describing each submitted sample; a list of proposed regulatory specifications; a detailed description of the methods of analysis; supporting data for accuracy, specificity, precision, and ruggedness; and complete results of the applicant's tests on each sample.

43. One comment urged that the current exclusion for sterility and pyrogen testing samples, which was not contained in the proposal, be retained.

Although FDA agrees that sterility and pyrogen testing samples are often unnecessary, particularly if the testing procedures are ones generally recognized as valid (for example, procedures established in the official compendia), new testing procedures may be developed (for example, the limulus amebocyte lysate test for pyrogens) that warrant FDA review. Accordingly, the final rule requires their submission, but FDA will consider waiver requests on a case-by-case basis.

44. One comment suggested that the final rule should follow the current practice and require the submission of only one finished market package.

FDA has revised the final rule to eliminate the suggestion that four samples of the finished market package are required. Samples of the finished market package are required to be submitted only if FDA requests them and, although the agency generally requests only one sample, two are sometimes needed. The final rule provides this flexibility.

Case Report Forms and Tabulations (§ 314.50(f))

45. FDA received many comments on the proposed submission of individual clinical data using a combination of case report forms and tabulations. A number of the comments misunderstood the meaning of the terms used and their interrelationship. For example, some comments erroneously equated "case report forms" with "raw data," while other comments mistakenly understood "tabulations" to be the same as "summaries." Before addressing the specific comments, therefore, these terms need to be clarified in the context of the current regulations and the NDA Rewrite proposal.

a. *Raw data.* The "raw data" from a clinical study are the clinical investigator's own records of the individual patients. These records include the patient charts, hospital records, x-rays or other laboratory test results, and notes of the attending physician. These raw data, even under current regulations, are not routinely submitted to FDA as part of a new drug application, but instead remain in the files of the clinical investigator or hospital for FDA audit, if necessary.

b. *Case report forms.* These are the documents that the clinical investigator sends to the drug sponsor that list all the data collected on each individual patient. There is 1 case report for every patient in each study, and case reports typically vary from 5 to 50 pages in length. Under current regulations, all case reports must be submitted to FDA as part of a marketing application. Because such applications frequently contain data on from 1,000 to 3,000 patients, case reports consume a great many volumes in a typical application.

c. *Tabulations.* These are tabular listings of the individual patient data, as taken from the case report forms. The tabulations are prepared by the drug sponsor, usually using an automated data processing system. By using tabulations, the results from a study of a given medical parameter (e.g., blood pressures for an anti-hypertensive drug) can be presented on one or two pages. These tabulations contain the very same numbers as the case report forms on which they are based, and the data are clearly identified by individual patient. Thus, tabulations are ordinarily a more concise and efficient representation of the data contained on the case report forms.

d. *Summaries.* These are usually narrative documents, often interwoven with summary tables and graphic presentations of data, that present the results of a study, using the analyses deemed appropriate. Summaries are the most common means of communication in science, and most scientific journal articles are summaries in this sense, as are the descriptions and analysis called for in the clinical section of the application. Summaries, however, are by their nature interpretive documents that select certain data as being important. Thus, summaries reflect a point of view about what the data mean, and the point of view and data selections are always shaped by the judgment of the writer.

e. *Current requirements.* Current regulations require the routine submission of all case report forms. Use of tabulations is voluntary with the applicant. Recognizing the inherent difficulty of relying on the case report forms themselves to find individual data elements, it is extremely common for applicants to submit tabulations voluntarily in some form to make the review of the data more efficient. Applicants use such tabulations in their own analyses, subjecting them to a variety of statistical procedures to develop analyses and summary tables presented for each study report.

f. *The proposal.* Based on the agency's positive experience with tabulations, FDA proposed to substitute tabulations for case report forms as the primary focus of the data review. Under the proposal, some case report forms would still be required routinely (i.e., for patients who died during or who dropped out of a clinical study due to an adverse event) because these cases are the ones most likely to reveal significant safety problems and demand individual case-by-case review. Also under the proposal, FDA would have access to additional case reports whenever a legitimate need existed. Thus, the intent of the proposal was to focus the agency's review on a more concise and efficient mode of data presentation, while still providing the agency with complete individual patient data. The proposal also contained a requirement for summaries, but only to complement and integrate the individual patient data contained in the case reports and tabulations.

46. FDA received a considerable number of comments on this provision, concerning primarily the concept of how data should be submitted (i.e., summaries versus tabulations versus case report forms). Comments on both these subjects covered a wide spectrum. Several comments argued that all case report forms should be routinely required, on the ground that FDA needed this "raw data" to conduct a full

scientific review. In contrast, other comments suggested that even the review of tabulations would be more time consuming than necessary, and that FDA should instead rely on summaries alone.

FDA believes that the proposal to require data submission through a combination of summaries, tabulations, and case report forms allows a scientific review that is both thorough and efficient. FDA believes that, for many purposes, tabulations can provide adequate information for review because these tabulations will be required to contain the same individual patient data listed on the case report forms. As described above, even case report forms are not actually "raw data" (but instead constitute individual patient data as transposed by the clinical investigator from the doctor's charts), so concerns raised about the agency no longer requiring "raw data" are misplaced.

FDA also disagrees with the suggestion that it rely on summaries alone, without a routine submission of individual patient data (either as case report forms or tabulations). As noted above, summaries are, by their very nature, interpretive documents. Although summaries are extremely useful in reviewing applications, FDA believes they need to be complemented by the underlying data (either in tabulations or case report forms) for the agency to be able to conduct a thoroughly independent and objective review.

In response to these comments, however, FDA has reevaluated the proper mix of tabulations and case report forms that should be required. Although FDA believes that tabulations will be extremely useful in promoting a more efficient review process, the agency also recognizes that there are some inherent limitations on the use of tabulations and that, in certain instances, direct reference to case reports will be necessary. Theses may include, for example, instances where important narrative or other information on the case report form is not amenable to tabular presentation, or where case reports are desired to spot check the accuracy of the tabulations.

Accordingly, in order for the agency to conduct a scientific review that is both thorough and timely, a complete set of case report forms will ordinarily be needed for the most critical studies. In order to choose these appropriately, and at a time when they can be provided without causing delay, FDA reviewers will designate, approximately 30 days after receipt of an application, the critical studies for which case reports will be requested. These studies will ordinarily also be the ones utilized by the Division of Scientific Investigations in conducting its on-site data audits, and that division will make use of the same case reports, whenever possible, in order to eliminate the need for duplicate submissions.

FDA believes this policy is consistent with its overall goal of improving the efficiency of the drug review process. By relying more heavily on summaries and tabulations, FDA's initial review will be focused onto a more concise form of data presentation. This initial review, however, may trigger the need to review certain patient histories in more detail, especially those from the most critical studies, and case reports provide the basis for that more detailed review. Requests for full case reports from certain critical studies does not necessarily imply the need for a case-by-case review of every patient; instead, such requests are intended to ensure that FDA reviewers can make reference to, when needed, case report forms for those patients requiring further review. By making such requests approximately 30 days into the review process, delay is unlikely to occur.

Even with this modification, FDA estimates that there will be an average reduction of about 75 percent in the number of case reports that are routinely requested, when compared to the current requirement of full submission. As reviewers become more comfortable with tabulations, and applicants become more skillful in making them usable, it is possible that requests for case reports will decrease. The regulation itself is general in nature so as to accommodate both the present expectation and any future changes.

47. Several comments that opposed the substitution of tabulations for most case report forms were concerned that this change could enhance the possibility that FDA would receive inaccurate data.

FDA does not believe that this change will decrease the accuracy of the data received or undermine the agency's ability to assure data accuracy. First, FDA's Division of Scientific Investigations routinely conducts a data audit on two or more critical studies in each marketing application. Such data audits compare the data on case report forms to the raw data retained by the clinical investigators. The policy of conducting these audits will continue. In addition, as noted above, medical reviewers may need to spot check the accuracy of tabulations for the most critical studies by comparing them to the data in the case report forms, and FDA can request the submission of case reports for that purpose.

48. FDA received a number of comments on the proposed standard that additional case reports could be obtained whenever a "legitimate need" existed to conduct an adequate review of the application. Comments generally believed that this provision was vague. Many interpreted it as an attempt to discourage requests for additional case report forms. Several comments, on the other hand, were concerned that the provision would lead to excessive requests and urged that the final rule contain explicit criteria for justifying request, and that requests should be made in writing with a supporting rationale.

FDA had modified this provision in the final rule to reflect the agency's central concern—namely, to permit the agency access to case report forms when it believes that they are needed to conduct a proper review of the application. The agency did not intend the phrase "legitimate need" to imply a barrier, and the final rule has been modified to contain more neutral language. FDA recognizes the concern expressed by several comments that some reviewers may be prone to request more case reports than the applicant believes are necessary. Although there will inveitably be differences among reviewers, FDA believes that assuring the reasonableness of requests for case report forms is the responsibility of FDA management. To strike what FDA believes is the appropriate balance between these competing interests, the final rule provides that all requests for additional case reports (other than those required to be routinely submitted) must be approved by the director of the division responsible for reviewing the application. Any applicant that feels it is being asked for an excessive number of case reports may raise the matter directly with the releveant division director or with the ombudsman.

FDA notes that the need for additional case reports will likely vary according to the type of drug under review. For example, case reports appear to contribute significantly less to the efficacy review of an anti-hypertensive drug because blood pressures can quite adequately be complied in a tabulation, patient dropouts are usually few, and most patients entered into a trial are analyzed. Conversely, FDA believes that case reports may be critical to the review of controlled studies for an antibiotic drug. This is because the efficacy determination for an antibiotic turns largely on which patients were included and which were excluded from

the study analysis, and the reasons for inclusion or exclusion often involve close judgments that cannot readily be shown in a tabulation. FDA will advise applicants, either in guidelines or in "pre-NDA" conferences, of particular case report needs for particular drug classes.

49. Several comments addressed the time aspect involved in FDA requesting additional case report forms or tabulations. One comment was concerned that the proposal might actually delay the review process, because reviewers would have to wait for the submission of additional case report forms. Another comment suggested that the 30 days for the submission of case report forms, as provided in the proposal, may not be adequate. A third comment suggested that, if additional case reports or tabulations are submitted more than 30 days following an FDA request, any extension to the review period should be limited to the number of days the submission was late.

FDA does not believe that this requirement will cause delay in the review process. Case report forms are still required to be maintained by drug sponsors, and the time needed to respond to requests should be relatively short. Moreover, applicants, who themselves seek an expeditious review, have an incentive to respond to such requests quickly. Finally, as noted above, the agency's policy of identifying needed case report forms early in the review process should also help reduce delay. When applicants do take more than 30 days to respond, the agency considers it reasonable to extend the review period in accordance with § 314.60. The length of such extension will involve not only the time taken to respond, but also other factors, such as the stage of the review process and the reasons for the request. For example, case reports requested to investigate data discrepancies may require a longer extension than requests for case reports to provide information not contained in the tabulations.

50. Several comments urged that FDA require the routine submission of case report forms for deaths and dropouts only for patients who receive the investigational drug, and that case reports for patients on placebo or a reference drug not be included. In addition, one comment asked whether the term "adverse event" in this section of the proposal would include a patient who dropped out of the study because of a "lack of expected pharmacological effect."

FDA believes that case report forms for deaths and dropouts are particularly useful for determining safety problems with a drug. In determining whether these events were drug-related, FDA's evaluation necessarily includes comparing safety problems for patients who took the test drug with patients in the control group who also died or dropped out of the study. Thus, the agency believes that this provision of the final rule should not distinguish between patients in a study on the basis of whether they actually received the investigational drug, and the final rule has been so revised. The term adverse event in this context (as distinguished from its use in § 314.80 concerning postmarketing surveillance) does not include "lack of expected pharmacologic effect."

51. Several comments addressed the level of detail required in the tabulations. A number of comments objected to requiring "every datum" obtained on each patient so that FDA reviewers can reanalyze the data already analyzed by the applicant. These comments preferred tabulating data on categories of patients, which is the standard procedure used in submitting papers to scientific journals. Another comment took the opposite view and suggested that the tabulations include full listings of individual patient data. One comment simply asked that FDA clarify the level of detail needed.

As a general rule, FDA believes that individual patient information that is important enough to be recorded on a case report form would be pertinent to the agency's review of the drug's safety and effectiveness. As noted earlier, the tabulations are intended to present essentially the same information as the case reports, except in a more efficient form.

Nevertheless, the agency recognizes that not all individual patient information will be needed for the agency to conduct a proper review of the application. The regulation, for example, exempts from submission tabulated data on effectiveness derived from uncontrolled Phase 2 and Phase 3 studies. This is because the agency's effectiveness review relies upon adequate and controlled studies, as required by law.

The regulation further provides that the applicant may delete additional tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. The regulation also provides that, barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during FDA's review.

Other Information (§ 314.50(g))

52. One comment suggested that applicants be permitted to submit English language abstracts that appear in original publications in foreign languages and that they be required to submit an English translation of the full publication only upon request.

The agency believes that it is not unreasonable to ask an applicant who relies upon an original literature publication in a foreign language to submit both the foreign publication and an English translation of it. Otherwise, FDA would not be able to review the full presentation. This is not a new requirement.

Format of an Original Application (§ 314.50(h))

53. Several comments addressed the provision whereby applicants could submit the archival copy of the application on microfiche. Comments generally suggested that limiting submissions to microfiche is too restrictive and that FDA should permit microfilm and other data storage forms. One comment suggested that roll microfilm is more economical and easier to make hard copies from than microfiche. Some comments stated that most applicants already submit copies of raw data on indexed microfilm to Canadian drug approval authorities, and that the same form should be acceptable in this country. One comment also suggested that case report forms should be permitted on microfiche or roll microfilm.

FDA has revised the final rule to provide that applicants may submit the relevant portion of an application on microfiche or, if FDA agrees, on another suitable microform system. This change would permit the use of new microform technologies while ensuring that the submission would be in a form usable by FDA. Although other currently available systems (such as indexed roll microfilm) have some advantages over other microform systems, they also have significant disadvantages when used under the circumstances of an FDA application review because of the difficulty in locating specific information even in well-indexed systems. Decisions on using alternative microform systems will be made on a case-by-case basis, as will decisions on whether a microform system may be used for case reports and tabulations.

Abbreviated Applications (§ 314.55)

Note.—On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417). A primary purpose of this law is to greatly expand the universe of drugs for which FDA will accept abbreviated applications. Pursuant to section 105(b) of the new law, on November 26, 1984, FDA began accepting such applications. Section 105(a) of the new legislation provides FDA with 1 year from the date of enactment to promulgate new implementing regulations. Section 105(b) further provides that, until such time as FDA has new implementing regulations in place, the currently existing regulations will be effective, absent a conflict with the new statute. Because the provisions in this final rule governing abbreviated applications merely restate, in slightly different form, the current regulations on this subject, FDA considers these provisions of the final rule to have the same effect under section 105 of the new law as do the current regulations governing abbreviated new drug applications.

54. One comment asked how the standard of "very closely related" in proposed § 314.56(c) for determining whether an abbreviated application is suitable differs from the standard of "identical, related, and similar drug products" in § 310.6 (21 CFR 310.6) for applying FDA's efficacy conclusions in the Drug Efficacy Study Implementation (DESI) project.

In the **Federal Register** on January 21, 1983 (48 FR 2751), FDA amended its new drug regulations to clarify its policy on when abbreviated new drug applications are suitable and will be accepted. That rule states that, when FDA finds that an abbreviated application is suitable for a drug product, the finding will apply only to drug products "identical" to the product that was the subject of the finding. At the same time, FDA established a petition procedure under which prospective applicants may ask FDA to determine whether an abbreviated application is suitable for similar or related products. Such decisions on suitability will be made on a case-by-case basis, and abbreviated applications will be accepted only if the safety and efficacy data on the first product are applicable to the product that is the subject of the petition. FDA has revised § 314.55 to conform to the text of that final rule.

In the preamble to the January 21, 1983 final rule, FDA addressed the relationship of this provision to the DESI policy contained in § 310.6. As stated in that preamble, a DESI finding of effectiveness for one drug product does not automatically apply to all similar or related products. Rather, "There will be * * * areas where the judgments of experts must determine the applicability of efficacy findings. The determination will be based on the chemical structure of the drug, recommended use, route of administration, its pharmacological properties and any other information available on the action or properties of the drug." (48 FR 2751 at 2753.) It is through the petition procedure described in § 314.55 that this determination will be made.

Application Development File

55. FDA has removed from the final regulations the proposed provision on the application development file (proposed § 314.57). The provision would have established a mechanism for prospective applicants of abbreviated applications to obtain agency comments on their formulation data, dissolution data, bioequivalence protocols, and pilot studies before conducting bioequivalence tests. FDA has determined that a codified procedure is unnecessary because less formal procedures for providing guidance to potential applicants exist. For example, FDA provides applicant with guidance on developing bioavailability studies through guidelines, meetings between applicants and agency staff, and general correspondence. Moreover, many applicants now rely upon contract laboratories to conduct bioavailability studies, and these laboratories are generally familiar with the requirements for performing acceptable bioequivalence studies. The agency also believes that providing general prospective guidance on bioavailability studies, as opposed to application-specific review, will consume significantly less agency resources while providing adequate guidance to potential applicant.

Amendments to an Unapproved Application (§ 314.60)

56. Several comments asked that FDA inform an applicant if the agency considers a submission to be a major amendment and the approximate amount of time the division needs to review it. Some of these comments urged FDA to reply within 30 days after the agency receives the amendment. Other comments urged that the final rule clarify that the maximum extension will be 180 days. One comment suggested that, if an amendment is made in response to an agency request, FDA should inform the applicant within 30 days of whether the response was adequate.

As stated in the proposal, the director of the reviewing division will inform an applicant that submits a major amendment if an extension is needed. The agency has clarified the final rule to state explicitly that the division director will also inform the applicant of the amount of time the division needs to review the amendment. The agency will strive to make such notifications as timely as possible. FDA has added a statement to the final rule to clarify that the maximum extension of the review period will be 180 days. Finally, FDA may notify the applicant of particular deficiencies found in the amendment and request further clarification or, depending upon the deficiency, may respond to it in an action letter. In this respect, agency comments on an amendment will be handled in the same way as on any other part of the application.

Supplements and Other Changes to an Approved Application (§ 314.70)

57. FDA views the requirements under which applicants can make manufacturing and controls changes in their approved applications as an area in which it can significantly reduce regulatory burdens on the drug industry without compromising public health protection. Currently, nearly all changes in the conditions originally approved in the application are subject to prior FDA approval in a supplemental application, with the few exceptions listed in the regulations. In the same manner suggested by the proposal, the final rule changes this scheme significantly by reducing the number of changes that require supplements and listing those changes (instead of the exceptions) in the regulations. Thus, the final rule retains the three proposed regulatory categories: (1) prior approval, for those changes in marketed drugs which could affect FDA's previous conclusions about the safety and effectiveness of the drug; (2) changes requiring supplements concurrent with the change but on which FDA prior approval is not necessary; and (3) annual reports for changes that do not fall into one of those two categories. The final rule, like the proposal, specifically lists the kinds of changes falling into the first two categories. The final rule also lists examples of changes that can be described in the annual report, but the list is not intended to be exhaustive because the annual report is the residual category.

In the proposed rule, FDA identified several areas where it believed applicants could make changes in their approved applications under less restrictive conditions than currently required. Since then, FDA has conducted an exhaustive examination of its current practices with respect to

supplements and has determined that, although significant improvements can be made in this area, for the reasons stated below, not all of the proposed changes have been implemented. As a result, FDA has realigned the specific types of changes among the three categories and is returning several kinds of changes to the prior approval category that, under the proposal, could have been reported to FDA following implementation. At the same time, however, FDA will permit annual reporting of some changes that, under the proposal, would have required prior approval. Under the final rule, FDA estimates that there will be a reduction in approximately 20 percent of manufacturing and controls supplements that now require prior approval, all in areas not likely to affect the safety or effectiveness of the finished drug product. Although FDA proposed to permit the following changes without prior approval, the agency is retaining in the final rule the current prior approval requirements for changing a contract laboratory or labeler, establishing new procedures for reprocessing a batch of a drug product that fails to meet specifications, changing the synthesis of a drug substance, and changing the facility or establishment for manufacturing the drug substance in certain instances. FDA has concluded that prior approval of these changes is needed because they can significantly affect existing agency safety and effectiveness conclusions about a product.

First, FDA has concluded that it should preapprove the ability of a contract laboratory or labeler to comply with CGMP regulations, for such compliance relates directly to the ability of the laboratory or labeler to produce a drug of acceptable quality and/or properly labeled. Second, with respect to the prior approval requirement for reprocessing a batch that fails to meet specifications, many critical factors affect the acceptability of reprocessed batches; for example, the reason for the original batch failure, the storage conditions of the original batch, the tests performed on the reprocessed batch, and the stability of the reprocessed batch. Prior approval of reprocessing procedures will best ensure that rejected batches are not blended with accepted batches, that stability data are used to support recovery or reprocessing operations, and that original control tests are adequate to monitor the reprocessed batch.

Third, prior approval to change the synthesis of the drug substance is needed to assure the safety and effectiveness of the finished product, as is the use of a new facility to manufacture it in certain instances. A change in the synthesis and the many changes in equipment and procedures that occur with a change in manufacturing facilities may significantly affect the finished product. For example, such a change may affect the particle size, crystalline form, stability, or dosage form dissolution of the drug and, thus, affect the bioavailability of the finished product. The method of synthesis of a drug substance is also linked to specifications needed to monitor its strength and purity. Prior approval will ensure that applicants who make a change in synthesis reexamine the adequacy of specifications in light of that change. A product from a different route of synthesis may yield a different purity profile and may require in vivo testing because the limits for specific impurities are normally developed with reference to their toxicity and pharmacological properties. Finally, impurities may also affect the stability of the finished product. In sum, given the significance these changes may have on product safety and integrity, FDA belives it necessary to maintain premarket approval with respect to them.

With respect to changing the facility or establishment that manufactures the drug substance, prior approval will be required where: (1) the manufacturing process in the new facility or establishment differs materially from that in the former facility or establishment, or (2) the new facility or establishment has not received a satisfactory current good manufacturing practice (CGMP) inspection within the previous 2 years covering that manufacturing process. However, the final rule also provides that an applicant may change the facility or establishment that manufactures the drug substance, without obtaining prior FDA approval, if: (1) The manufacturing process in the new facility or establishment does not differ materially from that in the former facility or establishment, and (2) the new facility or establishment has received a satisfactory CGMP inspection within the previous 2 years covering that manufacturing process. If those two criteria are met, the applicant may implement the change concurrent with submission to FDA of a supplement. In that instance, the supplement is to be plainly marked, "Special Supplement—Changes Being Effected."

FDA has also identified certain changes, in addition to those proposed, that may be reported to FDA on an annual basis rather than in a supplement. These include certain changes in the container and closure system for the drug product, and the addition or deletion of alternate analytical methods. These changes are described more fully below in response to comments on the proposal.

Finally, FDA has revised the final rule to provide a mechanism for applicants to obtain expedited review of supplements where special considerations exist. FDA generally reviews supplements subject to prior approval in the order in which they are received, taking into account other review priorities such as investigational new drug applications and applications for important new drugs. A longstanding and understandable concern of applicants is the cost of waiting for FDA to review and approve these supplements, particularly when extraordinary circumstances require a change in the conditions of approval; for example, when an unexpected event forces an applicant to use a different facility to continue manufacturing a product, or a technological breakthrough would greatly reduce costs. The agency has informally recognized the need to expedite such supplements, but believes that the regulations should specifically recognize this practice. Secondly, the agency has revised the final rule to permit applicants to request expedited review of a supplement for a change that requires prior approval. The agency emphasizes that expedited review is available only under extraordinary circumstances, for either public health or economic reasons, and is subject to the agency's discretion and available resources.

This section, like most of the final rule, will become effective May 23, 1985. If an applicant has submitted to FDA supplements for manufacturing and controls changes that do not require a supplement under the final rule, and those supplements have not yet been reviewed by FDA, the applicant should notify FDA in writing that it is withdrawing those supplements. Upon such notification to FDA, the applicant may proceed to implement those changes as permitted by the final rule.

58. Several consumer comments urged FDA to require prior approval of supplements for every change in an approved application to ensure the safety of the change.

FDA does not agree that prior approval of supplements for all changes in approved applications is necessary. For example, the deletion of an ingredient intended only to affect the color of the drug product is unlikely to

affect safety or effectiveness. This is the type of change that, under the final rule, can be implemented by the applicant and submitted to FDA as part of the annual report. FDA believes its combination of prior approval requirements, requirements for supplements not requiring prior approval, and annual reporting requirements focus FDA's resources and attention on those issues that must be monitored closely and properly tailor the time of the reporting to the nature of the change.

59. Several industry comments stated that FDA's proposed reductions in its supplemental application requirements represent a major improvement over current practices. FDA received several comments, however, suggesting that, even with the proposed changes, the regulation of supplements would still be too restrictive. For example, several comments noted that the categories of changes are stated generally and might apply to many changes for which prior approval of a supplement should not be required. Another comment observed that, although the preamble suggested it would be unnecessary to explain batch control numbers in an original application, changes in the batch numbering system would be required in an annual report. Finally, one comment suggested that the agency should permit a single supplement to cover all similar and related products; for example, a packaging change that may affect as many as 100 products should require only a single supplement.

FDA does not agree that the categories of changes are stated too generally. It must be remembered that applicants are to inform FDA about only those changes that affect the information previously submitted in the application. Thus, the application itself is a guide to the kinds of information for which, if changed, the applicant must submit a supplement. Moreover, as described more fully in the proposal, FDA will no longer require an original application to contain information about manufacturing practices that FDA monitors under its current good manufacturing practice (CGMP) regulations, a regulatory change that will also eliminate the need to submit supplements that would require prior approval under current regulations. Because batch control numbers fall under the CGMP regulations, an explanation of batch control numbers is not required in either the original application or the annual report.

Finally, the agency does not agree that a single supplement would be adequate to cover a change affecting similar and related products. Eliminating multiple supplements in favor of a single supplement would not affect the review time and speed of approval because FDA now combines those supplements and performs a single review if the applicant adequately notes the relationship of multiple submissions. Moreover, except for the submission of a supplemental application form for each application, the applicant may now make a single submission of the technical data and information necessary for the agency to review the change. Individual application forms are needed, however, because they are the mechanism by which the change is noted in each application. When approved, the supplement is placed in the application and becomes a part of the permanent record. The submission of a single supplement to cover multiple applications would impose an added burden on FDA to document the changes and is more likely than the current system to result in a failure to include documentation of the change in each application.

60. One comment asked whether changes in the manufacturing site of the drug substance require prior approval. Another comment objected that use of a facility for packaging a drug product should not require prior approval if the container and closure system and quality control procedures are unchanged, and the facility has undergone a recent CGMP inspection. Moreover, according to this comment, changes in the manufacturing site or the manufacturer of a drug product should not require prior approval if the method of manufacture and specifications of the ingredients are the same as those identified in the application and the drug product meets all specifications in the application.

FDA is obligated to see that approved new drugs are manufactured under circumstances that ensure that the marketed drug does not differ from the drug approved by FDA and, thus, that the agency's conclusions about safety and effectiveness apply to it. To accomplish these objectives, the agency must continually monitor the applicant's manufacturing and control operations, including packaging operations, to determine the applicant's ability to produce a product of acceptable quality. This includes prior approval of facilities for the manufacture of the drug substance and drug product and for packaging the product. Compliance with product specifications is important, but it cannot supplant the review process. The use of a new facility to manufacture a drug substance or drug product, or to package the product, invariably involves changes in procedures that may affect the agency's conclusions about the safety and effectiveness of the product. FDA encourages manufacturers to advise it early about plans to begin manufacturing or packaging operations in a new facility. When that is done, the agency and the applicant can work together to ensure that the requirement for prior approval of the supplemental application does not delay an applicant's use of the facility. Moreover, as described in paragraph 57 above and § 314.70(c)(3) of the final rule, prior FDA approval is not required when the applicant uses a new facility or establishment to manufacture a drug substance if certain criteria are met. Finally, FDA believes that the comment's confidence in the use of specifications to ensure product quality is too great. Quality is built into a product through the method of manufacture and in-process controls; end product testing is not viewed by FDA as a substitute for adequate control of the manufacturing process.

61. One comment noted that FDA's list of changes that would require prior approval of a supplement includes changes that can now be made at the time a supplement is submitted, and that FDA should continue to permit immediate implementation of all changes for which that practice now exists. Comments urged FDA to retain the provision in the current regulations that permits a change to be made when a supplement is submitted if the change gives increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess. One comment suggested that FDA go one step further and permit a change without prior approval if the change provides the same level of assurance that the drug will possess its represented characteristics.

FDA did not intend either to require prior approval of any change for which prior approval is not now required or to change current practice with respect to those changes already listed in the regulations (21 CFR 314.8(d)) as giving increased assurance that the drug will possess its represented characteristics. FDA has revised the final rule to retain the provision. The particular changes contained in the section can be made without prior approval because, by assuring to a greater degree that the drug will possess its represented characteristics, the change provides a public health benefit. A change that provides only the same level of assurance, however, does not provide

such a benefit and, thus, the agency finds no basis for making the additional modification suggested by the comment.

62. One comment suggested that the proposal is more restrictive than current requirements in proposing that the "method of manufacture of the drug product, including changing or relaxing an in process control" must be approved by FDA before the change is made. Another comment objected to the phrase "the method of manufacture" because it is too broad and could apply to any change in the procedure for the manufacture of a drug product. One comment suggested that this requirement be revised to apply to changes that "make a significant change to the method of manufacture of the drug product, including changing or relaxing an in process control; for this section a significant change in method of manufacture should be defined as a change resulting in altered product specifications or altered in process controls."

As discussed above, a change in the method of manufacture should be made in the context of the original method of manufacture described in the application and approved by the agency. Moreover, the final rule omits the current requirements under which changes in manufacturing practices covered by FDA's CGMP regulations must be described in a supplement. This change already eliminates the need to seek prior approval for the kinds of changes in the method of manufacture that FDA believes are not significant.

63. One comment suggested that the requirement for prior approval of a new regulatory analytical method is inconsistent with the preamble statement that changes in analytical methods for the drug substance may be made and reported in the next annual report unless there is also a change in synthesis. An applicant suggested that a change in an analytical method should be allowed without prior approval when results are comparable to the approved method. Another comment urged FDA to permit the substitution of a less discriminating analytical method with a more stringent method without prior approval to reward innovation, reduce costs, and introduce benefit from technological advances. Several comments suggested that the agency should permit without prior approval a change in the container and closure system if the applicant demonstrates stability equivalence with the approved container and closure system under an approved stability protocol or where there is no significant alteration in the material of the components.

FDA notes that the comment is correct about the inconsistency in references to changes in analytical methods for drug substances. The preamble statement was incorrect; a change in a regulatory analytical method for a drug substance requires prior FDA approval because it is the method FDA relies upon to determine whether the product meets legal requirements. An applicant may, however, tighten the limits on a specification, or add a new specification without prior FDA approval, if the change is described in the next annual report. FDA is also persuaded that prior approval is unnecessary when adding or deleting an alternate analytical method because FDA will continue to rely upon the regulatory methods, and changes in alternate analytical methods will let applicants take advantage of technological changes. This change will eliminate a large number of supplements, particularly with respect to abbreviated applications.

FDA has also closely examined its supplement requirements with respect to containers and closures. FDA agrees with the comment that an applicant should be permitted to change the container and closures within a particular container and closure system, put the change into effect, and notify FDA about the change in the annual report, if the applicant first determines that the approved and proposed container systems have equivalent stability profiles under an accepted protocol (that is, a protocol appearing in the official compendia or one that has received approval in the application, or a supplement to it). The agency is, however, returning to the prior approval category changes in the container size for nonsolid dosage forms because of the potential adverse effects a change in container size may have for liquids and other nonsolid dosage forms. For example, use of a larger container size for a multi-dose parenteral drug may result in an increase in the number of punctures of the vial stopper and, thus, may adversely affect the product's integrity in use over time.

64. Because CGMP regulations require manufacturers to have validated processes, ongoing stability testing programs, detailed written processes, and quality assurance units, comments urged FDA to permit applicants to make changes in packaging components, excipients, dyes, flavors, fragrances, preservatives, and other changes without prior approval if they do not result in changes in product specifications or performance, or product safety and efficacy. Some comments urged that the agency go even further in reducing the burden of supplements by permitting any change in manufacturing or controls without prior approval if it is properly validated using procedures already accepted by FDA.

FDA believes that these comments confuse the different objectives of the CGMP regulations and the drug approval process. The CGMP regulations establish primarily minimum standards for assuring that the drug is not contaminated during manufacture, and that the drug has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. Somewhat differently, the new drug approval process and the supplemental application requirements are intended to ensure that the drug is safe, that its benefits outweigh its risks, and that it is effective. Thus, premarket review is still needed to determine whether a change in packaging components, excipients, dyes, flavors, fragrances, and preservatives will affect the safety and effectiveness of the drug. Indeed, because a color may affect a product's stability, FDA concludes that prior approval of the addition of a color is also needed to assure the safety and effectiveness of the product. With these concerns in mind the agency has revised the final rule to require (as it does now) prior approval of a supplement to add a color.

65. One comment suggested that, under the proposal, prior approval of a supplement would be required to delete claims or indications which may now be made upon submission of a supplemental application and without prior approval. The comment urged FDA to permit applicants to delete, without prior approval, any indication for use or claim for effectiveness considered by the applicant to be unsupportable as a result of the applicant's reconsideration of the data or considered by the applicant to present an unacceptable safety to efficacy ratio.

FDA agrees with the comment and has revised the final rule to continue the current practice of permitting the applicant to remove from labeling false, misleading, or unsupported indications for use or claims for effectiveness at the time a supplement describing the change is submitted.

66. FDA received several comments concerning FDA notification of certain changes in the annual report. The United States Pharmacopeial Convention (USPC) supported FDA's proposal to permit changes in an approved application without requiring a supplement if the changes are made to

comply with a change in the compendia. Another comment suggested that the changes that may be described in the next annual report that were listed in the preamble to the proposal should be included in the regulation. One comment suggested that any attempt to list both those changes requiring supplements and those changes not requiring supplements would inevitably leave out some kinds of changes. Several comments suggested that the regulation should clearly identify the container size changes that may be made without a supplement if the applicant informs the agency in the next annual report. Finally, one comment asked that the final rule reflect the preamble statement that applicants would not be required to report changes in information not required in an original application; for example, information about manufacturing practices subject to CGMP regulations.

FDA appreciates the support of the USPC and notes that this change in the agency's supplemental application requirements is based upon close cooperation between FDA and the USPC in the development of compendial standards, including cooperation in the review of data and information supporting changes in standards. FDA has revised the final rule to add to the list of changes that may be described in the annual report. The list includes the following: Any change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied that does not involve a change in the dosage strength or dosage form; an editorial or similar minor change in labeling; the deletion of an ingredient intended only to affect the color of the drug product; an extension of the expiration date based upon full shelf-life data obtained from a protocol approved in the application; a change within the container and closure system for the drug product (for example, a change from one high density polyethylene to another), except a change in size for nonsolid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium; the addition or deletion of an alternate analytical method; a change in the size of a container for a solid dosage form, without a change in the container and closure system. FDA emphasizes, however, that the list is not intended to be exhaustive. All changes not falling under one of the two categories requiring supplements are to be described by the applicant in the next annual report to the application. Moreover, any change falling under one of the "supplement" categories that is made simply to comply with an official compendium is also to be described by the applicant in the next annual report. Although FDA believes it is impractical, if not impossible, to describe in the regulations every possible change that could occur in any application, the final rule lists the most significant and common changes that may be made and that are to be described in the annual report. Finally, FDA believes that a list of subjects, like changes under the CGMP regulations for which prior approval has been but is no longer required, would be of only historical interest and could be confusing.

67. One comment suggested that the agency permit applicants to add and update biopharmaceutic information in drug labeling in the annual report and without a supplement.

Drug labeling serves as the standard under which FDA determines whether a product is safe and effective. Substantive changes in labeling, which include changes in biopharmaceutic information, are more likely than other changes to affect the agency's previous conclusions about the safety and effectiveness of the drug. Thus, they are appropriately approved by FDA in advance, unless they relate to important safety information, like a new contraindication or warning, that should be immediately conveyed to the user.

68. One comment suggested that FDA create a fourth kind of supplement under which an applicant could implement a change 60 days after notifying the agency unless the agency advises otherwise within that time. Another comment suggested 30 days. These supplements might include changes in labeling or revisions to manufacturing or control procedures.

FDA has not adopted this suggestion because of the impact it would have on FDA's priorities. Were such a system instituted, FDA would be forced to rearrange its priorities to ensure that it acted within the required time frame, often with the effect of deferring action on other older and perhaps more important submissions that cannot be implemented without FDA approval. FDA recognizes applicants' concerns about obtaining timely review of supplements, and the agency is addressing this problem by eliminating unnecessary supplements which should, in turn, reduce any backlog. FDA now works closely with applicants who have a special need for timely review of a supplement and, as described above, FDA is establishing a procedure for applicants to request expedited review of certain supplements.

Procedures for Submission of a Supplement to an Approved Application (§ 314.71)

69. Noting that a supplemental application can sometimes be as significant as an original application, such as a supplement for a new indication, several comments found beneficial the application to supplements of all procedures and FDA actions on applications under proposed §§ 314.100 through 314.170. The comments urged, however, that the agency clearly state that § 314.60 on amendments to unapproved applications, § 314.65 on voluntary withdrawal, and § 314.103 on dispute resolution also apply to supplements.

FDA has revised the final rule to clarify that all procedures applicable to an original application also apply to supplements.

70. One comment suggested that the final rule should specify what actions FDA will take in the event that the agency refuses to approve a supplement for a change that the applicant placed into effect at the time the supplement was submitted. The comment stated that FDA should provide a reasonable time for the applicant to correct the problem, including time to exhaust supplies of the drug or labeling affected by the change, unless a significant safety concern exists.

If FDA refuses to approve a supplement for a change that the applicant has already placed into effect, the agency must consider all the factors surrounding its refusal to approve the supplement, including the applicant's reasons for making the change and the alternatives available to the applicant to resolve the problem. Applicants should be aware that they institute such changes subject to agency approval and that, if circumstances warrant, may be required to discontinue the change immediately. Nonetheless, if circumstances permit, FDA agrees that applicants should be able to correct a problem at minimal expense and without unnecessary waste. Because circumstances can vary greatly, however, FDA is not persuaded that a general statement in the regulations would be appropriate.

Postmarketing Reporting of Adverse Drug Experiences (§ 314.80)

71. *Overview.* a. *Comments received.* FDA received a considerable number of comments concerning the proposed reporting of adverse drug experiences of marketed drugs, especially the time

frames for such reporting. The current regulations base the reporting times on whether the adverse drug experience is expected or unexpected. All "unexpected" adverse drug experiences are required to be reported within 15 working days, and all "expected" adverse drug experiences are required to be reported in the next periodic report (quarterly in the first year following approval, semiannually in the second year, and annually thereafter). The proposal (with one exception) would have created a standard time frame of 30 working days for reporting almost all kinds of adverse reactions—serious, nonserious, expected, and unexpected. The one exception was a proposed 15-day alert report for fatal and life-threatening adverse drug experiences not mentioned in the product's approved labeling.

The primary criticism of the proposal made by the comments was that, except for the limited 15-day report, the proposal failed to distinguish the more important adverse drug experiences from the less significant ones. Without such focus, the comments argued, the public health would not be best served because both the agency and the pharmaceutical companies would be spending a disproportionate amount of time processing trivial, known reactions—time that could be better spent evaluating and following up on serious adverse drug experiences that are more likely to affect the public health. Comments also complained that, unlike current regulations, the proposal did not make the reporting requirements less frequent for known and nonserious experiences once the drug had been on the market for a period of time.

Given all of these factors, FDA has reevaluated the objectives of the adverse drug reporting system and the regulatory requirements most appropriate to implement them. Based on this review, the agency has modified the final rule in a number of ways designed to increase the system's efficiency and thereby improve public health protection. The details of these modifications are stated below, following a description of the objectives of the reporting system.

b. *Objectives of the reporting system.* Although premarket testing discloses a general safety profile of a new drug's comparatively common adverse effects, the much larger patient population and longer period of use associated with the marketing of a drug provides, for the first time, the opportunity to collect information on rare, latent, and long-term effects, some of which may be serious. Accordingly, the primary objective of the adverse drug experience reporting system is to signal potential serious safety problems with marketed drugs, especially newly marketed drugs. As described below, a signal may be received in a variety of ways. Receipt of the initial signal triggers considerable followup work and analysis before any conclusion about necessary action can be reached (e.g., a "Dear Doctor" letter, revised labeling, or, in rare cases, market withdrawal). Thus, the agency believes that the goal of any regulations in this area should be to direct attention to those reports most likely to contain information on potentially serious safety problems.

c. *The final rule.* The final rule has been modified in the following ways so that the reporting requirements are tailored to signal potentially serious, new information.

(1) *Requirement for 15-day Alert reports.* Under the final rule, all adverse drug experiences that are both "serious and unexpected," and any "significant increase in frequency" of an adverse drug experience that is both "serious and expected," will be required to be reported to FDA as soon as possible, but in any case within 15 working days. These are the adverse drug experiences most likely to reveal serious safety problems that were not revealed during the clinical trials and which, therefore, are likely to necessitate a labeling change or other action to protect the public health. FDA believes that the broadening of the 15-day reporting requirement from that in the proposal, which would have required that only unexpected fatal and life-threatening experiences be reported, will increase public health protection. Throughout the final rule, references to "15-day Alert reports" (unless specified otherwise) refer to reports of "serious and unexpected" adverse drug experiences as well as reports of a "significant increase in frequency" of a serious, expected adverse drug experience.

The final rule defines both "serious" and "unexpected" in order to clarify the 15-day reporting requirement. Both of these definitions have been adopted from a draft guideline that has been made available for public comment (see 48 FR 4049; January 28, 1983).

For purposes of the final rule, the term "serious" means an adverse drug experience that is life threatening, is permanently disabling, requires in patient hospitalization, or requires prescription drug therapy. In addition, an adverse drug experience that results in death, congenital anomaly, cancer, or overdose is always to be considered serious.

The term "unexpected" means an adverse drug experience that is not listed in the current labeling for the drug and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling listed only cerebral vascular accidents. This definition of "unexpected" is based on an evaluation of individual case reports of an adverse drug experience.

The regulation also defines "increased frequency," which is defined to mean an "absolute increase in the number of reports of an adverse drug experience received during a specified time period compared to the number of similar adverse drug experience reports received during an equivalent time period in the past." In contrast to the definition of "unexpected," the definition of "increased frequency" is necessarily based on an analysis of a series of previous adverse drug experience reports, rather than a single report.

The 15-day reporting requirement will apply to any "significant" increase in frequency of a serious, expected adverse drug experience. In order to meet this requirement, applicants are required to review periodically the frequency of reports of "serious" adverse drug experiences that are "expected." The regulation requires applicants to conduct this periodic review at least as often as the periodic reporting cycle, and FDA will provide written notice to applicants when the agency believes that circumstances warrant more frequent periodic review (e.g., approval of a major new indication or where previous reports signal possible safety problems with the drug). FDA will describe in a guideline the factors which would make an increased frequency "significant" so as to trigger the 15-day reporting requirement, including an increased "rate of occurrence" of the adverse drug experience based on some measure of use of the drug (such as total prescriptions). Given this periodic review and analysis, the final rule requires applicants to report to FDA any significant increase in frequency of a serious, expected adverse drug experience as soon as possible but in any case within 15-working days of

determining that a significant increase in frequency exists. Of course, if an applicant receives a large number of reports within a short period of time, so that a significant increase in frequency is readily apparent, a 15-day Alert report would be required at that juncture.

(2) *Format for 15-day Alert reports.* The final rule specifies the format for submission of 15-day Alert reports. This format differs, depending upon whether the report is based on a single "serios and unexpected" adverse drug experience or on a "significant increase in frequency" of a serious, expected adverse drug experience (i.e., a series of events). The final rule requires reports of "serious and unexpected" adverse drug experiences to be submitted on Form FDA–1639 because that form is designed to contain information on individual adverse drug experiences. In contrast, the final rule requires applicants to submit reports of significant increases in frequency in narrative form (including the time period on which the increased frequency is based, the method of analysis, and the interpretation of results) rather than using Form FDA–1639. This is because Form FDA–1639 is not well suited for reporting a group of adverse drug experiences. As stated below, however, the requirement for periodic reports requires that a Form FDA–1639 for each "serious and expected" (as well as "nonserious") adverse drug experience be included in each periodic report. Finally, in order to facilitate expedited processing by the agency, the final rule requires prominent identification of all 15-day Alert reports. .

(3) *Requirement for periodic reports.* For all other adverse drug experiences, the final rule requires periodic reporting at quarterly intervals for the first 3 years following approval, and at annual intervals thereafter. This requirement reflects the agency's experience that the most important safety problems with a new drug are usually discovered during the first 3 years of marketing. Although this periodic reporting requirement is less frequent than the 30-day time frame that was proposed, FDA believes that the quarterly/annual time frame reflects better than did the proposal the relative importance and relative urgency of the information being reported (i.e., known and nonserious adverse drug experiences). Moreover, the final rule is more stringent in this respect than the current regulations, under which quarterly reporting is required for only 1 year before less frequent reporting is permitted.

The final rule also provides that FDA may extend quarterly reporting requirements beyond 3 years (when warranted by adverse drug experience received to date), may reestablish the quarterly reporting requirements at a later point in time (such as following approval of a major supplement), or may require the applicant to submit reports at other specified intervals. Thus, the regulation provides for increased surveillance of drugs when the circumstances so warrant.

The final rule states that quarterly reports are due within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and that annual reports are due within 60 days of the anniversary date of approval of the application. The time frame for submission of annual reports conforms to other annual reporting requirements under § 314.81.

(4) *Format for periodic reports.* The final rule specifies the content of periodic reports. These reports are designed to perform two functions: (a) Report to FDA the adverse drug experiences not previously reported under the 15-day requirement; and (b) present an overview of all the safety-related information learned during that quarter or year. In order to serve this second function, each periodic report is required to contain a narrative summary and analysis of the information contained in the report and an analysis of the 15-day alert reports submitted during the reporting interval; an index of all adverse drug experiences reported for the first time in the periodic report; and a history of actions taken, if any, since the last report because of adverse drug experiences (e.g., labeling changes or studies initiated). FDA believes that this safety profile overview will improve the agency's ability to spot drug safety trends.

(5) *Followup reports.* Several comments addressed the issue of followup reports. These comments urged FDA to require followup reports to be submitted 30 days after the date of receipt of followup information, not 30 days after the date of the original report (as had been proposed). One comment proposed 60 working days for submission of complete followup information on 15-day reports. Another comment asked for clarification about appropriate action if followup information cannot be obtained.

Because FDA has substituted quarterly and annual reports for the proposed 30-day reports, the agency expects that followups will be needed principally for the 15-day alert reports for "serious and unexpected" adverse drug experiences. With respect to these, the final rule requires applicants to investigate them promptly. Along the lines suggested by a comment, FDA has revised the final rule to tie the timing for submission of followup reports to the receipt of new information, rather than to the original report. Thirty working days, however, as suggested by the comment, is too long a period, given the possible importance of the information. The final rule, therefore, requires the submission of these followup reports within 15 working days of the receipt of new information or as requested by FDA. If the applicant seeks, but cannot obtain, additional information about an experience, a followup report may be required that briefly describes the steps taken to obtain the information and the reason the new information is unobtainable. Any followup information for adverse drug experiences submitted as part of a periodic report may be submitted with the next periodic report.

Finally, like the proposal, the final rule requires that records of adverse drug experiences be retained by applicants for a 10-year period. The record retention requirement has been moved from the "annual reports" section to the "adverse drug experience" section so that all requirements concerning adverse drug experiences can be found in one place in the regulations.

d. *Other options considered.* FDA decided on the time frames described above only after consideration of a wide range of options. For example, several comments urged that fatal and life-threatening adverse drug experiences be reported sooner than 15 working days, such as "immediately," within 24 hours, or within 1 week. One comment argued that FDA should require applicants to submit early reports of all fatal and life-threatening adverse drug experiences, instead of only those that are unexpected. At the other end of the spectrum, several comments urged that reporting intervals should not only become less frequent the longer the drug is on the market, but that at some point in time (e.g., 10 years after approval) reporting of known reactions should be eliminated entirely.

In response to these comments, the agency notes that the final rule does provide for reporting of "serious and unexpected" adverse drug experiences "as soon as possible," with 15 working days being the maximum. FDA strongly encourages the promptest possible reporting of these adverse drug experiences. The agency believes, however, that reducing the time for submitting these reports would serve only to increase considerably the

number of incomplete reports received by the agency. A large volume of such reports would make it more difficult for FDA to decide on a course of action, and would tend to clog up the system with useless information. FDA's experience is that 15 working days is sufficient time for applicants to gather enough information to submit a meaningful report, even though some followup may still be required. Moreover, the agency believes that adverse drug experiences already described in a drug's approved labeling need not be reported within 15 days even if those experiences were fatal or life-threatening. The importance of information about such experiences would be limited primarily to the question of whether they occur more frequently than assumed. As discussed above, however, any significant increase in frequency of a serious, expected adverse drug experience is also subject to the 15-day reporting requirement.

With respect to the last comment, FDA has staggered the reporting intervals for known and nonserious adverse drug experiences depending on the length of marketing experience. However, FDA does not believe it would be prudent to eliminate annual reporting across-the-board, even after several years of marketing experience, because of the possibility that long-term or other rare or latent effects might be detected.

72. *Definition of adverse drug experience.* Several comments objected to the scope of the proposed definition of an adverse drug experience, which built certain examples into the definition itself. One comment suggested that the current, more general definition should be retained. Another comment, finding the proposed definition open-ended, urged that the final definition be specifically limited to the listed examples. A third comment suggested that the agency delete information about drug overdose, drug abuse, and drug withdrawal because such information could more efficiently be obtained from the Drug Abuse Warning Network (DAWN) system, sponsored by the National Institute on Drug Abuse. Finally, one comment suggested that the definition should be evaluated to include drug misuse, which would provide useful information for treating emergencies.

FDA disagrees with these comments. FDA believes that the proposed definition of an adverse drug experience, which is retained in the final rule, improves upon the current definition because the specific examples provide clearer notice to applicants of what is required. FDA also believes that the definition should be left open-ended because public health protection requires the reporting of all adverse drug experiences, even those that do not fit into one of the more common categories. With respect to use of the DAWN system, although FDA uses drug abuse information generated by that system, its inherent limitations limit its usefulness such that it should be viewed as complementary to the adverse drug reporting system, with each contributing to an assessment of the abuse liability of drugs. Finally, the agency does not agree that "drug misuse" should be added to the definition because drug misuse often does not result in an adverse event.

73. Several comments objected to including in the definition of an adverse drug experience any failure of a drug product to produce its expected pharmacological action. Because drug products are not expected to be effective in all patients, these comments urged that only significant or unusual failures be reported, a required by current regulations.

FDA agrees that the final rule should be revised so that, as with the current regulation, only a "significant" failure of a drug to produce its expected pharmacological action would be reportable. While most instances of drug failure would be understood by physicians to represent the usual variances of biological responses, some failures of action are more important, reflecting, for example, a drug interaction or an unresponsive patient subpopulation. Such failures may also indicate manufacturing problems or batch failures. It is these types of failure that are likely to appear in the literature or as reports to the applicant, and the final rule requires that they be submitted to FDA.

74. *Tabulation of adverse drug experiences.* Several comments contended that a tabulation in the annual report of adverse drug experience reports already reported on Form FDA–1639 is an unnecessary duplication of the other reporting requirements, and would add greatly to the work of applicants without any obvious benefit. One comment suggested that an applicant's tabulation of adverse drug experiences would be less complete and, thus, less useful than FDA's own data base, from which a tabulation could be made.

FDA has revised this section to require that the applicant provide only an index of all adverse drug experiences submitted for the first time in the periodic report. This index is to consist of a line listing of the applicant's patient identification number and adverse reaction term(s). The index is intended to order the potentially large volume of information being submitted and to provide FDA reviewers with ready access to particular reports when necessary.

75. *Published literature.* Several comments objected to the proposed requirement to transfer information from the published literature onto a Form FDA–1639 and urged, instead, that FDA retain its current rule of simply accepting the published articles themselves. These comments argued that such transfer is an unnecessary clerical exercise that would require major expenditures of time, effort, and money. One comment suggested that even an abstract of the article should be sufficient.

The efficient handling of adverse drug experience reports requires that they be made in a form that is convenient for the agency to process. FDA is currently receiving almost 40,000 adverse drug experience reports annually. To analyze those reports efficiently, the agency has developed a reporting form that reflects FDA's experience in monitoring drug safety in a centralized reporting program. Each item of information on a fully completed Form FDA–1639 (Drug Experience Report) fulfills one of the following four purposes: (1) Recordkeeing information, (2) information necessary to monitor compliance, (3) information relating to the seriousness of the report and the event or reaction, and (4) information relating to the sequential relationship between the drug and the event or reaction. Moreover, as constructed, Form FDA–1639 is also intended to facilitate data entry into FDA's computer base. Given the large number of reports submitted to the agency, and the agency's small staff for reviewing and processing them, FDA's system will work only if applicants transfer reports from the scientific literature to Form FDA–1639's. FDA believes, however, that preparation by the applicant of 1639 forms for literature reports represents a minimal burden because, as described below, the regulations limit the kinds of literature reports that need to be submitted, and because the applicant will necessarily have to review any given literature report to determine if it meets the criteria for reporting. Morever, if the applicant believes that the preparation of a 1639 form represents an undue hardship in any particular instance, the regulations provide that the applicant may arrange with the Division of Drug and Biological Product Experience for an acceptable alternative reporting format.

76. Several comments questioned the need for submitting adverse drug experience reports based on the scientific literature. For example, one comment argued that literature reports often do not contain the information needed to complete FDA's form and, therefore, that this requirement will provide FDA with little useful information. One company estimated that, under the proposed requirement, it would have to copy and submit to FDA almost three 5-drawer filing cabinets of literature articles each year, and that this would amount to over 100 filing cabinets industrywide. According to this comment, the number of additional employees needed by the industry and FDA to copy, submit, and review these articles would also be excessive. Other comments suggested that FDA limit the scope of the published reports falling under this section to, for instance, reports in the published literature "primarily concerned" with the occurrence of adverse drug experiences, or only those relating to fatal or life-threatening experiences. Finally, one comment asked whether the requirement applied to individual experiences reported in letters to a journal.

FDA agrees with those comments that urged FDA, in order to keep the amount of information manageable, to limit the scope of required reports from the scientific literature. FDA has revised the final rule in two ways. First, the final rule limits literature reporting to "serious and unexpected" adverse drug experiences and any "significant increase in frequency" of a serious, expected adverse drug experience (i.e., those subject to the 15-day reporting requirement). By focusing the literature review and reporting on the most important adverse drug experiences, this requirement achieves the objectives of a signaling system while maintaining a reasonable reporting burden on applicants. Reporting of the vast numbers of individual cases of known or nonserious adverse drug experiences recorded in the literature would not materially advance public health protection.

Second, the final rule limits the kind of literature reports subject to the 15-day requirement in the following ways. With respect to reporting "serious and unexpected" adverse drug experiences, the final rule limits literature reporting to adverse drug experiences appearing in scientific and medical journals as "case reports" or as the result of a formal clinical trial. Case reports are reports of experiences in individual patients, including those appearing in letters to the editor and in studies of adverse effects, but do not include literature reports of adverse drug experiences in clinical trials that do not tie experiences to individual patients. The limitation should help provide FDA with complete, rather than partial and less useful, information about events reported. In addition, limiting the requirement to reports in scientific and medical journals ensures that reports come from scientifically credible sources. As noted above, a Form FDA-1639 is required for each case report, even when a journal may contain less than all items of information needed to complete the form. With respect to reporting a "significant increase in frequency," the final rule limits literature reporting to scientific and medical journals containing reports of either formal clinical trials, or epidemiologic studies or analysis of experience in a monitored series of patients. Once again, this limitation is intended to focus attention on those types of literature reports most likely to yield useful information.

77. Several comments said that the proposal is unclear about when FDA considers an applicant to have knowledge of an experience in a published report. Unsure about when FDA will impute to an applicant knowledge of a published report known by one of the applicant's employees, one comment recommended that applicants be required to report only experiences that employees discover in the normal course of business through a literature review program, or that employees discover on their own time (e.g., while reading a scientific journal at home) and bring to their supervisor's attention at work. However, according to this comment, the regulation should not require that applicants establish literature review programs.

As was clear in both the proposal and the final rule, adverse drug experiences an applicant discovers through an organized literature review program must be reported. Although the final regulations do not require applicants to establish literature review programs, an applicant is obligated to report those experiences that come to its attention in the normal course of business. Whether an employee's knowledge of a report in a scientific journal would be imputed to the applicant will depend upon the factors surrounding the employee's knowledge of the report. As a general rule, however, FDA will consider companies responsible for information known to employees, and companies should adopt procedures that require employees to bring important information to the attention of superiors.

78. Several comments suggested that the regulations should permit a single initial Form FDA-1639 for an adverse drug experience in multiple patients from nonliterature sources because the number of patients is often exaggerated. According to these comments, individual forms could be required for followups of documented patients.

FDA believes that permitting the use of a single initial report for multiple patients with individual forms for followup, while it might reduce by a small number of the forms required, has the potential for creating confusion about the number of experiences reported. It is necessary for FDA, if it is to utilize the data properly, that information on the number of adverse events be received in an unambiguous manner so as to reflect clearly the extent of a problem. The submission of multiple events on a single reporting form is inconsistent with the agency objective. Moreover, a practice of grouping reports on one form would make it harder for FDA to determine whether an experience was covered by an initial report and thus was reported in a timely way, and whether appropriate followup was conducted in each case.

79. *Identification of patients.* Several comments objected to the provision under which FDA would have access to individual patient information. For example, comments suggested that the review of patient records by FDA raises questions about their continued confidentiality. Several comments urged that submission of patient records should require a determination in writing by the Director of the Center for Drugs and Biologics that there is good cause to believe that the reports in the application do not represent actual cases or actual results obtained, or that FDA should provide examples of situations where good cause to review actual reports would exist. Some comments suggested that the proposal did not provide the same types of protection for patient confidentiality accorded by State statutes. These comments suggested that FDA should describe the safeguards the agency will employ to protect and ensure patient privacy.

FDA believes that these comments misunderstood the proposal as it relates to FDA access to patient records. FDA disagrees with the suggestion that its safeguards for information that identifies patients are inadequate. As noted in the proposal, FDA urges applicants not to include names and

addresses of individual patients in adverse drug experience reports, although applicants should inlcude some other identifier, such as initials or code numbers. Initials and codes are useful for eliminating duplicate reports of an adverse drug experience. As noted in the regulations, names of patients, health care practitioners, hospitals, and any geographic identifier are not releasable to the public under FDA's public information regulations in Part 20 (21 CFR Part 20). Moreover, FDA's Division of Drug and Biological Product Experience routinely deletes information that could identify patients, health care professionals, and hospitals before copies of adverse drug experience reports are provided to the public, or even to other components within FDA itself. Thus, FDA believes that the final rule adequately protects confidential information about patients.

80. Several comments also believed that the proposal implied that applicants should maintain in their records the names and addresses of patients. One comment stated that its practice is to retain only identifying information that permits it to find the name and address of a patient, using records maintained by the investigator. Another comment noted that an applicant may be unable to obtain the patient's name, as some hospitals will not release patient identification. The comment suggested that the phrase "upon written request by FDA the applicant shall submit individual patient identification information from designated reports" should be changed to "the applicant shall maintain sufficient patient identification information to permit FDA, by using that information alone or along with records maintained by the investigator of a study, to identify the name and address of individual patients."

FDA agrees with this comment and has revised the final rule to provide that an applicant need only retain identifying information that permits FDA to find the name and address of a patient using records maintained by the applicant or maintained by the investigator in a study.

81. *Postmarketing clinical trials.* Several comments urged that adverse drug experiences from clinical investigations conducted on marketed drugs under an investigational new drug application (IND) should be exempt from the reporting requirements because study blinding will make it impossible to identify whether the adverse drug experience was associated with either the test drug or the control drug. Accordingly, this comment suggested that adverse drug experiences from these studies should be reported to FDA in the final study report. One comment noted that in double-blind studies it is not known whether an experience is associated with a placebo, a control drug, or the study drug, and the code should only be broken for fatal or life-threatening reactions. One comment urged that the regulations clearly specify whether adverse experiences occurring with an approved drug product used in a clinical study under an IND should be reported to the application or the IND. Another comment objected to the use of Form FDA–1639 for reporting experiences from clinical investigations conducted under an IND. According to this comment, those experiences are best reported in the final clinical report, which should be submitted after the study is completed.

FDA agrees with the general thrust of these comments and has revised the final rule to provide that only "serious and unexpected" experiences or a "significant increase in frequency" of a serious, expected experience (i.e., those subject to the 15-day reporting requirement) must be reported when they occur in clinical trials conducted using marketed drugs. As noted above, the 15-day reports are the most important part of the adverse drug experience reporting system, and it is important to keep these reports current. FDA does not interpret this requirement as requiring clinical investigators to break the blinding code, but this requirement does apply to serious, unexpected adverse drug experiences when the code is normally broken anyway (such as when the patient dies or drops out of the study).

82. Several comments also objected to FDA prohibiting the reporting of adverse drug experiences from Phases I and II studies on Form FDA–1639.

The prohibition objected to has been deleted from the final rule. FDA agrees that reporting of "serious and unexpected" adverse drug experiences from clinical trials on marketed drugs required under this section should be submitted on a Form FDA–1639. As noted above, the review of adverse drug experiences by FDA's Division of Drug and Biological Product Experience is geared to this form, and its use also facilitates entry of the information into the computer base for marketed drugs. This interpretation does not apply to 15–day reports of significant increases in frequency which, for reasons described above, are to be reported in narrative form. It should be noted, however, that the final rule does not apply to reporting requirements under the IND regulations (Part 312), where a more detailed type of reporting may be required because much less is known about the safety of unmarketed drugs and, therefore, more extensive information on individual incidents is needed.

83. *Postmarketing surveillance/epidemiological studies.* One comment objected to the submission of adverse drug experience information from postmarketing surveillance/epidemiological studies on Form FDA–1639 in the same fashion as information from spontaneous reports because these studies would generate a large number of reactions that would overwhelm the spontaneous reporting system. The comment suggested that only unexpected adverse drug experiences from those studies be submitted under the schedule for spontaneous reporting, with other experiences summarized and submitted later.

FDA has revised the final rule in response to this comment. First, FDA recognizes that reports occurring in a structured study must be evaluated separately from spontaneous reports. Thus, the agency asks that reports of adverse drug experiences clearly note when an experience occurred in a postmarketing study. The agency will file these study reports separately from spontaneous reports. Second, as with postmarketing clinical trials, the 15–day reporting requirement will apply to these studies only where there is no blinding or when the blinding code is otherwise broken, and these reports are required to be submitted on Form FDA–1639. However, other adverse drug experiences from these studies will be subject to periodic reporting and will be required to be reported following the completion of the study (a study is considered completed 1 year after it is concluded); applicants are encouraged to submit these adverse drug experiences in a format different from Form–1639, if agreed to in advance by the Division of Drug and Biological Product Experience.

84. *Recordkeeping.* Several consumers objected to requiring recordkeeping of adverse drug experience reports for only 10 years, arguing that such data may be useful later if a drug is found to have serious adverse effects that do not show up for many years; for example, if the drug is found to be carcinogenic. In contrast, another comment argued that the requirement that adverse drug experience records be maintained for 10 years is excessive, suggesting instead that complete records be retained for 5 years and a summary of adverse drug experiences be retained for an additional 5 years.

FDA has not found it necessary to rely upon applicant records that are more than 10 years old for evaluating current adverse effects, including delayed effects like carcinogenicity. Thus, the agency cannot now justify a record retention requirement of more than 10 years. In addition, FDA would prefer to be able to obtain full rather than summary records when and if needed. The agency is not persuaded that retaining complete records for 5 years and then reducing them to a summary is less burdensome than simply retaining the records for 10 years. Therefore, the final rule will remain as proposed.

85. *Miscellaneous issues.* On its own initiative, FDA has made several additional modifications to the final rule relating to adverse drug experiences. First, the agency has limited the reporting of adverse experiences from foreign marketing to those considered to be "serious and unexpected" as well as those representing a "significant increase in frequency" of a serious, expected adverse drug experience (i.e., those subject to the 15-day reporting requirement), consistent with other efforts to target FDA resources on the most important adverse experiences.

Second, the final rule, like the current regulations, requires any person (in addition to the applicant) whose name appears on the label of an approved drug product (i.e., a manufacturer, packer, or distributor) to comply with the 15-day reporting provisions on adverse drug experiences. Although FDA proposed to delete this requirement for nonapplicants as part of a broader effort to reduce recordkeeping and reporting requirements generally, FDA believes that the 15-day reporting of adverse drug experiences is sufficiently important, and that it is sufficiently likely that any person whose name is on the approved label will be a recipient of adverse drug experience complaints, that this reporting requirement should be retained. In order to avoid unnecessary duplication of reporting, however, a nonapplicant's obligation under this section may be met by forwarding the adverse drug experience information it receives to the applicant within 3 working days, and by retaining a record of that transmittal.

Third, the agency has continued the current rule of requiring two copies of adverse drug experience reports, rather than the proposal's requirement of only one copy, to expedite review of the reports by the Division of Drug and Biological Product Experience and the Office of Drug Research and Review or the Office of Biologics Research and Review, which both evaluate adverse drug experiences. Because of the large volume of reports received, copying by FDA will unnecessarily delay the review of this important information. The agency believes that spreading this burden among all applicants is both reasonable and efficient. Applicants should send both copies of these reports in the same envelope or package directly to the Division of Drug and Biological Product Experience, and the agency will route the second copy to the Office of Drug Research and Review or the Office of Biologics Research and Review. The final regulation also contains a provision for waiver of the requirement for a second copy (for example, in the quarterly/annual report, the reviewing division may want only the tabular listing of non-15-day reports, rather than full Form FDA-1639's).

Fourth, the final rule contains a caution against the submission of multiple reports for the same adverse drug experience. Thus, an applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

Finally, FDA has added a provision stating that an adverse drug experience report submitted in accordance with these regulations does not necessarily reflect a conclusion by either the applicant or FDA that the report conatitutes an admission that the drug caused or contributed to an adverse effect. This "disclaimer" provision parallels a similar provision recently added to the Medical Device Reporting (MDR) regulation (49 FR 48272; December 12, 1984) in response to comments raised concerning products liability consequences of reporting possible adverse effects. FDA advises, however, as it did in the December 12, 1984 notice, that although FDA does not intend for such a report to be viewed as an admission of liability, whether a court will treat a submission to FDA as an admission will depend on factors outside of the agency's control, such as the contents of the report itself.

FDA believes this disclaimer incorporates long-standing agency policy in the drugs area. Both the previous and the new drug regulations require reporting of adverse events, whether or not considered to be caused by the drug in question. FDA is adding the disclaimer provision for purposes of articulating consistency with the new MDR regulation. For the reasons stated in the December 12, 1984 notice, this provision does not require notice and comment rulemaking and will be made effective along with the other adverse drug experience reporting provisions of this final rule.

86. Several comments suggested that FDA combine the adverse drug experience and annual reporting requirements into a single section of the regulation, because the separate sections in the proposal were confusing and duplicative.

FDA believes that separate sections describing the "adverse drug experience reporting" requirements and the "annual reporting" requirements are helpful because both FDA and some applicants have separate organizational components devoted to each of these areas. For example, in FDA, the adverse drug experience reports are evaluated first by the Division of Drug and Biological Product Experience, whereas the annual reports are reviewed by the Office of Drug Research and Review or the Office of Biologics Research and Review.

Nevertheless, FDA agrees that the proposal did not adequately segregate the requirements applicable to adverse drug experience reports from those relating to the more general records and reports, and, therefore, the agency has made the following changes in the final rule: First, the section relating to the "postmarketing reporting of adverse drug experiences" will include all the regulatory requirements relating to this topic, including the provisions relating to the retention of records and the annual tabulation, both of which were located in the "records and reports" section of the proposal. Second, the reporting requirements for adverse drug experiences have been deleted from the "other postmarketing reports" section (called "records and reports" in the proposal) because they are also found in the section in the final rule on adverse drug experience reporting (the proposal had listed them in both sections).

87. One comment suggested that the agency monitor more closely applicants' compliance with reporting requirements and suggested that the proposal was unclear about who is responsible for submitting reports of adverse drug experiences. The comment also asked how the information is made publicly available.

FDA urges health care professionals to submit adverse drug experience

reports to FDA on Form FDA-1639. Many professionals submit reports to manufacturers, however, and many manufacturers routinely review the literature on their products. It is the reports obtained by the manufacturer with which these regulations are concerned. The regulations clearly place the responsibility for submitting those reports to FDA on the manufacturer. With respect to public disclosure, § 20.111(c)(3) of FDA's public information regulations governs how this information is made publicly available.

88. One comment stated that FDA's regulatory impact analysis on the proposal did not adequately discuss the impact of the changes in the adverse drug experience reporting system.

This comment was made in conjunction with an objection to the proposed requirement that all adverse drug experiences be submitted within 30 working days, a change which the comment believed was excessive and did not provided a corresponding public health benefit. Because FDA has modified that aspect of the proposal, the corresponding economic concern with respect to the proposed 30-day provision is moot. However, the final regulatory impact analysis does address the economic aspects of the major changes between the current regulations and the final rule.

89. Two comments suggested that over-the-counter drugs that are subject to approved applications and that are not intended for systemic absorption, like antimicrobial mouthwashes or soaps and antidandruff shampoos, should be exempt from frequent reporting of consumer complaints, like rashes or minor skin irritations, particularly if the manufacturer provides a toll free telephone number on labels.

FDA believes that the changes in the final rule—to require only "serious and unexpected" adverse drug experiences to be reported quickly—meets the concerns of the comments.

Other Postmarketing Reports (§ 314.81)

90. *NDA—Field alert report (§ 314.81(b)(1)).* Two comments objected to the proposal specifying that certain reports, required under current regulations to be submitted "immediately," be submitted within 3 working days. These reports covered: (i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; and (ii) information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specifications established for it in the application. Two other comments, mistakenly believing that the agency intended to require immediate reporting of a broader category of information than currently required, urged that the current language of the requirement be retained because the comments found it preferable to and clearer than the proposed revision. Other comments suggested that FDA allow reports by telephone with written followup information.

Although the agency has retained the proposed wording regarding the kinds of information that are required to be reported under this section, FDA intends the final rule to require the same kinds of reports submitted under the current regulation. The major change from current practice is to require the report within 3 working days. FDA has also revised the final rule to state that this reporting requirement applies only to distributed drug products and that the report should be made to the FDA district office that is responsible for the facility that is the subject of the report. To help the district offices recognize these submissions quickly, these reports have been designated "NDA—Field alert reports" in the final rule. Because these reports can lead to preventing potential safety hazards from products already in distribution, the agency emphasizes that the reports are required for both confirmed and unconfirmed problems. Telephone reports will be permitted, with prompt written followup.

91. *Annual report (§ 314.81(b)(2)).* Several comments stated that the proposal to require an annual report within 30 days of the anniversary date of approval is unnecessarily burdensome, particularly if adverse drug experiences are reported earlier. One comment suggested a due date of 60 days after the anniversary date, and another comment suggested 6 months. Finally, one comment suggested that annual reports should be eliminated after 3 years of marketing because little new information is obtained after that time.

FDA is persuaded that 30 days may be inadequate for an applicant to compile and prepare an annual report. An annual report under the final rule will differ from current annual reports in that it will contain, in addition to what is currently reported, both a summary of new information about the drug and a description of actions the applicant has taken or proposes to take as a result of that information. Thus, to ensure that the summary is clear, concise, and thoughtful, FDA has revised the final rule to require the submission of an annual report 60 days after the anniversary date of the application.

FDA does not agree, however, that annual reports should be eliminated after 3 years. Animal and clinical data may become available long after a drug is first marketed, and the annual reporting requirement is the most effective means for an applicant to provide it to FDA. Moreover, the annual report is necessary for applicants to inform the agency about changes in the application that are not covered by supplements. Thus, FDA relies upon the annual reporting requirement to monitor continuously the safety and quality of approved drugs while they are marketed.

92. *Summary (§ 314.81(b)(2)(i)).* One comment objected to the requirement for an annual report summary containing a description of the actions an applicant intends to take as a result of new information because, according to this comment, action by an applicant should not wait until the applicant prepares its annual report.

FDA believes that this comment misunderstood the proposal. The final regulations, like the proposal, do not require that an applicant delay action until an annual report is made: instead, the summary is simply required to contain a description of actions the applicant has taken and actions the applicant proposes to take.

93. *Distribution data (§ 314.81(b)(2)(ii)).* One comment objected to what was perceived as a requirement for a single report of units distributed for domestic and foreign use. According to this comment, the requirement would make it difficult for FDA to estimate the incidence of a drug's adverse effects because applicants usually will have much less information about adverse experiences in foreign countries.

FDA has revised the final rule to state clearly that quantities of a drug product distributed for domestic use and quantities distributed for foreign use should be stated separately.

93a. *Chemistry, manufacturing, and controls changes (§ 314.81(b)(2)(iv)).* The final rule retains the current requirement for annual reporting of experiences, investigations, studies, or tests involving chemical or physical properties of the drug that may affect the drug's safety or effectiveness. This provision was inadvertently omitted from the proposal.

94. *Nonclinical laboratory studies (§ 314.81(b)(2)(v)).* Several comments urged that requirements for reporting nonclinical laboratory studies be limited to active ingredients. One comment

asked FDA to require applicants to submit routinely published literature about commonly used drug ingredients, such as acetaminophen, codeine, and atropine, rather than to submit them in annual reports on specific drug products. According to this comment, submission of data on the ingredients rather than on individual products would better enable FDA to monitor the drug products adequately. Another comment urged that summaries of published reports be permitted because the reports themselves often contain lengthy reviews of previous literature. Finally, noting that there is no reason to supply FDA with required information it already has, one comment suggested that FDA limit required submissions to "new" toxicological findings in animal and in vitro studies.

The final rule retains the proposed requirement for reporting nonclinical laboratory studies of inactive ingredients, because both active and inactive ingredients can cause safety problems. FDA has also retained the requirement for submitting study results for inclusion in specific applications rather than making a general submission to the agency. This is because each report an ingredient must be separately evaluated with respect to the drug products that contain it. With respect to published literature, the final rule has been revised to require only summaries of published studies, although the applicant will be required to submit a copy of the published study upon request. FDA has retained in the final rule the requirement for full copies of unpublished nonclinical studies. Finally, the final rule, like the proposal, does limit submissions to "new" toxicological findings in animal and in vitro studies.

95. *Clinical data (§ 314.81(b)(2)(vi)).* One comment objected to the required submission of articles from the scientific literature, rather than simply a bibliography, because the articles are readily available to the agency. Two comments suggested that an applicant should only be required to submit published or unpublished reports that present new and different information that has not been previously submitted, instead of requiring applicants to submit all available reports. One comment suggested a revision of the phrase "review articles, papers, and abstracts in which the drug is used as a research tool," to clarify that papers (as well as abstracts) in which the drugs is used as a research tool should not be reported.

Although FDA has access to the scientific literature, it would impose a significant burden on the agency if its reviewers were required to obtain reprints of literature references. It is properly the responsibility of the applicant to assure that the application is kept current. Since the applicant is expected to monitor the literature for developments relating to its products, it is not, in FDA's opinion, unduly burdensome to require the applicant to copy relevant articles and send them to FDA.

As suggested by two comments, applicants are not required to resubmit information previously submitted. However, the final rule retains the requirement for the submission of information from any new clinical trials (i.e., not previously submitted). Even if such trials do not contain dramatically different information, they often provide new information about, or insights into, the safety or effectiveness of the drug product. Finally, FDA agrees that reports of papers (as well as abstracts) in which the drug is used as a research tool need not be reported, and the agency has revised the final rule to so provide.

96. *Status reports (§ 314.81(b)(2)(vii)).* One comment contended that status reports for postmarketing studies are unnecessary because FDA will be receiving adverse drug experience data on a timely basis.

FDA believes that this comment misunderstood the proposal. All that is required is a "statement of the current status of any postmarketing studies." This is simply a requirement to advise the agency about which postmarketing studies, if any, are ongoing, and what the status of such studies is, such as how close a study is to completion. Detailed reporting of adverse drug experiences is not required under this section.

Time Frames for Reviewing Applications (§ 314.100)

97. Several comments objected to establishing limits to the application review time and urged that FDA should emphasize the thoroughness and carefulness of its review instead of merely the speed with which approval decisions are made. One comment suggested that it is unlikely that faster approval could be accomplished without compromising the reliability of FDA's safety and effectiveness decisions. These comments were concerned that the 180-day deadline for reviewing applications may place too much pressure on reviewers and thus reduce the quality of the review. Other comments considered the time frames unrealistic, particularly in view of the proposed changes to increase the number of communications and meetings with applicants. Another comment suggested that the agency's time frames for action on applications may create unreasonable expectations, given the restrictions on the agency's personnel and budget resources.

This final rule, like the proposal, is intended to establish efficient procedures, including time frames for review, under which the approval process operates, without reducing the high level of public health protection the approval process now provides. The 180-day review period reflects the statutory requirements that apply to the approval process. FDA believes that improvements in the regulations (such as those relating to the format and content of applications), together with managerial improvements, provide a reasonable basis for concluding that the time frames in the final rule can usually be met.

98. One comment suggested that the agency's two 180-day time limits for reviewing and filing applications (which overlap by 60 days) are confusing. The proposal was unclear, according to this comment, about whether an action letter will issue within 180 days of FDA's receipt or within 180 days of FDA's filing of the application. Another comment urged FDA to adopt a single time frame under which the agency would file the application 30 days from the date of its receipt, thus starting the 180-day clock. Finally, one comment suggested that FDA establish a special deadline for action by the Directors of the Office of Drug Research and Review and the Office of Biologics Research and Review on division recommendations on applications.

Although the agency recognizes that there is a potential for confusion, it believes that its separate time frames for reviewing and filing applications are necessary and are not unduly complicated. The agency suggests that reviewers and applicants should focus on the provision for issuance of an action letter (either an approval, approvable, or not approvable letter) within 180 days of FDA's initial receipt of the application. This is the "review clock" (i.e., the period in which the application will be reviewed) and it is not affected by the date of filing. Thus, moving the deadline for filing from 60 days to 30 days would not have the effect anticipated by the comment: The 180-day review period would be already running when either filing date (30 to 60 days) was reached.

The second 180-day period, or "filing clock," plays an important role in only that small number of cases where the applicant chooses to enter the formal evidentiary hearing process following

the agency's refusal to approve its application. The reason for the "filing clock" is legal: section 505 of the act requires FDA, within 180 days of "filing," either to approve the application or to issue a notice of opportunity for hearing. The preparation of a notice of opportunity for hearing is far more time consuming than the preparation of a not approvable letter. Therefore, by placing the date of "filing" 60 days into the review cycle, the agency gives itself 60 days at the end of the normal review cycle (i.e., issuance of an action letter) to prepare a notice of opportunity for hearing if one is necessary. (As noted below, this 60 days includes 10 days for the applicant to respond to the action letter, so FDA's time is really 50 days.)

What this means, therefore, is that applicant should rely on the 180-day "review clock" as the measure of review time regarding their applications. As described above, this provision calls for the completion of FDA's review and issuance of an action letter within 180 days of initial receipt of the application. The filing notice after 60 days serves as a status report to the applicant that the application has been found to be sufficiently complete for review purposes, and does not affect the period in which applicants are notified of the approvability of their applications. Except in those rare cases that may culminate in a formal evidentiary hearing, the 180-day "filing clock" has no practical significance.

FDA has retained the proposed provision that the "clocks" may be extended by mutual agreement or by the submission of a major amendment. Any extension applies equally to both the "review clock" and "filing clock." This change is consistent with comments, discussed elsewhere in this preamble, that advocated increased use of advisory committees. These comments recognized that bringing a matter before an advisory committee could raise a need to extend the review period.

Filing an Application (§ 314.101)

99. FDA received several comments on the proposed provisions concerning filing an application and procedures to be followed when the agency refuses to file an application. Several comments suggested that the regulations should provide for FDA to file the application within the 60-day period instead of on the 60th day after receipt. Several comments objected, as being insufficient, the 10 days provided in the proposal for an applicant to decide whether to request an informal conference on the agency's refusal to file its application. One comment suggested that the agency allow 30 days for a response, with extensions for good cause. Another comment asked whether an applicant needs to resubmit an application that it files over protest and suggested that references to "automatic filing" are inconsistent with the requirement that the applicant initiate a conference to file an application over protest.

FDA does not believe a change in the final rule to provide for filing an application in less than 60 days would have any practical effect. As noted above, an earlier filing date would not affect the deadline for issuance of an action letter, which remains 180 days after initial receipt of the application. Moreover, because FDA's time to prepare a notice of opportunity for a hearing (following a not approvable letter, when requested by the applicant) is to be the same as the time for filing the application, an earlier filing would limit the time, which is already short, for the agency to prepare the requisite notice of opportunity for hearing.

In response to comments, FDA has revised the procedures for filing over protest. Under the final rule, when FDA refuses to file an application, the applicant will have 30 days to decide whether to request an informal conference with agency officials (rather than 10 days, as provided in the proposal). The final rule also priovides that such an informal conference must be held before an application may be filed over protest. However, these changes also necessitate modifications of the "review clock" with respect to applications filed over protest, because an informal conference requested on the 30th day following a refusal to file would leave FDA only 90 days (30 days plus the 60 days before filing) in which both to hold the informal conference and complete the review of the application. Under the final rule, an application which the agency refuses to file will be considered received, for purposes of commencing the 180-day review period, on the date the informal conference is requested. This change is needed to ensure that FDA will have enough time to review any application that is subsequently filed over protest. Moreover, dating receipt from the date the applicant requests an informal conference will result in conferences being held promptly because the review period will already have commenced.

In response to one comment, the agency has modified the final rule to provide that an applicant need not resubmit a copy of the application when it is filed over protest.

FDA agrees with the last comment and has removed the reference to automatic filing of an application. Nevertheless, FDA believes that it is clear from the final rule that FDA will file a complete application in 60 days, and that even an incomplete application can be filed over protest (at a somewhat later point) if the applicant insists.

100. One comment suggested that the provision under which FDA can refuse to file an application that is incomplete should include the following phrase "other than case reports and other information not expressly required under this part." According to the comment, this change would clarify that the provisions in the regulations for the routine submission of less than all case report forms does not conflict with section 505(b)(1) of the act (21 U.S.C. 355(b)(1)), which requires "full reports of investigations."

FDA believes that the additional wording suggested by the comment is unnecessary. The comment erroneously assumes that only submission of all case report forms satisfies the full reports requirements of the statute. As discussed above, however, case report forms are simply one way in which data from a clinical study can be presented. The final rule requires applicants to submit a combination of summaries, analyses, tabulations, and case report forms, with additional case reports available upon request. These materials satisfy the "full reports" requirements of the act, regardless of whether all case reports are submitted.

101. One comment asked for clarification of the provision under which FDA will refuse to file an application if the drug product that is the subject of the submission is already covered by an approved application. The comment suggested that this should prohibit only an applicant who holds an approved application from filing another application for the same product. The comment stated that the provision should not apply to another applicant filing an application for the drug product.

This provision will permit FDA to refuse to review spurious applications. For example, FDA publishes an "Approved Drug Products List" that identifies applicants who hold approved applications, but this list does not identify distributors. Because some State regulatory officials rely upon the list as an index to legal marketers of drugs, distributors may seek applications for products they already distribute in their own names. FDA's review of such an application would require a commitment of resources, but

would not affect the marketing status of the drug under Federal law. Distributors that encounter problems with State procurement or other systems keyed to NDA status should resolve those problems by means that do not involve inappropriate and wasteful use of the NDA process.

Communications Between FDA and Applicants (§ 314.102)

102. Several comments agreed with the policies stated in the preamble to the proposal that open communication between FDA and applicants should be fostered and that FDA should promptly communicate with applicants about deficiencies or the need for additional data. These comments, however, urged that these policies be codified in the regulations in order to institutionalize them more formally.

FDA agrees with these comments and, to reflect its commitment to increasing and improving communication between the agency and applicants, has revised the final rule in the following ways.reviewing an application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. The final rule also requires communications to be appropriately documented, in accordance with § 10.65.

b. The final rule directs FDA reviewers to make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The final rule also provides that FDA will inform applicants promptly of its need for more data or information in the application or for technical changes in the application needed to facilitate the agency's review. This policy is designed to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. However, under the final rule, such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application by agency managers as well as the reviewing staff. Instead, these major scientific issues will ordinarily be addressed in an action letter.

c. The final rule contains a new provision for applicants to have an opportunity for an "end-of-review conference" with agency officials. This meeting would be held at the conclusion of FDA's review of an application, as designated by the issuance of an approvable or not approvable letter. The purpose of this type of meeting is to discuss what further steps need to be taken by the applicant before the application can be approved. This meeting will be available on all applications, with priority given to all applications for new chemical entities and major new indications for marketed drugs.

d. The final rule states that FDA will make every effort to grant requests for other meetings that involve important issues and that can be scheduled at mutually convenient times. This policy is designed to facilitate the free exchange of information between FDA and applicants. However, the final rule discourages "drop-in" visits (except for urgent matters, such as to discuss an important new safety issue) in order to minimize disruption of reviewers' work time.

FDA has revised its staff manual guide on communication between FDA and applicants to conform to the provisions of the final rule.

This expanded provision in the final rule embodies FDA's belief that there should be a continuing dialogue between FDA and applicants throughout the IND/NDA process. In the **Federal Register** of June 9, 1983 (48 FR 26720), FDA proposed revisions to the investigational new drug regulations (IND Rewrite). That proposal encourages all applicants to participate in "end-of-Phase 2" meetings in order to reach an agreement on the overall plan for Phase 3 clinical investigations and the objectives and designs of particular studies. That proposal further encourages applicants to participate in "pre-NDA" meetings in order to ensure that marketing applications present data in a manner suitable for efficient agency review. Moreover, this final rule, as did the proposal, provides for FDA to notify an applicant 60 days after receipt of the application about whether it is acceptable for filing, thus providing early feedback on the application. Finally, the final rule gives applicants a right to an informal meeting approximately 90 days into the review cycle on applications for all new chemical entities and major new indications for marketed drugs. FDA believes that these changes, when seen as a whole, will foster open and timely discussions between reviewers and applicants.

103. FDA also received several comments on the 90-day conference. These comments suggested that FDA extend 90-day conferences to include not only new chemical entities and major new indications, but also all other NDA's and major supplements, such as new dosage forms. In addition, believing the meeting would be held 90 days after filing, which would be 150 days after receipt of the application, one comment suggested that FDA should be prepared to make an intial determination of approvability at the meeting.

FDA has limited the right to a 90-day conference to new chemical entities and major new indications because these are the most complex applications and because the resources needed to extend this right to all drugs are not now available. The agency believes that the provisions described above for presubmission meetings, notice of filing, and early notice of easily correctible deficiencies will in most cases provide adequate feedback to applicants on less complex applications and supplements. However, as noted above, the agency will entertain requests by applicants for other meetings, and so a 90-day meeting could be requested on applications other than those provided in the final rule.

The agency has revised the final rule to clarify that the 90-day meeting will be held approximately 90 days after the agency receives the application (rather than 90 days after filing) and thus 90 days before the agency would be expected to provide an action letter on it. Because the meeting will be held only midway through the review process, FDA will rarely be able to give its views on the ultimate approvability of the application.

Dispute Resolution (§ 314.103)

104. FDA received a number of comments on the issue of dispute resolution. The proposal outlined a new appeals process which the agency implemented at the time of the proposal through a staff manual guide. Several comments suggested that the appeals process is too complex too address minor administrative and procedural disputes which could be resolved more easily and more promptly by an ombudsman. Several comments also felt that the appeals process is inadequate to resolve major scientific and medical policy disputes which, according to these comments, should be referred (as a matter of right) to one of the agency's standing advisory committees.

FDA is committed to resolving disputes with applicants in a prompt, amicable, and equitable way, and it was towards this end that the appeals process referred to above was implemented. In light of these

comments, however, together with the agency's newly articulated policy on communication with applicants, FDA has reevaluated the entire issue of dispute resolution and has revised this provision in the final rule in the following ways.

First, FDA agrees with the comments that an ombudsman should be designated to resolve administrative and procedural disputes, and the final rule has been so revised. The role of the ombudsman is to investigate what the facts are and to facilitate a timely and equitable resolution of the issue. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings, obtaining timely replies to inquiries, and obtaining timely completion of pending reviews. Further details on this procedure are available in a staff manual guide that is publicly available.

Second, upon reevaluation, FDA believes that the recently implemented appeals process is too complex to meet the needs of the NDA review period, and that the same goals can be achieved through alternative means. This conclusion is based in part on the fact that the appeals process was rarely used during its first year, possibly due to the inhibiting effects of the detailed procedure. The appeals process was conceived in response to industry complaints that "stalemates" were often reached with individual reviewers whereby applications could be delayed indefinitely without the involvement of upper lever FDA managers. In addition, applicants appear to perceive FDA as being unreceptive to attempts by applicants to resolve problems informally during the application review process. The new appeals process was designed to meet these concerns by legitimizing access to the system and by requiring automatic review by higher level agency managers. However, FDA believes that other specific provisions of the final rule meet these concerns, and thereby obviate the need for a formal appeals process.

For example, the time frame imposed for review of applications ensures that issues are raised in a timely fashion with upper level managers, including both division directors and the Directors of the Office of Drug Research and Review and the Office of Biologics Research and Review. Moreover, the "ninety-day conference" and "end-of-review conference," described above, provide a timely mechanism for applicants to meet with appropriate agency officials to discuss and resolve, if possible, important issues. For other scientific or medical disputes that arise during the NDA review process, the final rule provides that applicants should first discuss the matter directly with the responsible reviewing officials. If the issue is still unresolved, applicants may request an informal meeting with the appropriate reviewers and supervisors. Ordinarily, such meetings would be held first with the Division Director, then with the Office Director, and finally with the Center Director if the matter is still unresolved. As noted in the provision on communication between FDA and applicants FDA will make every effort to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

FDA recognizes the advantages of utilizing the advice of outside scientific experts in the dispute resolution process, where practical and feasible to do so. The final rule therefore provides that, in requesting a meeting with the agency to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other agency consultants, as designated by the agency. The applicant is also free to bring its own consultants. The final rule also provides that, for major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations. Although this section does not provide the "right" to advisory committee review requested by some comments, FDA does intend to integrate outside experts more fully into the drug approval process. FDA believes that providing applicants a right to advisory committee review for any disputed issue is impractical from the standpoint of the potential number of controversial issues and the relatively infrequent number of advisory committee meetings. Moreover, utilization of outside advisory committees is committed to the discretion of the agency, and not properly delegated to members of the public. Nonetheless, by involving individual advisory committee members or consultants in the dispute resolution process on a more informal basis, FDA believes that the goal of interacting with the scientific community can be achieved without the delays, resources, and scheduling problems associated with full advisory committee involvements. The role of outside experts in the drug approval process is discussed more fully in the next section of this preamble.

In sum, the dispute resolution procedures in the final rule center on utilizing the most appropriate mechanisms—be it the ombudsman, informal meetings with outside input, or referral to full advisory committees—to suit the needs of the particular matter under discussion. Thus, the final rule presents a more comprehensive approach to dispute resolution than did the proposal, and FDA believes these procedures will be useful in addressing the full range of issues that arise during the NDA review process.

In the **Federal Register** of October 19, 1982 (47 FR 46622, 46634), FDA announced that the appeals process would be implemented 30 days after publication, as detailed in a Staff Manual Guide (CDB 4820.5). That Staff Manual Guide extended the applicability of the new appeals process to the IND phase as well. However, in light of the factors discussed above, FDA is reevaluating the utility of that process in the IND phase also. The agency will announce the results of this reevaluation in the IND Rewrite final rule. In the interim, Staff Manual Guide CDB 4820.5 is suspended, pending that reevaluation, and sponsors should utilize the procedures set forth in § 314.103 of this final rule for disputes regarding IND's as well.

Role of Outside Experts

105. FDA received several comments relating to the role of outside experts in the new drug approval process. Several comments expressed disappointment that the proposal did not formally establish a role for outside experts in the routine review of applications. These comments, believing that involving outside experts would add to the credibility and quality of the decisionmaking process, urged that applicants be given a "right" to advisory committee review of any marketing application.

FDA agrees that the utilization of outside experts adds to the quality and credibility of the decisionmaking process, and FDA intends to improve utilization of experts from the scientific community during the new drug approval process. For example, FDA has centralized oversight of its human prescription drug advisory committees by establishing a separate office for this purpose within the Office of the Center Director of the Center for Drugs and Biologics. The agency has also begun, on a more regular basis, to include individual advisory committee members in meetings with applicants to discuss scientific issues. The advisory committee issue was not addressed in

the proposal because current regulations were seen as providing the necessary flexibility to accomplish these goals. However, in order to respond to comments, this preamble sets forth FDA's policy in this area.

FDA solicits advice from outside experts who serve as either members of advisory committees or as individual consultants. Fifteen standing public advisory committees provide FDA with advice on human prescription drugs. The committees correspond to the drug review groups in the six new drug evaluation divisions, and operate under charters subject to renewal (or cancellation) every 2 years, as required by the Federal Advisory Committee Act.

These advisory committees are also subject to FDA regulations (21 CFR 14.160–14.174), which provide for the committees to advise the Commissioner "generally" on the safety and effectiveness and regulatory control of human prescription drugs, and "specifically" on any particular matter before the agency, including whether the available information is adequate to support a determination that a particular drug meets the statutory standards for proof of safety and effectiveness necessary for marketing approval. High priority items include drugs subject to active IND's and pending NDA's that offer potential therapeutic advances, that pose significant safety hazards, that present narrow benefit/risk considerations, that have novel delivery systems or formulations, that are the subject of a major scientific or public controversy, or that are the subject of special regulatory requirements, such as a limitation on clinical trials, a patient followup requirement, postmarketing studies, or boxed warnings. In addition, applicants can ask to have any relevant matter brought before a full committee.

Advisory committees are used to bring outside experts into the new drug evaluation process in order to: (1) Supplement FDA's in-house expertise; and (2) help agency staff maintain familiarity with current state-of-the-art technology by fostering a close working relationship between FDA scientists and outside experts actively involved in the field. Advisory committee meetings also serve an important function by providing a public forum for discussion of issues.

Advisory committees review, at FDA request, certain critical studies or critical elements of studies on drug products under consideration and labeling issues. They respond to specific questions posed by the agency to identify the adequate and well-controlled studies which demonstrate effectiveness, the seriousness of certain adverse effects, and whether additional studies or data are necessary before a decision can be reached.

FDA also seeks outside advice on clinical research issues. For example, FDA developed approximately 25 clinical guidelines with the help of its advisory committees and others, including the American Academy of Pediatrics' Committee on Drugs and consultants to the Pharmaceutical Manufacturers Association. The guidelines contain generally accepted principles for reaching valid conclusions about the safety and effectiveness of drugs, and they contain views of recognized experts about appropriate methods for studying specific classes of drugs.

Individual advisory committee members have also become involved in the IND process by attending the "end-of-Phase 2" conference, where they aid in the planning of Phase 3 studies. This involvement is explicitly recognized in the IND Rewrite proposal (48 FR 26732).

In addition to advisory committee members, FDA also employs representatives from the scientific community as special consultants or expert reviewers. These persons are called upon for advice on technical matters on an ad hoc basis, or are asked to undertake special review assignments in areas where the agency staff may lack particular expertise or available resources. These consultants may also be present at advisory committee meetings.

In summary, FDA believes that the primary goal of the advisory committee (and outside consultant) system should be to help the agency make sound decisions based upon the reasoned application of good science, and the IND/NDA Rewrites reflect this goal. As noted earlier, the IND proposal provides for the inclusion of outside experts in "end-of-Phase 2" conferences during which the design of the major Phase 3 studies is planned. In addition, as described in the preceding section of this preamble, this final rule envisions the participation of outside experts in informal meetings to resolve scientific and medical disputes, and provides for the referral by FDA, if necessary, of major disputes to a full advisory committee.

The principal and perhaps only issue on which the agency disagrees with the comments is whether applicants should be permitted to utilize advisory committees on demand to review applications or resolve scientific disputes. FDA believes that only the agency is in a position to decide the relative importance of which issues advisory committees should consider. Whether to refer a particular marketing application or scientific dispute to an advisory committee is partly a resource issue given the limitations on time and scheduling that restrict the use of advisory committees, and partly a matter of judgment, based on whether FDA decides that the committee is needed to supplement the agency's internal expertise in evaluating the type of data under review. FDA believes strongly, however, that areas of legitimate scientific debate greatly benefit from the broader views that can be provided by an outside advisory committee, and that committee participation significantly enhances the scientific credibility of any decisions reached. Accordingly, FDA intends to make full use of its advisory committees to ensure that this result is achieved. As noted above, it is agency policy to include, as a priority for advisory committee review, marketing applications where the approval decision is a "close call," from either a safety or efficacy standpoint. This policy, together with an applicant's ability to request advisory committee review under § 14.172, should provide applicants adequate access to advisory committees while still allowing the agency to set reasonable priorities.

106. A number of comments addrressed the subject of conflict of interest. Several comments believed that current conflict-of-interest barriers prevent FDA from using many qualified outside experts and recommended that (1) FDA issue clear guidelines to resolve conflict-of-interest problems; (2) the Commissioner waive conflict of interest rules more often where a closer examination of the facts would show that the expert will be able to serve in an unbiased manner; and (3) FDA solicit a less restrictive interpretation of Federal conflict-of-interest statutes and regulations from the Department of Justice. Other comments expressed concern about FDA'a outside experts and asked for assurance that such advisors will be free of conflicts of interest.

FDA's procedures for employing outside experts appear in staff manual guides and in materials provided to outside experts who are employed to advise the agency. These procedures are designed to ensure that advisors' private interests do not conflict with their public responsibilities. Thus, FDA's guidelines with respect to conflict-of-interest issues are quite clear and widely disseminated. Where highly qualified persons are not free from nongovernmental or private financial interests that present a conflict or potential conflict, FDA may appoint

those individuals to serve on a particular committee but exclude them from participation in certain specific matters in which a real or potential conflict of interest exists. In addition, the Commissioner may waive FDA's conflict-of-interest rules in those instances where FDA is persuaded that an outside expert can, despite a conflict of interest, make an impartial and essential contribution to FDA's mission and strict application of the rules would frustrate the best interests of the public. Because of the high level of interest on this issue, however, FDA is reviewing its conflict-of-interest rules to ensure that a proper balance is struck between obtaining advice from those experts most knowledgeable in the field and ensuring that such advice is free from potential bias.

Approval of an Application (§ 314.105)

107. FDA received several comments concerning the proposed policy, stated in the preamble, that the agency would approve an application based on draft labeling if the only deficiencies found in the labeling were editorial or otherwise minor in nature. Two comments suggested that FDA codify this policy in the final rule. Another comment suggested that FDA should not approve an application on the basis of draft labeling, because of the importance of labeling during the introduction of a product into the market and the possibility that final printed labeling would not conform exactly to the approved draft labeling. One comment asked how the agency intends to determine whether appropriate changes have been made in final printed labeling after the agency has approved an application on the condition that deficiencies in draft labeling are corrected before marketing.

FDA has concluded that it should approve an application before submission of final labeling if the agency determines that only editorial or similar minor deficiencies exist in the draft labeling, and the final rule has been so revised. This change in practice should expedite drug approvals without compromising the safety or efficacy of drugs. As described elsewhere in this preamble, when FDA anticipates approving an application based on draft labeling, the agency will request a final safety update report under § 314.50(d)(5)(vii)(*b*) to ensure that the approval is based on the most up-to-date safety information available. When an application is approved under this provision, the approval letter will detail the specific changes required in the labeling and state that approval of the application is conditioned upon incorporating those changes exactly as directed. The approval letter will also require applicants to submit to FDA a copy of the final printed labeling prior to marketing. Although applicants will not have to wait for prior approval of the final printed labeling, this procedure will enable FDA to ensure that the final labeling conforms to the conditions of the approval.

108. One comment urged that FDA revise the final rule to state that approval of an application not be dependent upon the availability of the summary basis of approval.

FDA disagrees with this comment. An SBA is prepared for all original applications and supplemental applications for a new use or a substantially different dosage. The SBA is prepared by the supervisory medical officer (group leader) within the reviewing division and becomes part of the final approval recommendation forwarded to the Division Director and the Director of the Office of Research and Review or the Office of Biologics Research and Review. Because FDA supervisors may rely, in part, upon the SBA in determining whether to approve a drug, the agency believes that the SBA needs to be prepared before an application is approved. FDA notes, however, that approval of the application may be based on a draft SBA and precede completion of the final version of that document.

109. One comment, who agreed that FDA must exercise flexibility when applying approval standards to different kinds of drugs, argued that FDA must be even handed when applying the standards within a class of drugs.

FDA agrees generally that applications for similar drugs should be handled in the same manner. Nevertheless, applications for new members of an established class of drugs should take into account experience gained with that class, as FDA will take such information into account in making approval decisions. This may involve, for example, more detailed safety data if marketing experience with the class has revealed special safety concerns.

Foreign Data (§ 314.106)

110. FDA received a number of comments on the proposed provision setting forth conditions for approving an application based solely on foreign data. In the past, FDA's policy has been, with rare exceptions, to require some U.S. data (in the form of adequate and well-controlled studies) before approving a new drug for marketing. Nevertheless, while requiring the inclusion of U.S. data in applications, FDA has also relied increasingly upon foreign data in its approval decisions, consistent with the increasing quality and quantity of research performed in other countries. Based upon this experience with foreign data, the agency, like the medical community in general, has come to recognize the very high quality of drug testing that has emerged from a number of foreign research institutions.

The proposal built on this experience and sought to balance the ability to place increased reliance on foreign data with appropriate safeguard designed to ensure the quality of those data. The proposal removed the "presumption" in current policy that U.S. data would be required and replaced this with the principle that FDA's foremost consideration would be the quality of the data submitted, regardless of the country of origin. Thus, the proposal presupposed that some foreign studies are of comparable quality to U.S. data such that repeating the studies in this country would be neither scientifically necessary nor in the public interest.

At the same time, however, the proposal recognized that foreign data do present three unique problems not associated with domestic data. These involve (1) medical, genetic, and cultural differences between countries; (2) lack of FDA's familiarity with many foreign clinical investigators and facilities; and (3) FDA's inability to conduct on-site verification of many foreign studies. To meet these concerns, the proposal specified that three criteria must be met before the agency could approve a new drug based solely on foreign data. These three criteria were (1) that the foreign data were applicable to the U.S. population and U.S. medical practice; (2) that the studies had been performed by clinical investigators of recognized competence; and (3) that the data could be considered valid without the need for an on-site inspection by FDA or, if FDA considered such an inspection to be necessary, that FDA would be able to validate the data through on-site inspection or other appropriate means.

Thus, the proposal was cast so as to convey both a more open attitude on the part of FDA to consider the merits of foreign data in their own right, but also to safeguard the public health by imposing rigorous criteria that must be met before approval based on those data could be granted. In this way, the proposal sought to focus attention on the scientific merit of the data rather than on unnecessarily rigid rules regarding domestic data requirements.

111. The major concern raised by comments was the possibility that FDA's proposed policy could result in

lower quality drugs being approved based on foreign studies. For example, one comment suggested that foreign studies may not meet U.S. standards because foreign research is less concerned with peer review and institutional review boards, features less vigorous controls and lower reporting of adverse drug experiences, and, unlike studies in this country, is not publicly reviewed in the current U.S. medical literature. Several comments believed that the policy should be drafted more narrowly so as to apply only to major medical breakthroughs. Opponents of the foreign data policy also cited the recommendation of the Commission on the Federal Drug Approval Process that suggested that some U.S. clincial experience be required before approving a new drug in this country.

FDA has reviewed these comments in detail, but has concluded that the arguments raised do not warrant any change in the proposed regulation. The essence of the comments was a concern that the three safeguards would be insufficient to ensure the quality of drugs approved solely on the basis of foreign data. FDA does not believe that this concern is valid. The criteria contained in the regulation are rigorous, and the agency intends to apply them with the utmost regard for the public health. The rationale for these criteria is discussed at length in the preamble to the proposed regulation (47 FR 46643–46644; October 19, 1982). The agency believes that if the foreign data are applicable to the U.S. population and U.S. medical practice, if the studies are performed by recognized, competent investigators, and if there are no concerns over the validity of the data, then there is no justifiable public health reason not to approve the drug on the basis of the data. In this regard, the agency notes that comments did not suggest inclusion of additional safeguards that, in their minds, would ensure the quality of a drug based solely on foreign data.

As noted in the preamble to the proposed regulations, the agency does agree with comments that the nature of the drug should be taken into account in applying this policy, and that drugs representing major medical breakthroughs would be among those at the upper end of the spectrum. Other drugs falling into this category would be those for diseases that are uncommon in the United States (e.g., tropical diseases and orphan drugs), and drugs on which decisionmaking is less difficult from a risk-benefit point of view (e.g., topical products). However, the agency does not believe that the policy should be applied exclusively to these types of drugs; rather, any drug meeting the criteria should be included.

Finally, FDA does not agree with the recommendation of the Commission on the Federal Drug Approval Process that at least some U.S. experience with a drug be required before it is approved for marketing in this country. Under the Commission's recommendation, such U.S. experience could be in the form of uncontrolled trials where clinicians administer the drug to patients in settings closely resembling normal clinical practice. The agency believes that the Commission's emphasis on uncontrolled trials in this context is misplaced. First, as described above, FDA believes that the three criteria in the regulation adequately ensure the safety and effectiveness of new drugs prior to marketing and that, in those situations, uncontrolled trials would not add significantly to the body of data supporting approval. Second, when the regulation's criteria are not met, FDA does not believe that the mere inclusion of U.S. experience in the form of an uncontrolled trial would be sufficient to meet the test for marketing approval. (See 47 FR 46644.)

112. Several comments supported FDA's proposal to accept foreign data as the sole basis for approval of an application because it recognizes the international nature of clinical research and brings FDA into line with other countries that accept data based exclusively on scientific merit. Some comments, however, suggested that because FDA has inadequate resources and funding to monitor the validity of foreign research and to make on-site inspections, FDA should require more extensive documentation of foreign studies than of domestic studies, including the submission of all case report forms from each foreign study.

FDA agrees that foreign studies forming the sole basis for approval may require more extensive documentation than domestic studies, but the agency believes that the regulations are already flexible enough to accommodate this need. As discussed elsewhere in this preamble, the provisions for submission of summaries, analyses, data tabulations, and certain case report forms should be adequate for FDA's initial review of foreign clinical studies, and FDA will have additional access to data and information, including case report forms, if these are needed. In addition, as noted above, FDA may request full case reports from the most critical studies, and this would include foreign studies as well.

113. Several comments argued generally that the proposed policy was too restrictive. The only specific comments on this point concerned FDA's intention to consider the international reputation, publication experience, participation in meetings, and other factors relating to the competence of foreign investigators. One comment found these tests to be inappropriate, arguing that they are not applied to domestic investigators. Another comment that agreed with the standards urged that FDA establish a mechanism for collecting biographical information to assess the competence of foreign investigators so that individual applicants did not have to.

As noted above, FDA believes that the regulation's three criteria, including the requirement for the clinical investigators to be of recognized competence, are necessary to safeguard the safety and effectiveness of any drugs so approved. Although the review of clinical investigators' competence is highlighted in the foreign data policy, that review is not unique to foreign studies. FDA reviews the qualifications of all clinical investigators, but such a review is more easily conducted with respect to domestic investigators because FDA is generally familiar with them and their institutions. Indeed, FDA has refused to rely on data compiled by domestic investigators who are found to be unreliable. A review of the competence of foreign investigators is therefore also necessary, and FDA believes it appropriate to require the applicant to submit the necessary documentation. FDA believes that this approach will be more practical and efficient than relying on an FDA-compiled biographical library of foreign clinical investigators, which may be incomplete, out-of-date, or otherwise insufficient.

114. Two comments objected to the foreign data policy because it may encourage applicants to conduct more testing abroad. According to these comments, such "export of testing" would have adverse consequences for the United States both economically and scientifically.

Although FDA recognizes there is some merit in the concerns raised by these comments, the agency does not believe it justifiable to impose domestic testing requirements solely for trade restriction purposes, particularly when such requirements might produce an adverse effect on the public health through the delay of approval of new drugs. Moreover, FDA believes that there are two factors mitigating against the concerns raised by these comments.

First, in the IND Rewrite, the agency has proposed to give sponsors greater freedom to conduct the early phases of clinical research, in part due to complaints that U.S. regulatory requirements are too strict and are causing U.S. companies to conduct more and more research abroad. Thus, the purported incentive for moving research abroad is being addressed. Second, as discussed in the preamble to the NDA Rewrite proposal, the agency believes that even with the new foreign data policy, most applications will continue to contain some U.S. data. This is due, in part, to the high quality of U.S. clinical investigators as well as to the view that having some domestic physicians familiar with a new drug once it is approved enhances its prospects in the marketplace.

115.–116. One comment asked that FDA hold a presubmission meeting at which an applicant can present to FDA its proposal to rely upon foreign data. Another comment suggested that the agency's appeals process should be available to applicants if FDA refuses to accept foreign data, and that FDA should raise issues regarding the quality or acceptability of foreign data before the relevant standing advisory committee.

The final regulation, like the proposal, specifically encourages applicants to meet with the agency to discuss their plans to submit applications that rely solely upon foreign data. It should be understood, however, that the adequacy of the data cannot always be assessed prior to a detailed review, and the review can occur only after the application is submitted. The dispute resolution procedures described in the final rule would be applicable to foreign data issues, and this would include referral of those issues, at FDA's option, to an advisory committee.

117. Several comments argued that FDA should be required to accept foreign data unless the agency can demonstrate that the data should not be accepted for some valid scientific or medical reason. These comments also urged that the final rule require FDA to explain in writing its refusal to accept foreign data to ensure that duplicative domestic studies would not be required except for good reason.

FDA disagrees with these comments to the extent that they suggest that the burden of proof should be on the agency to show why foreign data are inadequate. Rather, the final rule, like the proposal, places the burden on the applicant to demonstrate to the agency's satisfaction that the foreign data are sufficient, by themselves, for approval. The agency emphasizes that there are no hidden criteria for evaluating the acceptability of foreign data. FDA will approve an application that relies upon foreign data unless one of the grounds identified in the statute or regulations for refusing to approve an application applies. If the agency concludes that the application is not approvable, it will give the applicant the basis for the conclusion in a deficiency letter or a not approvable letter and, if the applicant wishes, in a notice of opportunity for hearing. Thus, a mechanism already exists under which FDA will explain to the applicant, in writing, its reasons for refusing to approve an application based solely on foreign data.

Approvable and Not Approvable Letters (§§ 314.110 and 314.120)

118. One comment understood an approvable letter to mean that, except for matters specifically identified in it, the information already submitted in the application is acceptable and will not be further reviewed, and, except for safety update reports, no more information will be required before approval. Another comment suggested that an applicant's unconditional agreement to comply with conditions in an approvable letter should be sufficient for the agency to approve the application immediately, and that no extension of the review period or additional submission should be needed.

FDA agrees that an approvable letter means that FDA, at the time the letter issues, intends to approve the application if the applicant submits the requested data or information. Nevertheless, the issuance of an approvable letter does not preclude FDA from reexamining any part of the application in light of the applicant's response to the letter, or any other data or information before the agency bearing on the application. Although applicants have long argued that FDA should not re-review parts of an application that it has once determined are acceptable (and FDA agrees that in most cases another review is unwarranted), the agency considers all parts of an application to market a new drug to be interrelated, so that a change in one part may affect other parts of the application. Thus, FDA will continue to consider the impact of new submissions on other sections of the application. With respect to the second comment, except in the situation where the only changes to be made are editorial or affect minor aspects of the draft labeling, FDA believes that responses to approvable letters must be reviewed by FDA prior to final approval of the application because the information submitted could affect the safety or effectiveness of the drug.

119. Several comments argued that 10 days is inadequate time for an applicant to respond to an approvable or not approvable letter and that an applicant should have at least 30 days from the date of receipt of the letter, with an opportunity for extensions of time for good cause. According to these comments, in many cases the applicant must gather a number of experts in several disciplines together to consider FDA's letter, recommend a course of action to management, and obtain a management decision on it.

FDA does not believe that the 10-day period for a response to an approvable or not approvable letter will necessarily be insufficient for applicants to determine whether they will seek to amend an application, or request that the agency issue a notice of opportunity for hearing. In some cases, applicants may have enough information regarding the status of their applications prior to receipt of the action letter to know whether anticipated deficiencies are amenable to remedial action by the firm, or whether they are so great as to require pursuit of an administrative hearing. More importantly, however, the primary purpose in revising this section of the regulations was to provide for agency action within the 180-day time frame specified by the act. In meeting its obligations to reach a decision within the statutory period, the agency has undertaken to observe strict time limits in the review of new drug applications. As meeting the statutory period will necessitate industry responses to agency action, reasonably strict time limits are appropriately applied to industry as well.

Nonetheless, the agency recognizes that in many cases applicants may find 10 days inadequate to respond to an approvable or not approvable letter. For example, the applicant may wish to delay such a decision until after it has had an opportunity to meet with FDA officials in an "end-of-review conference," as provided in § 314.102(d). Thus, FDA has amended the regulations to permit applicants to respond by agreeing to an extension of the approval time, as provided under section 505(c) of the act. Moreover, the regulation makes clear that FDA will honor any reasonable request for such an extension. The 10-day provision, therefore, should not create any undue hardship on applicants. This resolution of the issue presented by the comments accommodates both the comments' concern and the agency's need to adhere to the 180-day period provided for by

statute. The agency considered shortening the time necessary to prepare a notice of opportunity for hearing to accommodate a longer period for an applicant's response to an action letter, but has determined that it is impracticable to shorten the period in which a notice of opportunity for hearing can be prepared to less than 50 days.

120. Several comments objected to the automatic 45-day extension of the review period when an applicant decides to file an amendment in response to an approvable letter. Two comments suggested a provision permitting extensions of "up to" 45 days, while two other comments suggested that 30 days is appropriate. Another comment suggested that the agency should advise the applicant in writing about what the time will be, but that it should be no more than 45 days.

FDA selected 45 days as the maximum time for FDA action on the applicant's response to an approvable letter because it believes it will generally take that long to review the applicant's response, prepare an approval letter recommendation, and issue the approval. If that process is completed sooner, the approval letter will issue in less than 45 days. The agency believes, however, that a significant number of applications would fail to meet the 30-day time period suggested by the comments and, thus, the agency has not adopted it. In addition, FDA believes that the requested change would distract reviews from evaluating the submission by requiring them to decide on a feasible extension shorter than 45 days, and thus would be more likely to disrupt the review process than to benefit applicants.

Refusal To Approve an Application (§ 314.125)

121. Noting that the first six reasons for refusing to approve an application rephrase the statutory grounds in section 505(d) of the act, one comment argued that the agency failed to assert a legal basis for the remaining eight reasons and that, accordingly, those eight reasons should be deleted.

FDA does not agree. The agency views each of the grounds stated to be within the scope of section 505(d) of the act. Each of the grounds asserted, both those stated explicitly in section 505(d) of the act and those not, reflect FDA's authority to prohibit marketing of drug products that do not comply with regulatory standards that marketed drugs be safe, effective, and properly labeled. FDA would view as unreasonable a requirement that, for a ground not specifically listed in section 505(d) of the act but included in § 314.125, it must approve such a product and immediately take action against it under some other section of the act. Rather, FDA views it as a reasonable exercise of its rulemaking authority to include within the reasons for refusing to approve an application under section 505(d) of the act reasons consistent with the agency's authority to establish marketing requirements for, or withdraw approval of, new drugs. Moreover, FDA believes that the list of additional grounds in the regulations will give applicants more specific notice of the kinds of grounds on which the agency will refuse to approve applications.

122. One comment objected to FDA removing the characteristics of an adequate and well-controlled study from this part of the current regulation, fearing that it suggested a predisposition of FDA not to involve qualified experts in the evaluation of clinical investigations to determine whether substantial evidence of effectiveness exists.

FDA disagrees and concludes that changing the location in the regulation of the provision in question will have no substantive effect on the agency's refusal to approve an application for a lack of substantial evidence of effectiveness, nor will it affect the role of experts in the review process. The regulation retains almost verbatim the grounds cited in the act for refusal to approve an application because of a lack of substantial evidence of effectiveness. The discussion of the characteristics of adequate and well-controlled studies, although placed in a separate section and somewhat revised in language, is still comprehensive in nature and can be cited by the agency in any decision not to approve an application.

123. One comment urged FDA to exempt minor deviations in proposed labeling when determining whether it complies with the requirements for labels and labeling in 21 CFR Part 201. Other comments objected to the suggestion that bioavailability or bioequivalence data are intended to show that a drug is safe or effective, while one comment asked FDA to retain the wording from the current rule under which approval may be refused if the data in the application do not meet the requirements in 21 CFR Part 320. One comment stated that it is unnecessary to include the provision for refusal to approve an application if a deficiency noted in a refusal-to-file letter had not been corrected. Finally, one comment objected to FDA's assertion that it can refuse to approve an application if the applicant does not permit an FDA investigator to inspect the facilities, controls, and any records relevant to the application. The comment contended that that provision goes well beyond FDA's inspectional authority in section 704(a) of the act (21 U.S.C. 374(a)).

Although FDA has reaffirmed its policy to approve an application if editorial or similar minor changes in draft labeling will be made in the final printed labeling, FDA cannot sanction deviations from the standards in Part 201 that would cause the drug to be misbranded. The agency agrees that the current wording under which FDA may refuse to approve an application if bioavailability and bioequivalence data do not meet the requirements in Part 320 is more informative than the proposed wording and the agency has revised the regulation to retain it. Because an applicant can file an incomplete application over protest, FDA sees a need to retain the provision permitting the agency to refuse to approve an incomplete application. Finally, FDA is obligated to refuse to approve an application if it believes (in the absence of an inspection that would demonstrate otherwise) that the facilities and controls are inadequate or the information in the application based on records holds by the applicant is insufficient to determine that the drug is safe or effective. An inspection under this provision derives from section 505 of the act and the result of an inspection refusal is the possibility that the agency will not have adequate information to approve the application. The agency notes that although it has suggested it would refuse to consider a particular study if records of the study could not be inspected, it does not take the position that it will reject an entire application solely because a part of the records could not be inspected (so long as they were not considered essential to the approval).

Adequate and Well-Controlled Studies (§ 314.126)

124. Several comments objected to FDA's statement that the characteristics set forth in its regulations are recognized by the scientific community as the "essentials" of an adequate and well-controlled study. Comments suggested that the listed characteristics do not uniquely define such a study. A study may, according to comments, include an additional characteristic or lack one or more of the listed characteristics and still be adequate and well-controlled. For example, one comment suggested that the characteristics of an adequate

and well-controlled study should include an explanation of the difference between the study's objectives and its results so that deviations from the original objectives can be justified, while other comments urged that the characteristics should not include the method of selection of subjects, the method of assigning subjects to treatment groups, the measures taken to minimize bias on the part of analysts of the data, the method of assessment of subjects' responses, or an assessment of a study's ability to detect more than a "clinically significant" difference between treatments. Another comment suggested that study characteristics should appear in a guideline instead of a regulation. That change, according to the comment, would recognize that appropriate alternative characteristics exist, and would provide clinical investigators and sponsors with flexibility to adopt them without first obtaining a waiver.

FDA has long considered the characteristics listed in the regulation as the essentials of an adequate and well-controlled study, and the proposal modified these characteristics only slightly. In general, the regulation on adequate and well-controlled studies has two overall objectives: (1) To allow the agency to assess methods for minimizing bias; and (2) to assure a sufficiently detailed description of the study to allow scientific assessment and interpretation of it. Many of the characteristics identified in the regulation are relevant to the second objective (rather than the first, as implied by the comments) and are needed by the agency to conduct a proper review of the study. Thus, FDA is not persuaded that these types of changes in the regulation are now warranted. The agency emphasizes, however, that it applies the regulation with judgment, not as a check-list. A scientifically acceptable study is not rejected because of minor technical deficiencies if it is apparent that the study is basically sound. Moreover, the regulation permits applicants to seek a waiver of individual requirements with respect to investigations.

125. Several comments were concerned that the agency's reordering of the types of controls that may be applied in a study was intended to establish a preferential order for the types of studies supporting an application. One comment said that because the proposal listed placebo concurrent control first, it implied that such a study is preferred over, for instance, a study using a historical control that was listed last. Several comments objected to this implied preferential order of studies because it would encourage researchers to adopt one type of study over another based on FDA's views, instead of considerations about the treatment of patients. These comments recommended that the final rule should clearly state that no study method is preferred over another.

Although the final rule lists the types of controlled studies in a different order than in the current regulation, the reordering does not mean that FDA considers one type of control to be necessarily preferred over another. The reordering is intended simply to reflect FDA's experience that some types of studies (e.g., placebo-controlled studies) are often easier to interpret than other kinds of studies (e.g., those using a historical control). Thus, FDA has listed the types of controls in descending order roughly in accordance with the ease of interpretation. (For this reason, the dose-comparison concurrent control has been moved to second on this list, rather than fourth.) FDA recognizes, however, that ethical and practical considerations will play a central role in the type of study selected, a decision that will ordinarily depend upon the type and seriousness of the disease being treated, availability of alternative therapies, and the nature of the drug and the patient population. In each case, applicants must choose the particular type of study they will use based on ethical, scientific, and practical reasons. So long as these judgments are justifiable, and the studies are properly designed, the approvability of an application will not be affected. Thus, the regulation lists five different kinds of controls that are acceptable; it does not state a perference for one kind over another.

126. Two comments suggested that the final rule distinguished between therapeutic and diagnostic new drugs in determining the appropriate features of an adequate and well-controlled study of the drug. For example, according to thes comments, a placebo concurrent control study would neve be indicated for diagnostic products, such as radiopharmaceutical and contrast media that are intended to have no physiological or therapeutic effect. One comment suggested that current regulations be modified to recognized more clearly this distinction.

FDA agrees that there are good reasons for using different study designs in particular situations, and the agency believes that the regulation is sufficiently flexible to accommodate the needs of applicants in this respect. As a matter of past practice, the agency has approved products whose safety and effectiveness were established using each of the controls listed in the regulation. However, because of the many situations involved, the agency believes it is neither necessary nor feasible to describe them specifically in the regulation.

127. One comment urged that the standard for obtaining a waiver from the adequate and well-controlled study criteria should be changed to require a statement of why a particular criterion need not be applied to the particular clinical investigation "in view of other factors," instead of a statement of why the criteria are not "reasonably applicable."

FDA disagrees with the comment and has retained the current wording in the final rule. The act states that adequate and well-controlled studies are needed to demonstrate the effectiveness of drug products. The agency's regulation describing the characteristics of adequate and well-controlled studies, which is modified only slightly in this final rule, has served satisfactorily as a basis for approvals over time and, as discussed above, contains the essential elements of such studies. Thus FDA concludes that a narrow waiver provision that requires well-justified bases for an exemption should be retained.

128. FDA has, on its own initiative, made the following changes in the final rule describing adequate and well-controlled studies.

First, FDA proposed to delete the current requirement that the method of analysis be included in the plan or protocol of a study. The rationale for this proposed change was that, although having the method of analysis in the plan or protocol has been listed as a characteristic of an adequate and well-controlled study, many protocols, especially those developed years ago, lacked this characteristic. While FDA does not believe the omission of this information means a study is not well-controlled, there is no doubt that the development of a tentative plan for analysis: (a) Minimizes the potential for analyst bias; and (b) helps focus attention on whether it is practical to collect the data and whether variables to be obtained are analyzable. Accordingly, the final rule encourages inclusion of such a plan for analysis in the protocol but permits, as an alternative, the study report to include a description of how the analysis was selected.

Second, at a number of points the regulation has been modified to address potential problems associated with multiple or interim data analyses. These

do not render a study less than well-controlled, but they must be described and reflected in the analysis.

Finally, FDA has modified the description of the active treatment concurrent control. This is because a demonstration of effectiveness by means of showing similarity of the test drug to an active control is an indirect demonstration of effectiveness (the active control treatment serving as an intermediary in a comparison between the test drug and placebo). Under this study design, similarity of test drug and active control drug can mean either that both drugs were effective or that neither was effective. Thus, the agency has added a requirement that the analysis of the study provide an explanation of why the active control drug should be considered to have been effective in the completed study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

Withdrawal of Approval of an Application (§ 314.150)

129. One comment suggested that the final rule provide that if FDA found a study to be adequate and well-controlled when it approved the application, that conclusion should remain unchanged even if FDA later adopted new standards under which the study would not be considered adequate and well-controlled. The conclusion would thus preclude withdrawal of the drug's approval upon the basis of new information and an FDA determination that there is a lack of substantial evidence from adequate and well-controlled investigations that the drug is effective.

FDA disagrees with the comment. The factors leading to a determination of what is an adequate and well-controlled study, which is the basis for determining drug efficacy, may, as the comment recognizes, evolve. FDA has an obligation to judge a drug's effectiveness by contemporary scientific standards. If those standards change to the extent that it is questionable whether a drug can be regarded as having been shown to be effective, FDA may under the act appropriately review the drug's status.

Adulteration and Misbranding of an Approved Drug (§ 314.170)

130. One comment supported FDA's proposed clarification of the relationship between the new drug and antibiotic approval provisions of the act and the adulteration and misbranding provisions. In contrast, several comments urged that this section be deleted, believing that the only lawful procedure for dealing with adulterated or misbranded approved new drugs is by withdrawal of approval of the application.

FDA has retained this provision in the final rule. The comments that opposed it submitted no persuasive argument that FDA is incorrect in its position that the new drug provisions do not insulate approved drugs and antibiotics from the general adulteration and misbranding provisions of the act. As FDA has previously noted, the statutory scheme contemplates FDA's application of the adulteration and misbranding standards to all drugs, irrespective of whether those drugs have been subject to the premarket approval requirements of the act.

Hearing Procedures for New Drugs (Subpart D)

131. FDA agrees with one comment that objected to a change in the hearing procedure to remove the requirement that the Director of the Center for Drugs and Biologics serve a proposed order to, and provide for a response from, a person who submits required data or information and requests a hearing following a general or specific notice of an opportunity for hearing. The final rule retains the current requirement.

Administrative Procedures For Antibiotics (Subpart E)

132. One comment suggested that the procedure for issuing antibiotic regulations should be revised to make it as consistent as possible with the approval procedure for new drugs and to expedite the petitioning, rulemaking, and hearing process required under section 507(f) of the act (21 U.S.C. 357(f)) when FDA refuses to approve a new antibiotic.

FDA believes it has already taken adequate steps to conform the administrative procedures that apply to refusals to approve (or withdrawals of approval of) antibiotics and new drugs. The procedures for withdrawing approval of an NDA apply to approved antibiotics (which are now all exempt from certification requirements under § 433.1 (21 CFR 433.1)). A full discussion of the regulatory process applicable to antibiotic drugs maybe found in the final rule exempting antibiotic drugs from certification (47 FR 39155; September 7, 1982) and in the proposed rule preceding that action (47 FR 19954; May 7, 1982). Because the potential exists for a manufacturer to apply voluntarily for batch certification of an antibiotic drug or for FDA to revoke the exemption from batch certification requirements granted to a drug, this final rule retains those provisions necessary for certification of an antibiotic drug, if necessary. In the case of refusals to approve an antibiotic application, while the statutorily based regulatory scheme for the publication of monographs has been retained, the procedures preceding the refusal to approve are, as a practical matter, the same as those employed in a refusal to approve a nonantibiotic application.

Miscellaneous Provisions

133. *Imports § 314.410(a).* Although several comments supported the agency's proposal to permit an individual to bring into the United States a reasonable quantity of an unapproved drug product that is intended only for personal use, several comments argued that the proposal was illegal and would expand illegal trade in unapproved drugs in this country. These comments were especially concerned about what they believed would constitute FDA's sanctioning of the commercialization of drugs generally regarded by the medical community as being useless. One comment suggested that legislation would be needed to make this change. Another comment suggested that FDA would find it difficult to monitor and regulate this exemption.

The proposal was intended to state the agency's discretionary enforcement policy that it can apply to accommodate the health needs of individuals entering the United States with personal supplies of unapproved drugs. Upon reevaluation, however, FDA finds that policy related to enforcement discretion is better stated in a compliance policy guide. Accordingly, this provision has been deleted from the final rule.

134. *Exports (§ 314.410(b)).* One comment suggested that FDA seek legislative changes to permit the export of new drug substances and products under the same conditions that apply to the export of antibiotics. Others suggested that, even without legislation, FDA could permit the export of unapproved drug products and of bulk substances which are not covered by an approved application for a drug product. Another comment stated that the current restrictions on exports of unapproved new drugs discourage the manufacture of human drugs in the United States before approval for marketing in this country. According to this comment, because U.S. approval often occurs after foreign approval, these restrictions require that foreign facilities be built to supply foreign markets, resulting in a significant loss of domestic jobs.

Although FDA recognizes the practical impact of current restrictions on the export of unapproved new drug products and bulk new drug substances,

FDA believes that it is obligated to reject the comments recommending changes in the final rule. The definition of "interstate commerce" in section 201(b)(1) of the act (21 U.S.C. 321(b)(1)), when read together with the prohibitions on interstate shipment of unapproved new drugs in sections 301(d) and 505(a) (21 U.S.C. 331(d) and 355(a)), prohibit the exportation of an unapproved new drug. Section 801(d) of the act (21 U.S.C. 381(d)), which grants an exemption from the adulteration and misbranding sections of the act for export purposes, does not grant a similar exemption from the new drug provisions. Therefore, FDA has interpreted the act as reflecting a Congressional intent that unapproved new drugs not be exported, though it has, in the past, supported modification of the statutory export provisions (see, for example, proposed section 135 of the Drug Regulation Reform Act of 1978).

135. One comment, believing that the exporter of a drug substance might have no relationship with the domestic marketer of an approved product, expressed concern that the proposal to broaden the rules on exporting a drug substance could result in exports of a drug substance unsuitable for use in an approved product. Thus, the comment recommended that that provision be limited to manufacturers of approved drug products or exporters of bulk substances that have filed drug master files with the agency covering the manufacturing operations and specifications for the drug substance. Another comment suggested that this proposal was inconsistent with § 201.122(c) of FDA's labeling regulations.

Because FDA believes the first comment misunderstood this provision, the agency has revised the final rule to clarify it. The statutory scheme provides that a new drug substance can be exported only if it is the subject of an approved application. Through this new regulation, FDA is interpreting the application approval to extend to a supplier of a new drug substance under that approved application. Currently, only the applicant who holds the approved application may export the drug substance that is used in the manufacture of the approved drug product, whether or not the applicant is itself the manufacturer of the drug substance. The final rule extends to the person (and only to that person or persons) who is identified in an approved application as the source of the drug substance, but is not itself the applicant, permission to export the drug substance, if the substance meets the specifications in the approved application. Thus, FDA will consider the supplier to be covered by the application both when it ships the drug substance to the applicant and when it exports it. Domestic shipment to a party not the applicant, however, will not be permitted.

FDA does not believe this regulatory change will present the safety concerns raised by the comment because FDA will have already conducted a thorough examination of the drug substance, either in the original application or in a supplement.

However, because the drug substance manufacturer's opportunity to export the substance is dependent upon its inclusion in an approved application, it is also dependent on the applicant's continued inclusion as a supplier in its application. The applicant is always free to supplement its application to change suppliers. Such action, under the final rule, would also have the effect of terminating the former supplier's export rights. Moreover, because no approval has been provided to suppliers under the act, FDA does not view the hearing requirement of section 505 of the act to apply to a drug substance supplier who is so terminated by an applicant.

In response to the second comment, FDA does not agree that the filing of a drug master file should be sufficient to acquire a right to export a drug substance. FDA does not review a drug master file except in the context of the agency's review of an application or supplement that references it. Thus, the submission of a drug master file does not now result in any agency action. FDA does not intend to revise this practice by reviewing drug master files independently. Resource constraints on FDA and the lack of a drug product and proper labeling by which to measure the suitability of the drug substance for any purpose warrant maintaining the current practice. Finally, FDA has revised § 201.122(a) to clarify that a drug substance may be exported under the labeling exemption provided by that section, if it is covered by an approved application.

136. *Drug master files (§ 314.420).* Several comments objected to the proposed requirement that a drug master file holder notify each person authorized to refer to information if the holder adds, changes, or deletes the information. Some comments stated that drug master file holders generally give umbrella authorization to others for use of their master files and that the regulations are unclear about how specific a notification must be made to persons authorized to reference information when the holder adds, changes, or deletes information in the file. Thus, according to these comments, the provision is unnecessarily burdensome and could result in the unwarranted disclosure of trade secrets.

FDA has retained the provision in the final rule. FDA believes that applications that depend upon information in drug master files may quickly become outdated if the drug master file holder does not notify the persons authorized to reference the file about changes in the information in it. Because FDA reviews the contents of a drug master file only in the context of its review of an application or a supplement to an application, a change in important information in a drug master file that may affect the safety and effectiveness of a drug product is not likely to be reviewed unless the owner of the master file notifies the applicant who, in turn, submits a supplement to incorporate the change in its approved application. Recognizing that one of the primary functions of the drug master file system is to maintain the confidentiality of trade secret information, FDA agrees that a file holder's notification about changes in the file does not have to be so specific that the confidentiality of information in the file is compromised.

137. One comment asked whether the requirement that the drug master file contain a complete list of persons currently authorized to reference it can be met by individual letters whenever a person is authorized or an authorization is revoked.

FDA notes that some drug master files are voluminous and subject to substantial amendments over time. Thus, it may be impossible to determine from individual letters submitted at different times the person who is currently authorized to reference a file. For that reason, FDA believes that a single list of persons currently authorized to reference the file should be maintained.

138. One comment urged that the changes in the regulation on drug master files should apply only to information added to the master file after the date of publication of the final rule. Another comment urged that the changes apply only to applications submitted after the effective date which incorporate a drug master file reference.

FDA believes that a uniform effective date for changes in the regulation on drug master files is necessary. Applying the regulations only to information added to a file after publication of the final rule, or applications submitted after the effective date of the final rule,

would lead to continual confusion about what part of the file is subject to the rule.

139. *Designated journals (§ 310.9).* One comment objected to FDA removing its list of designated journals from the regulations. The comment urged FDA to retain a list of journals that are available to it and waive requirements for submission or reprints and summaries of reports in those journals.

As discussed elsewhere in this preamble, FDA does not believe it to be a wise expenditure of its resources to retrieve copies of referenced journals from its library, given the minimal burden on applicants to submit relevant copies. FDA notes that the change is more likely to expedite rather than delay review of applications. In addition to removing § 310.9, FDA also is deleting the references to § 310.9 that appear in 21 CFR 510.3(1) and 510.95.

140. *Public information (§ 314.430).* One comment contended that FDA's classification of what constitutes confidential safety and effectiveness data in an application is overbroad and that, instead, the agency should require the applicant to index confidential records within its application in a manner similar to the procedure in § 20.53 (21 CFR 20.53) of FDA's public information regultions. If a person requests a copy of a record the applicant considers confidential, the applicant's reasons for considering it confidential could be forwarded to the requestor, who may then ask the agency to determine whether the record is disclosable.

FDA does not agree with this comment. An applicant is required to itemize and index its records under § 20.53 only in a legal action contesting an FDA denial of a request for records because they are exempt from public disclosure as a trade secret or confidential commercial or financial data and information. The agency believes that the comment's suggestion that this procedure be established absent litigation, and before FDA makes an initial determination about the status of a document, would impose a significant burden on applicants to index large numbers of records whose confidential status will never be disputed. It would also add to FDA's already heavy workload in responding to freedom of information requests by requiring the agency to provide the requestor with a preliminary response detailing the applicant's reasons for considering a record nondisclosable.

141. In § 314.430(f) of the proposal, FDA proposed to modify § 314.14(f) of the current regulations in identifying the situations in which safety and effectiveness data and information are available for public disclosure. Consideration of that proposal, as it relates to disclosure rules for drugs submitted under section 505(b) of the act, was rendered moot, however, by section 104 of the Drug Price Competition and Patent Term Restoration Act of 1984, enacted on September 24, 1984, because the new law itself provides when data and information in such submissions are publicly disclosable. Accordingly, FDA has conformed this final rule (§ 314.430(f)) to be consistent with section 104 of the new law.

In doing so, FDA calls attention to one specific point. Section 314.14(f)(5) of the current regulations provides that safety and effectiveness data and information are publicly disclosable when a final determination has been made that the drug may be approved without the submission of such data and information. In the past, "final determination" (for drugs approved under section 505) was interpreted to require publication of a final **Federal Register** notice under the Drug Efficacy Study Implementation (DESI) program. Under the new law, however, this provision means such data and information are publicly disclosable as soon as an abbreviated application under section 505(j) of the act for the product can be made effective, and that point in time will be identifiable through the list pubished monthly in accordance with section 505(j)(6) of the act.

For applications submitted under sections 505(j), 506, and 507 of the act, FDA has added § 314.430(f)(6) which states that safety and effectiveness data and information will be publicly disclosable when FDA sends an approval letter to the applicant. To prevent redundancy, FDA had deleted proposed § 314.430(e)(1) for the final rule.

142. *Waivers (§ 314.90).* One comment suggested that FDA not issue a final provision permitting it to waive requirements for the submission of information in an application. This comment feared that the waiver provision would permit applicants to market new products without having to submit adequate clinical information and other data about its safety and efficacy.

FDA believes this comment misunderstands the scope of the waiver provision, which is intended to give applicants the flexibility to seek alternative ways of complying with the regulatory requirements for drug approval. FDA is unable, and does not view the provision as authorizing it, to waive statutory requirements.

143. *Other changes.* On its own initiative, FDA has revised the final rule to retain current requirements, described below, that were inadvertently omitted from the proposal in the sections concerning contents of an application (§ 314.50), refusal to file an application (§ 314.101(d)), refusal to approve an application (§ 314.125), and/or withdrawal of approval of an application (§ 314.150).

First, the final rule provides that an application must contain reports of all investigations of the drug sponsored by the applicant, and all other information pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. To correspond to this requirement, the final rule also provides that FDA may refuse to approve (or withdraw approval of) an application if it does not explain the omission of a report of any investigation of a drug sponsored by the applicant, or the omission of other information pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. Although the proposal contained a requirement that the applicant submit all information pertinent to the evaluation of the application, it did not clearly require an applicant to submit reports of all the studies it sponsors nor did it provide for FDA to refuse to file or approve, or to withdraw approval of, an application that omits required reports or an explanation of the omission (all of which are current requirements).

Second, the final rule underscores the importance of conducting clinical investigations involving human subjects in compliance with the institutional review board regulations in Part 56 and the informed consent regulations in Part 50. In this regard, the final rule provides that the application must contain a statement for each clinical study subject to those regulations that the study was conducted in compliance with them. The agency may refuse to file an application, under the final rule, if the requisite statement is not provided. Also under the final rule, FDA may refuse to approve (or withdraw approval of) an application if the noncompliance results in the rights or safety of human subjects not being adequately protected. These requirements were added to the current regulations in the **Federal Register** of January 27, 1981 (46 FR 8942, 8954), but they were inadvertently omitted from the proposal. The language used in the final rule constitutes a minor change from current regulations to clarify that FDA would not refuse to approve (or withdraw approval of) an application

because of minor technical deviations from these regulations not affecting the rights of safety of human subjects. For purposes of consistency, FDA is also revising § 312.1(d)(11) to conform the provision respecting termination of an IND to the language used in this final rule.

Similarly, the final rule, like the current regulations and the proposal, underscores the importance of conducting nonclinical laboratory studies in compliance with the good laboratory practice regulations in Part 58. The language in the final rule has been revised to state that for each nonclinical study not conducted in compliance with these regulations, the application must contain a brief statement of the reason for the noncompliance (rather than a detailed description of all differences between the practices used in the study and those in the regulations). The language used in the final rule reflects advice that FDA has been providing to applicants with respect to interpretation of the current regulatory provision. The section on refusing to file an application has been conformed accordingly. For purposes of consistency, FDA is also revising the following sections of Title 21 of the Code of Federal Regulations with respect to applications submitted to FDA for research or marketing permits where the submission includes the results of nonclinical laboratory studies subject to Part 58, in order to conform those sections to the language used in this final rule: §§ 71.1, 71.6, 170.35, 171.1, 171.6, 180.1, 312.1, 330.10, 511.1, 514.1, 514.8, 514.15, 514.110, 570.35, 571.1, 571.6, 602.1, 812.27, 1003.31, 1010.4, and 1010.5.

Finally, also with respect to compliance with Part 58, the final rule, like the proposal, provides that FDA may refuse to approve an application if the nature of the noncompliance does not support the validity of the study. This language is intended to clarify that FDA would not refuse to approve an application because of minor technical deviations from these regulations. The final rule also contains a parallel provision in the section on withdrawal of approval, which was inadvertently omitted from the proposal. For purposes of consistency, FDA is also revising §§ 312.1(d)(12), 514.111(a)(11), and 514.115(b)(4) to conform these provisions governing investigational new drug and new animal drug applications to the language used in this final rule.

List of Subjects

21 CFR Part 71

Administrative practice and procedure, Color additive certification, Color additive petitions, Color additives, Cosmetics, Drugs.

21 CFR Part 170

Administrative practice and procedure, Definitions, Food additives, Food additive safety.

21 CFR Part 171

Administrative practice and procedure, Food additive petitions, Food additives.

21 CFR Part 180

Food additives, Interim listed food additives.

21 CFR Part 201

Drugs, Labeling.

21 CFR Part 310

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

21 CFR Part 312

Drugs, Medical research.

21 CFR Part 314

Administrative practice and procedure, Drugs.

21 CFR Part 330

Over-the-counter drugs.

21 CFR Part 430

Administrative practice and procedure, Antibiotics.

21 CFR Part 431

Administrative practice and procedure, Antibiotics.

21 CFR Part 433

Antibiotics, Labeling.

21 CFR Part 510

Administrative practice and procedure, Animal drugs, Labeling, Reporting requirements.

21 CFR Part 511

Animal drugs, Medical research.

21 CFR Part 514

Administrative practice and procedure, Animal drugs.

21 CFR Part 570

Animal feeds, Animal foods, Food additives.

21 CFR Part 571

Administrative practice and procedure, Animal feeds, Animal foods, Food additives.

21 CFR Part 601

Biologics.

21 CFR Part 812

Health records, Investigational device exemptions, Medical devices, Medical device research, Reporting requiements.

21 CFR Part 1003

Administrative practice and procedure, Defects, Electronic products, Noncompliance, Radiation protection.

21 CFR Part 1010

Administrative practice and procedure, Electronic products, Exemptions, Exports, Radiation protection, Standards, Variances.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 409, 501, 502, 503, 505, 506, 507, 512–516, 520, 701, 706, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 82 Stat. 343–351, 90 Stat. 540–560 (21 U.S.C. 348, 351, 352, 353, 355, 356, 357, 360b–360f, 371, 376)) and the Public Health Service Act (secs. 215, 301, 351, 354–360f, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 241, 262, 263b–263n)) and under 21 CFR 5.11, Parts 71, 170, 171, 180, 201, 310, 312, 314, 430, 431, 433, 510, 511, 514, 570, 601, 812, 1003, and 1010 are amended as follows:

PART 71—COLOR ADDITIVE PETITIONS

1. Part 71 is amended:

a. In § 71.1 by revising paragraph (g), to read as follows:

§ 71.1 Petitions.

* * * * *

(g) If nonclinical laboratory studies are involved, petitions filed with the Commissioner under section 706(b) of the act shall include with respect to each nonclinical study contained in the petition, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

b. In § 71.6 by revising the third sentence of paragraph (b), to read as follows:

§ 71.6 Extension of time for studying petitions; substantive amendments; withdrawal of petitions without prejudice.

* * * * *

(b) * * * If nonclinical laboratory studies are involved, additional information and data submitted in

support of filed petitions shall include, with respect to each nonclinical laboratory study contained in the petition, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. * * *

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PART 170—FOOD ADDITIVES

2. Part 170 is amended in § 170.35 by revising paragraph (c)(1)(vi), to read as follows:

§ 170.35 Affirmation of generally recognized as safe (GRAS) status.

* * * * *

(c) * * *

(1) * * *

(vi) If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

PART 171—FOOD ADDITIVE PETITIONS

3. Part 171 is amended:

a. In § 171.1 by revising paragraph (k), to read as follows:

§ 171.1 Petitions.

* * * * *

(k) If nonclinical laboratory studies are involved, petitions filed with the Commissioner under section 409(b) of the act shall include, with respect to each nonclinical study contained in the petition, either a statement that the study has been, or will be, conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

b. By revising § 171.6, to read as follows:

§ 171.6 Amendment of petition.

After a petition has been filed, the petitioner may submit additional information or data in support thereof. In such cases, if the Commissioner determines that the additional information or data amount to a substantive amendment, the petition as amended will be given a new filing date, and the time limitation will begin to run anew. Where the substantive amendment proposes a substantial change to any petition that may affect the quality of the human environment, the petitioner is required to submit an environmental analysis report pursuant to § 25.1 of this chapter. If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

PART 180—FOOD ADDITIVES PERMITTED IN FOOD ON AN INTERIM BASIS OR IN CONTACT WITH FOOD PENDING ADDITIONAL STUDY

4. Part 180 is amended in § 180.1 by revising paragraph (c)(4), to read as follows:

§ 180.1 General.

* * * * *

(c) * * *

(4) If nonclinical laboratory studies are involved, studies filed with the Commissioner shall include, with respect to each study, either a statement that the study has been or will be conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, or, if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

PART 201—LABELING

5. Part 201 is amended in § 201.122 by revising paragraph (a), to read as follows:

§ 201.122 Drugs for processing, repacking, or manufacturing.

* * * * *

(a) An approved new drug application or new animal drug application covers the production and delivery of the drug substance to the application holder by persons named in the application, and, for a new drug substance, the export of it by such persons under § 314.410 of this chapter; or

* * * * *

PART 310—NEW DRUGS

6. Part 310 is amended:

§ 310.3 [Amended]

a. In § 310.3 *Definitions and interpretations* by removing and reserving paragraph (m).

§ 310.9 [Removed]

b. By removing § 310.9 *Designated journals.*

§ 310.300 [Removed]

c. By removing § 310.300 *Records and reports concerning experience on drugs for which an approval is in effect.*

§ 310.301 [Removed]

d. By removing § 310.301 *Reporting of adverse drug experiences.*

§ 310.302 [Removed]

e. By removing § 310.302 *Records and reports on new drugs and antibiotics for use by man for which applications or certification forms 5 and 6 became effective or were approved prior to June 20, 1963.*

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

7. Part 312 is amended:

a. In § 312.1 by revising item 16 in Form FD–1571 in paragraph (a)(2) and by revising paragraph (d) (11) and (12), to read as follows:

§ 312.1 Conditions for exemption of new drugs for investigational use.

(a) * * *

(2) * * *

Form FD–1571 * * *

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

(d) * * *

(11) Any clinical investigation involving human subjects, subject to the institutional review board regulations in Part 56 of this chapter or informed consent regulations in Part 50 of this chapter, is not being conducted in compliance with those regulations such that the rights or safety of human subjects are not adequately protected; or

(12) Any nonclinical laboratory study that is described in the notice of claimed investigational exemption and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter and no reason for the

noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study; or

* * * * *

b. In § 312.20 by revising paragraph (c), to read as follows:

§ 312.20 Clinical data generated outside the United States and not subject to a "Notice of Claimed Investigational Exemption for a New Drug."

* * * * *

(c) Data from studies performed outside the United States and conducted in accordance with the requirements of this section may be utilized without duplication of the studies in the United States, as appropriate.

* * * * *

8. By revising Part 314 to read as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

Subpart A—General Provisions

Subpart B—Applications

Subpart C—FDA Action on Applications

Subpart D—Hearing Procedures for New Drugs

Subpart E—Administrative Procedures for Antibiotics

Subpart F—Miscellaneous Provisions

Authority: Secs. 409, 501, 502, 503, 505, 506, 507, 512–516, 520, 701, 706, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 stat. 463 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 82 Stat. 343–351, 90 Stat. 540–560 (21 U.S.C. 351, 352, 353, 355, 356, 357, 360b–360f, 371, 376); sec. 215, 301, 351, 354–360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 241, 262, 263b–263n).

Subpart A—General Provisions

§ 314.1 Scope of this part.

(a) This part sets forth procedures and requirements for the submission to, and the review by, the Food and Drug Administration fo applications and abbreviated applications, as well as amendments, supplements, and postmarketing reports to them, by persons seeking or holding approval from FDA of the following:

(1) An application under section 505 of the Federal Food, Drug, and Cosmetic Act to market a new drug.

(2) An application under section 507 of the Federal Food, Drug, and Cosmetic Act to market an antibiotic drug.

(b) This part does not apply to drug products subject to licensing by FDA under the Public Health Service Act (58 Stat. 632 as amended (42 U.S.C. 201 et seq.)) and Subchapter F of Chapter I of Title 21 of the Code of Federal Regulations.

(c) References in this part to regulations in the Code of Federal Regulations are to Chapter I of Title 21, unless otherwise noted.

§ 314.2 Purpose.

The purpose of this part is to establish an efficient and thorough drug review process in order to: (a) Facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective. These regulations are also intended to establish and effective system for FDA's surveillance of marketed drugs. These regulations shall be construed in light of these objectives.

§ 314.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

"Act" means the Federal Food, Drug, and Cosmetic Act (sections 201–901, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301–392)).

"Applicant" means any person who submits an application or abbreviated application or an amendment or supplement to them under this part to obtain Food and Drug Administration approval of a new drug or an antibiotic drug and any person who owns an approved application.

"Application" means both the application described under § 314.50 and the abbreviated application under § 314.55, including all amendments and supplements.

"Approvable letter" means a written communication to an applicant from FDA stating that the agency will approve the application if specific additional information or material is submitted or specific conditions are met. An approvable letter does not constitute approval of any part of an application and does not permit marketing of the drug that is the subject of the application.

"Approval letter" means a written communication to an applicant from FDA approving an application. An approval letter permits marketing of the drug product that is the subject of the application.

"Drug product" means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

"Drug substance" means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

"FDA" means the Food and Drug Administration.

"Not approvable letter" means a written communication to an applicant

from FDA stating that the agency does not consider the application approvable because one or more deficiencies in the application preclude the agency from approving it.

Subpart B—Applications

§ 314.50 Content and format of an application.

Applications, including abbreviated applications, and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Two copies of the application are required, an archival copy and a review copy. An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling. Other applications will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an application for a duplicate of a marketed drug product (such as a "paper NDA," which relies primarily on published literature to provide substantial evidence of effectiveness and adequate scientific evidence of safety for the claimed indications), an abbreviated application, an amendment, and a supplement. The application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. The Food and Drug Administration will maintain guidelines on the format and content of applications to assist applicants in their preparation.

(a) *Application form.* The applicant shall submit a completed and signed application form that contains the following:

(1) The name and address of the applicant; the date of the application; the application number if previously issued (for example, if the application is a resubmission, an amendment, or a supplement); the name of the drug product, including its established, proprietary, code, and chemical names; the dosage form and strength; the route of administration; the identification numbers of all investigational new drug applications that are referenced in the application; the identification numbers of all drug master files and other applications under this part that are referenced in the application; and the drug product's proposed indications for use.

(2) A statement whether the submission is an original submission, a resubmission, an abbreviated application under § 314.55, or a supplement to an application under § 314.70.

(3) A statement whether the applicant proposes to market the drug product as a prescription or an over-the-counter product.

(4) A check-list identifying what enclosures required under this section the applicant is submitting.

(5) The applicant, or the applicant's attorney, agent, or other authorized official shall sign the application. If the person signing the application does not reside or have a place of business within the United States, the application is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(b) *Index.* The archival copy of the application is required to contain a comprehensive index by volume number and page number to the summary under paragraph (c) of this section, the technical sections under paragraph (d) of this section, and the supporting information under paragraph (f) of this section.

(c) *Summary.* (1) An application is required to contain a summary of the application in enough detail that the reader may gain a good general understanding of the data and information in the application, including an understanding of the quantitative aspects of the data. The summary is not required for abbreviated applications under § 314.55 and supplements under § 314.70. Resubmissions of an application should contain an updated summary, as appropriate. The summary should discuss all aspects of the application, and synthesize the information into a well-structured and unified document. The summary should be written at approximately the level of detail required for publication in, and meet the editorial standards generally applied by, refereed scientific and medical journals. In addition to the agency personnel reviewing the summary in the context of their review of the application, FDA may furnish the summary to FDA advisory committee members and agency officials whose duties require an understanding of the application. To the extent possible, data in the summary should be presented in tabular and graphic forms. FDA has prepared a guideline under § 10.90(b) that provides information about how to prepare a summary. The summary required under this paragraph may be used by FDA or the applicant to prepare the Summary Basis of Approval document for public disclosure (under § 314.430(e)(2)(ii)) when the application is approved.

(2) The summary is required to contain the following information:

(i) The proposed text of the labeling for the drug, with annotations to the information in the summary and technical sections of the application that support the inclusion of each statement in the labeling, and, if the application is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57.

(ii) A statement identifying the pharmacologic class of the drug and a discussion of the scientific rationale for the drug, its intended use, and the potential clinical benefits of the drug product.

(iii) A brief description of the marketing history, if any, of the drug outside the United States, including a list of the countries in which the drug has been marketed, a list of any countries in which the drug has been withdrawn from marketing for any reason related to safety or effectiveness, and a list of countries in which applications for marketing are pending. The description is required to describe both marketing by the applicant and, if known, the marketing history of other persons.

(iv) A summary of the chemistry, manufacturing, and controls section of the application.

(v) A summary of the nonclinical pharmacology and toxicology section of the application.

(vi) A summary of the human pharmacokinetics and bioavailability section of the application.

(vii) A summary of the microbiology section of the application (for anti-infective drugs only).

(viii) A summary of the clinical data section of the application, including the results of statistical analyses of the clinical trials.

(ix) A concluding discussion that presents the benefit and risk considerations related to the drug, including a discussion of any proposed additional studies or surveillance the applicant intends to conduct postmarketing.

(d) *Technical sections.* The application is required to contain the technical sections described below. Each technical section is required to contain data and information in sufficient detail to permit the agency to

make a knowledgeable judgment about whether to approve the application or whether grounds exist under section 505(d) or 507 of the act to refuse to approve the application. The required technical sections are as follows:

(1) *Chemistry, manufacturing, and controls section.* A section describing the composition, manufacture, and specification of the drug substance and the drug product, including the following:

(i) *Drug substance.* A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, specifications relating to stability, sterility, particle size, and crystalline form. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(ii) *Drug product.* A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product); and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; the name and address of each manufacturer the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including, for example, specifications relating to sterility, dissolution rate, containers and closure systems; and stability data with proposed expiration dating. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(iii) *Environmental impact analysis report.* An environmental impact analysis report under § 25.1 analyzing the environmental impact of the manufacturing process and the ultimate use of the drug product.

(iv) The applicant may, at its option, submit a complete chemistry, manufacturing, and controls section 90 to 120 days before the anticipated submission of the remainder of the application. FDA will review such early submissions as resources permit.

(2) *Nonclinical pharmacology and toxicology section.* A section describing, with the aid of graphs and tables, the nonclinical laboratory studies with the drug, including the following:

(i) Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.

(iii) Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.

(v) For each nonclinical laboratory study a statement that it was conducted in compliance with the good laboratory practice regulations in Part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(3) *Human pharmacokinetics and bioavailability section.* A section describing the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the submission of in vivo bioavailability data under Subpart B of Part 320, including the following:

(i) A description of each of the bioavailability and pharmacokinetic studies of the drug in humans performed by or on behalf of the applicant that includes a description of the analytical and statistical methods used in each study and a statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in Part 50.

(ii) If the application describes in the chemistry, manufacturing, and controls section specifications or analytical methods needed to assure the bioavailability of the drug product or drug substance, or both, a statement in this section of the rationale for establishing the specification or analytical methods, including data and information supporting the rationale.

(iii) A summarizing discussion and analysis of the pharmacokinetics and metabolism of the active ingredients and the bioavailability or bioequivalence, or both, of the drug product.

(4) *Microbiology section.* If the drug is an anti-infective drug, a section describing the microbiology data, including the following:

(i) A description of the biochemical basis of the drug's action on microbial physiology.

(ii) A description of the antimicrobial spectra of the drug, including results of in vitro preclinical studies to demonstrate concentrations of the drug required for effective use.

(iii) A description of any known mechanisms of resistance to the drug, including results of any known epidemiologic studies to demonstrate prevalence of resistance factors.

(iv) A description of clinical microbiology laboratory methods (for example, in vitro sensitivity discs) needed for effective use of the drug.

(5) *Clinical data section.* A section describing the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

(iii) A description of each uncontrolled clinical study, a summary of the results, and a brief statement explaining why the study is classified as uncontrolled.

(iv) A description and analysis of any other data or information relevant to an

evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended, and modifications for specific subgroups (for example, pediatrics, geriatrics, patients with renal failure).

(vi) A summary and updates of safety information, as follows:

(*a*) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (a)(5)(ii) of this section.

(*b*) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(*a*) of this section. In addition, the reports are required to include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant shall submit these reports (*1*) 4 months after the initial submission; (*2*) following receipt of an approvable letter; and (*3*) at other times as requested by FDA. Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

(vii) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

(ix) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in Part 50.

(6) *Statistical section.* A section describing the statistical evaluation of clinical data, including the following:

(i) A copy of the information submitted under paragraph (d)(5)(ii) of this section concerning the description and analyses of each controlled clinical study, and the documentation and supporting statistical analysis used in evaluating the controlled clinical studies.

(ii) A copy of the information submitted under paragraph (d)(5)(vi)(*a*) of this section concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

(e) *Samples and labeling.* (1) Upon request from FDA, the applicant shall submit the samples described below to the places identified in the agency's request. FDA will generally ask applicants to submit samples directly to two or more agency laboratories that will perform all necessary tests on the samples and validate the applicant's analytical methods.

(i) Four representative samples of the following, each sample in sufficient quantity to permit FDA to perform three times each test described in the application to determine whether the drug substance and the drug product meet the specifications given in the application:

(*a*) The drug product proposed for marketing;

(*b*) The drug substance used in the drug product from which the samples of the drug product were taken; and

(*c*) Reference standards and blanks (except that reference standards recognized in an official compendium need not be submitted).

(ii) Samples of the finished market package, if requested by FDA.

(2) The applicant shall submit the following in the archival copy of the application:

(i) Three copies of the analytical methods and related descriptive information contained in the chemistry, manufacturing, and controls section under paragraph (d)(1) of this section for the drug substance and the drug product that are necessary for FDA's laboratories to perform all necessary tests on the samples and to validate the applicant's analytical methods. The related descriptive information includes a description of each sample; the proposed regulatory specifications for the drug; a detailed description of the methods of analysis; supporting data for accuracy, specificity, precision and ruggedness; and complete results of the applicant's tests on each sample.

(ii) Copies of the label and all labeling for the drug product (4 copies of draft labeling or 12 copies of final printed labeling).

(f) *Case report forms and tabulations.* The archival copy of the application is required to contain the following case report tabulations and case report forms:

(1) *Case report tabulations.* The application is required to contain tabulations of the data from each adequate and well-controlled study under § 314.126 (Phase 2 and Phase 3 studies as described in § 312.1(a)(2), Form FDA–1571), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in § 312.1(a)(2), Form FDA–1517), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the application. If such unforeseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the application, in

accordance with paragraph (f)(3) of this section.

(2) *Case report forms.* The application is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.

(3) *Additional data.* The applicant shall submit to FDA additional case report forms and tabulations needed to conduct a proper review of the application, as requested by the director of the FDA division responsible for reviewing the application. The applicant's failure to submit information requested by FDA within 30 days after receipt of the request may result in the agency viewing any eventual submission as a major amendment under § 314.60 and extending the review period as necessary. If desired by the applicant, the FDA division director will verify in writing any request for additional data that was made orally.

(4) Applicants are invited to meet with FDA before submitting an application to discuss the presentation and format of supporting information. If the applicant and FDA agree, the applicant may submit tabulations of patient data and case report forms in a form other than hard copy, for example, on microfiche or computer tapes.

(g) *Other.* The following general requirements apply to the submission of information within the summary under paragraph (c) of this section and within the technical sections under paragraph (d) of this section.

(1) The applicant ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously is required to identify the file by name, reference number, volume, and page number in the agency's records where the information can be found. A reference to information submitted to the agency by a person other than the applicant is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(2) The applicant shall submit an accurate and complete English translation of each part of the application that is not in English. The applicant shall submit a copy of each original literature publication for which an English translation is submitted.

(h) *Format of an original application.* (1) The applicant shall submit a complete archival copy of the application that contains the information required under paragraphs (a) through (f) of this section. FDA will maintain the archival copy during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application, to give other agency personnel access to the application for official business, and to maintain in one place a complete copy of the application. An applicant may submit on microfiche the portions of the archival copy of the application described in paragraphs (b) through (d) of this section. Information relating to samples and labeling, described in paragraph (e) of this section, is required to be submitted in hard copy. Tabulations of patient data and case report forms, described in paragraph (f) of this section, may be submitted on microfiche only if the applicant and FDA agree. If FDA agrees, the applicant may use another suitable microform system.

(2) The applicant shall submit a review copy of the application. Each of the technical sections (described in paragraph (d) (1) through (6) of this section) in the review copy is required to be separately bound with a copy of the application form required under paragraph (a) of this section and a copy of the summary required under paragraph (c) of this section. The applicant may obtain from FDA sufficient folders to bind the archival and review copies of the application.

§ 314.55 Abbreviated application.

(a) An abbreviated application is an application in which reports of nonclinical laboratory studies and reports of clinical investigations (except those pertaining to in vivo bioavailability of the drug product) may be omitted. The information may be omitted when the Food and Drug Administration has determined that the information already available to it is adequate to establish that a particular dosage form of a drug meets the statutory standards for safety and effectiveness. An abbreviated application will usually be reserved for duplicates of drug products previously approved under a full application under §314.50. An abbreviated application is not required to comply with the requirements in § 314.50 (c), (d)(2), (4), (5), (6), and (f).

(b) FDA will file an abbreviated application only if it has made a finding that an abbreviated application is suitable for a drug product. If FDA finds that a drug product may be approved for marketing on the basis of an abbreviated application, it will make that finding publicly available, as follows:

(1) If the finding applies to a broad category of drug products, the agency will amend § 314.56 to identify the category in that section.

(2) If the finding applies to a drug product because it is so closely related to a product for which an abbreviated application is suitable that the same conclusions about safety and effectiveness apply to it, the agency will make the finding public by updating its list of drug products for which abbreviated applications are suitable. The list is available from the National Technical Information Service, Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161.

(3) If the finding applies to duplicates of a drug product that is subject to FDA's Drug Efficacy Study Implementation program (a review of drug products approved as safe between 1938 and 1962), the agency will make that finding public through a notice published in the **Federal Register.**

(c)(1) A finding by FDA that an abbreviated application is suitable for a drug product applies only to a product that is the same in active ingredient, dosage form and strength, route of administration, and conditions of use as the drug product that was the subject of the finding. For drug product that is similar but different in one or more of these characteristics, an abbreviated application will be accepted only if FDA has made a separate finding of suitability. However, filing of an abbreviated application for a drug product does not signify that the product is safe and effective until the application is approved.

(2) A finding that a drug product is a new drug because it is similar to a product that is a new drug, and is therefore subject to the requirements of this part, does not include a finding that an abbreviated application is suitable for the similar product.

(3) A finding that a single-active-entity drug product is safe and effective and that an abbreviated application is suitable is not a basis for determining that a combination drug product containing that entity as one of its ingredients is either safe or effective or that an abbreviated application is suitable. The finding also is not a basis for determining that the combination drug product meets all of the requirements for combination drugs as described in § 300.50.

(d) (1) A person may seek a determination of the suitability of an abbreviated application for a product that the person believes is similar or related to a drug product that has been declared to be suitable for an abbreviated application. Extension of the finding that a drug product is safe and effective to another product will ordinarily be limited to other dosage forms for the same route of administration or to closely related ingredients. If preclinical or clinical evidence is needed to support the safety, or if clinical evidence is needed to support the effectiveness, of the proposed product, then an abbreviated application is not appropriate for the similar or related drug product.

(2) A person seeking a determination that an abbreviated application is suitable for a similar or related drug product shall use the petition procedures established in § 10.30. The petitioner shall set forth the reasons that justify extending the finding that an abbreviated application is suitable for one product to the similar or related product proposed to be marketed.

(3) An application submitted in the form of an abbreviated application for a drug product that has not been the subject of a finding that allows an abbreviated application for the product will be considered to be a petition under § 10.30 and will be processed as such.

(e) Each abbreviated application is required to contain a reference to FDA's finding that an abbreviated application is suitable for the specific product that is the subject of the application and to contain both an archival and a review copy of the application.

(1) The applicant shall submit a complete archival copy of the application that contains the information required under § 314.50 (a), (b), (d)(1) and (3), (e), and (g). An applicant may submit the archival copy of the application on microfiche or, if FDA agrees, another suitable microform system.

(2) The applicant shall submit a review copy that contains the technical sections described in § 314.50(d)(1) and (3). Each of the technical sections in the review copy is required to be separately bound with a copy of the application form required under § 314.50(a).

(3) The applicant may obtain from FDA sufficient folders to bind the archival and the review copies of the application.

§ 314.56 Drug products for which abbreviated applications are suitable.

Abbreviated applications are suitable for the following drugs within the limits set forth in § 314.55(c):

(a) Duplicates of drug products that were first approved before October 10, 1962, and reformulations of these products, if the original or reformulated product has been evaluated as part of the drug efficacy study and announced by notice in the **Federal Register** as effective for one or more indications, and if the Food and Drug Administration has made a finding that an abbreviated application is suitable.

(b) [Reserved]

(c) Drug products that are very closely related to a product described in paragraph (a) of this section and that are subject to a separate finding of suitability for marketing under an abbreviated application.

(d) Drug products that contain a chlorofluorocarbon determined to be an essential use and identified in § 2.125(h)(2) as suitable for an abbreviated application.

(e) Duplicates of an antibiotic drug for which FDA has approved an application.

§ 314.60 Amendments to an unapproved application.

The applicant may submit an amendment to an application that is filed under § 314.100, but not yet approved. The submission of a major amendment (for example, an amendment that contains significant new data from a previously unreported study or detailed new analyses of previously submitted data), whether on the applicant's own initiative or at the invitation of the agency, constitutes an agreement by the applicant under section 505(c) of the act to extend the date by which the agency is required to reach a decision on the application. Ordinarily, the agency will extend the review period for a major amendment but only for the time necessary to review the new information. However, the agency may not extend the review period more than 180 days. If the agency extends the review period for the application, the director of the division responsible for reviewing the application will notify the applicant of the length of the extension. The submission of an amendment that is not a major amendment will not extend the review period.

§ 314.65 Withdrawal by the applicant of an unapproved application.

An applicant may at any time withdraw an application that is not yet approved by notifying the Food and Drug Administration in writing. The agency will consider an applicant's failure to respond within 10 days to an approvable letter under § 314.110 or a not approvable letter under § 314.120 to be a request by the applicant to withdraw the application. A decision to withdraw the application is without prejudice to refiling. The agency will retain the application and will provide a copy to the applicant on request under the fee schedule in § 20.42 of FDA's public information regulations.

§ 314.70 Supplements and other changes to an approved application.

(a) *Changes to an approved application.* The applicant shall notify the Food and Drug Administration about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant shall notify FDA about it in a supplemental application under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the application under paragraph (d) of this section. Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant shall make a change provided for in those paragraphs (for example, the deletion of an ingredient common to many drug products) in accordance with a guideline, notice, or regulation published in the **Federal Register** that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report).

(b) *Supplements requiring FDA approval before the change is made.* An applicant shall submit a supplement, and obtain FDA approval of it, before making the changes listed below in the conditions in an approved application, unless the change is made to comply with an official compendium. An applicant may ask FDA to expedite its review of a supplement if a delay in making the change described in it would impose an extraordinary hardship on the applicant. Such a supplement and its mailing cover should be plainly marked: "Supplement—Expedited Review Requested."

(1) *Drug substance.* A change affecting the drug substance to accomplish any of the following:

(i) To relax the limits for a specification;

(ii) To establish a new regulatory analytical method;

(iii) To delete a specification or regulatory analytical method;

(iv) To change the synthesis of the drug substance, including a change in solvents and a change in the route of synthesis.

(v) To use a different facility or establishment to manufacture the drug substance, where: (*a*) the manufacturing process in the new facility or established differs materially from that in the former facility or establishment, or (*b*) the new facility or establishment has not received a satisfactory current good manufacturing practice (CGMP) inspection within the previous 2 years covering that manufacturing process.

(2) *Drug product.* A change affecting the drug product to accomplish any of the following:

(i) To add or delete an ingredient, or otherwise to change the composition of the drug product, other than deletion of an ingredient intended only to affect the color of the drug product;

(ii) To relax the limits for a specification;

(iii) To establish a new regulatory analytical method;

(iv) To delete a specification or regulatory analytical method;

(v) To change the method of manufacture of the drug product, including changing or relaxing an in-process control;

(vi) To use a different facility or establishment, including a different contract laboratory or labeler, to manufacture, process, or pack the drug product;

(vii) To change the container and closure system for the drug product (for example, glass to high density polyethylene (HDPE), or HDPE to polyvinyl chloride) or change a specification or regulatory analytical method for the container and closure system;

(viii) To change the size of the container, except for solid dosage forms, without a change in the container and closure system.

(ix) To extend the expiration date of the drug product based on data obtained under a new or revised stability testing protocol that has not been approved in the application.

(x) To establish a new procedure for reprocessing a batch of the drug product that fails to meet specifications.

(3) *Labeling.* Any change in labeling, except one described in paragraph (c)(2) or (d) of this section.

(c) *Supplements for changes that may be made before FDA approval.* An applicant shall submit a supplement at the time the applicant makes any kind of change listed below in the conditions in an approved application, unless the change is made to comply with an official compendium. A supplement under this paragraph is required to give a full explanation of the basis for the change, identify the date on which the change is made, and, if the change concerns labeling, include 12 copies of final printed labeling. The applicant shall promptly revise all promotional labeling and drug advertising to make it consistent with any change in the labeling. The supplement and its mailing cover should be plainly marked: "Special Supplement—Changes Being Effected."

(1) Adds a new specification or test method or changes in the methods, facilities (except a change to a new facility), or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess;

(2) Changes labeling to accomplish any of the following:

(i) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(ii) To add or strengthen a statement about drug abuse, dependence, or overdosage; or

(iii) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product.

(iv) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

(3) To use a different facility or establishment to manufacture the drug substance, where: (i) The manufacturing process in the new facility or establishment does not differ materially from that in the former facility or establishment, and (ii) the new facility or establishment has received a satisfactory current good manufacturing practice (CGMP) inspection within the previous 2 years covering that manufacturing process.

(d) *Changes described in the annual report.* An applicant shall not submit a supplement to make any change in the conditions in an approved application, unless otherwise required under paragraph (b) or (c) of this section, but shall describe the change in the next annual report required under § 314.81. Some examples of changes that can be described in the annual report are the following:

(1) Any change made to comply with an official compendium.

(2) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength or dosage form.

(3) An editorial or similar minor change in labeling.

(4) The deletion of an ingredient intended only to affect the color of the drug product.

(5) An extension of the expiration date based upon full shelf-life data obtained from a protocol approved in the application.

(6) A change within the container and closure system for the drug product (for example, a change from one high density polyethylene (HDPE) to another HDPE), except a change in container size for nonsolid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.

(7) The addition or deletion of an alternate analytical method.

(8) A change in the size of a container for a solid dosage form, without a change from one container and closure system to another.

§ 314.71 Procedures for submission of a supplement to an approved application.

(a) Only the applicant may submit a supplement to an application.

(b) All procedures and actions that apply to an application under § 314.50 and an abbreviated application under § 314.55 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change. A supplement is required to contain an archival copy and a review copy that include an application form and appropriate technical sections, samples, and labeling.

(c) All procedures and actions that apply to applications under this part, including actions by applicants and the Food and Drug Administration, also apply to supplements.

§ 314.72 Change in ownership of an application.

(a) An applicant may transfer ownership of its application. At the time of transfer the new and former owners are required to submit information to the Food and Drug Administration as follows:

(1) The former owner shall submit a letter or other document that states that all rights to the application have been transferred to the new owner.

(2) The new owner shall submit an application form signed by the new owner and a letter or other document containing the following:

(i) The new owner's commitment to agreements, promises, and conditions made by the former owner and contained in the application;

(ii) The date that the change is ownership is effective; and

(iii) Either a statement that the new owner has a complete copy of the approved application, including

supplements and records that are required to be kept under § 314.81, or a request for a copy of the application from FDA's files. FDA will provide a copy of the application to the new owner under the fee schedule in § 20.42 of FDA's public information regulations.

(b) The new owner shall advise FDA about any change in the conditions in the approved application under § 314.70, except the new owner may advise FDA in the next annual report about a change in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor.

§ 314.80 Postmarketing reporting of adverse drug experiences.

(a) *Definitions.* The following definitions of terms apply to this section:

"Adverse drug experience" means any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any significant failure of expected pharmacological action.

"Increased frequency" means an absolute increase in the number of reports of an adverse drug experience received during a specified time period compared to the number of similar adverse drug experience reports received during an equivalent time period in the past.

"Serious" means an adverse drug experience that is life threatening, is permanently disabling, requires inpatient hospitalization, or requires prescription drug therapy. In addition, an adverse drug experience with one of the following outcomes is always considered serious: death, congenital anomaly, cancer, or overdose.

"Unexpected" means an adverse drug experience that is not listed in the current labeling for the drug and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

(b) *Review of adverse drug experiences.* Each applicant having an approved application under § 314.50 or § 314.55 shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.

(c) *Reporting requirements.* The applicant shall report to FDA adverse drug experience information, as described in this section. The applicant shall submit two copies of each report described in this section to the Division of Drug and Biological Product Experience (HFN-70), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. FDA may waive the requirement for the second copy in appropriate instances.

(1) *Fifteen-day "Alert reports."* (i) The applicant shall report each adverse drug experience that is both serious and unexpected, regardless of source, as soon as possible but in any case within 15 working days of initial receipt of the information. These reports are required to be submitted on Form FDA-1639 (Drug Experience Report). The applicant shall promptly investigate all adverse drug experiences that are the subject of these 15-day Alert reports and shall submit followup reports within 15 working days of receipt of new information or as requested by FDA. If additional information is not obtainable, a followup report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained. These 15-day Alert reports and followups to them are required to be submitted under separate cover and may not be included, except for summary or tabular purposes, in a periodic report.

(ii) The applicant shall review periodically (at least as often as the periodic reporting cycle) the frequency of reports of adverse drug experiences that are both serious and expected, regardless of source, and report any significant increase in frequency as soon as possible but in any case within 15 working days of determining that a significant increase in frequency exists. Upon written notice, FDA may require that applicants review the frequency of reports of serious, expected adverse drug experiences at intervals different than the periodic reporting cycle. Reports of a significant increase in frequency are required to be submitted in narrative form (including the time period on which the increased frequency is based, the method of analysis, and the interpretation of the results), rather than using Form FDA-1639. Fifteen-day Alert reports based on increased frequency are required to be submitted under separate cover and may not be included, except for summary purposes, in a periodic report.

(iii) The requirements of paragraph (c)(1) (i) and (ii) of this section, concerning the submission of 15-day alert reports, shall also apply to any person (other than the applicant) whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor. However, in order to avoid unnecessary duplication in the submission to FDA, and followup to, reports required by paragraph (c)(1) (i) and (ii) of this section, obligations of a nonapplicant may be met by submission of all reports of serious adverse drug experiences to the applicant. If a nonapplicant elects to submit adverse drug experience reports to the applicant rather than to FDA, it shall submit each report to the applicant within 3 working days of its receipt by the nonapplicant, and the applicant shall then comply with the requirements of this section. Under this circumstance, the nonapplicant shall maintain a record of this action which shall include:

(*a*) A copy of the drug experience report.

(*b*) Date the report was received by the nonapplicant.

(*c*) Date the report was submitted to the applicant.

(*d*) Name and address of the applicant.

(iv) Each report submitted under this paragraph shall bear prominent identification as to its contents, i.e., "15-day Alert report" or "15-day Alert report—followup."

(2) *Periodic adverse drug experience reports.* (i) The applicant shall report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals. The applicant shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Upon written notice, FDA may extend or reestablish the requirement that an applicant submit quarterly reports, or require that the applicant submit reports under this section at different times than those stated. For example, the agency

may reestablish a quarterly reporting requirement following the approval of a major supplement. Followup information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report is required to contain: (*a*) a narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification number, adverse reaction term(s), and date of submission to FDA); (*b*) a Form FDA–1639 (Drug Experience Report) for each adverse drug experience not reported under paragraph (c)(1)(i) of this section (with an index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s); and (*c*) a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing clinical trials (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d) *Scientific literature.* (1) A 15-day Alert report based on information from the scientific literature is required to be accompanied by a copy of the published article. The 15-day reporting requirements in paragraph (c)(1)(i) of this section (i.e., serious, unexpected adverse drug experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial. The 15-day reporting requirements in paragraph (c)(1)(ii) of this section (i.e., a significant increase in frequency of a serious, expected adverse drug experience) apply only to reports found in scientific and medical journals either as the result of a formal clinical trial, or from epidemiologic studies or analyses of experience in a monitored series of patients.

(2) As with all reports submitted under paragraph (c)(1)(i) of this section, reports based on the scientific literature shall be submitted on Form FDA–1639 or comparable format as prescribed by paragraph (f) of this section. In cases where the applicant believes that preparing the Form FDA–1639 constitutes an undue hardship, the applicant may arrange with the Division of Drug and Biological Product Experience for an acceptable alternative reporting format.

(e) *Postmarketing epidemiological/surveillance studies.* Adverse drug experiences from postmarketing epidemiological/surveillance studies, except for 15-day Alert reports, may be submitted following the completion of the study in the next periodic report. (A study is considered completed 1 year after it is concluded.) The applicant shall separate and clearly mark reports of adverse drug experiences that occur during such a postmarketing study as being distinct from those experiences that are being reported spontaneously to the applicant. Applicants are encouraged to submit such reports utilizing an alternative format to Form FDA–1639, as provided in paragraph (f)(3) of this section.

(f) *Reporting Form FDA–1639.* (1) Except as provided in paragraphs (c)(1)(ii) and (f)(3) of this section, the applicant shall complete a Form FDA–1639 (Drug Experience Report) for each report of an adverse drug experience.

(2) Each completed Form FDA–1639 should refer only to an individual patient or a single attached publication.

(3) Instead of using Form FDA–1639, an applicant may use a computer-generated FDA–1639 or other alternative format (e.g., a computer-generated tape or tabular listing) provided that: (i) The content of the alternative format is equivalent in all elements of information to those specified in Form FDA–1639; and (ii) the format is agreed to in advance by the Division of Drug and Biological Experience (HFN–730).

(4) Single copies of Form FDA–1639 may be obtained from the Division of Drug and Biological Product Experience (HFN–730), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Supplies of Form FDA–1639 may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857.

(g) *Multiple reports.* An applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

(h) *Patient privacy.* An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code number to each report, preferably not more than eight characters in length. The applicant should include the name of the reporter from whom the information was received. Names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not resaleable to the public under FDA's public information regulations in Part 20.

(i) *Recordkeeping.* The applicant shall maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.

(j) *Guideline.* FDA has prepared under § 10.90(b) a guideline for the submission of reports of adverse drug experiences and suggested followup investigation of reports.

(k) *Withdrawal of approval.* If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(l) *Disclaimer.* A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect. For purposes of this provision, the term "applicant" also includes any person reporting under paragraph (c)(1)(iii) of this section.

§ 314.81 Other postmarketing reports.

(a) *Applicability.* Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and sections 505(j) and 507(g) of the act.

(b) *Reporting requirements.* The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

(1) *NDA—Field alert report.* The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility

involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: "NDA—Field Alert Report."

(i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.

(ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specifications established for it in the application.

(2) *Annual report.* The applicant shall submit the following information in the order listed each year within 60 days of the anniversary date of approval of the application. The applicant shall submit the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA-2252 (Transmittal of Periodic Reports for Drugs for Human Use) which may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857, and is required to include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval which ends on the anniversary date. The report is required to contain the following:

(i) *Summary.* A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of the new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study.

(ii) *Distribution data.* Information about the quantity of the drug product distributed under the approved application, including that distributed to distributors. The information is required to include the National Drug Code (NDC) number, the total number of dosage units of each strength or potency distributed (e.g., 100,000/5 milligram tablets, 50,000/10 milliliter vials), and the quantities distributed for domestic use and the quantities distributed for foreign use. Disclosure of financial or pricing data is not required.

(iii) *Labeling.* Currently used professional labeling, patient brochures or package inserts (if any), a representative sample of the package labels, and a summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

(iv) *Chemistry, manufacturing, and controls changes.* (*a*) Reports of experiences, investigations, studies, or tests involving chemical or physical properties, or any other properties of the drug (such as the drug's behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug). These reports are only required for new information that may affect FDA's previous conclusions about the safety or effectiveness of the drug product.

(*b*) A full description of the manufacturing and controls changes not requiring a supplemental application under § 314.70 (b) and (c), listed by date in the order in which they were implemented.

(v) *Nonclinical laboratory studies.* Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi) *Clinical data.* (*a*) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(*b*) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(vii) *Status reports.* A statement on the current status of any postmarketing studies performed by, or on behalf of, the applicant. To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application.

(3) *Other reporting*—(i) *Advertisements and promotional labeling.* The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. Form FDA-2253 may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857.

(ii) *Special reports.* Upon written request the agency may require that the applicant submit the reports under this section at different times than those stated.

(c) *General requirements*—(1) *Multiple applications.* For all reports required by this section, the applicant shall submit the information common to more than one application only to the application first approved, and shall not report separately on each application. The submission is required to identify all the applications to which the report applies.

(2) *Patient identification.* Applicants should not include in reports under this section the names and addresses of individual patients; instead, the applicant should code the patient names whenever possible and retain the code in the applicant's files. The applicant shall maintain sufficient patient identification information to permit FDA, by using that information alone or along with records maintained by the investigator of a study, to identify the name and address of individual patients; this will ordinarily occur only when the agency needs to investigate the reports further or when there is reason to believe that the reports do not represent actual results obtained.

(d) *Withdrawal of approval.* If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug

product that is the subject of the application.

§ 314.90 Waivers.

(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under §§ 314.50 through 314.81. An applicant may ask FDA to waive under § 314.126(c) any criteria of an adequate and well-controlled study described in § 314.126(b). A waiver request under this section is required to be submitted with supporting documentation in an application, or in an amendment or supplement to an application. The waiver request is required to contain one of the following:

(1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved;

(2) The applicant's alternative submission satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

Subpart C—FDA Action on Applications

§ 314.100 Time frames for reviewing applications.

(a) Within 180 days of receipt of an application, the Food and Drug Administration will review it and send the applicant either an approval letter under § 314.105, an approvable letter under § 314.110, or a not approvable letter under § 314.120. This 180-day period is called the "review clock."

(b) During the review period an applicant may withdraw an application under § 314.65 and later resubmit it. FDA will then follow the same procedure as if a new application were submitted.

(c) The time period may be extended by mutual agreement between FDA and an applicant or, as provided in § 314.60, as the result of a major amendment.

§ 314.101 Filing an application.

(a) Within 60 days after the Food and Drug Administration receives an application, the agency will determine whether the application may be filed. The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review.

(b) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the application apply, the agency will file the application and notify the applicant in writing. The date of filing will be the date 60 days after the date FDA received the application. The date of filing begins the 180-day period described in section 505(c) of the act. This 180-day period is called the "filing clock."

(c) If FDA refuses to file the application, the agency will notify the applicant in writing and state the reason under paragraph (d) or (e) of this section for the refusal. If FDA refuses to file the application under paragraph (d) of this section, the applicant may request in writing within 30 days of the date of the agency's notification an informal conference with the agency about whether the agency should file the application. If following the informal conference the applicant requests that FDA file the application (with or without amendments to correct the deficiencies), the agency will file the application over protest under paragraph (b) of this section, notify the applicant in writing, and review it as filed. If the application is filed over protest, the date of filing will be the date 60 days after the date the applicant requested the informal conference. The applicant need not resubmit a copy of an application that is filed over protest. If FDA refuses to file the application under paragraph (e) of this section, the applicant may amend the application and resubmit it and the agency will make a determination under this section whether it may be filed.

(d) FDA may refuse to file an application if any of the following applies.

(1) The application does not contain a completed application form.

(2) The application is not submitted in the form required under § 314.50 or § 314.55.

(3) The application is incomplete because it does not on its face contain information required under section 505(b) (1), (2), (3), (4), (5), and (6) or section 507 of the act and § 314.50 or § 314.55.

(4) The application does not contain an environmental impact analysis report analyzing under § 25.1 the environmental impact of the manufacturing process and the ultimate use or consumption of the drug.

(5) The application does not contain an accurate and complete English translation of each part of the application that is not in English.

(6) The application does not contain a statement for each nonclinical laboratory study that it was conducted in compliance with the requirements set forth in Part 58, or, for each study not conducted in compliance with Part 58, a brief statement of the reason for the noncompliance.

(7) The application does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in Part 50; or, if the study was subject to but was not conducted in compliance with those regulations, the application does not contain a brief statement of the reason for the noncompliance.

(e) The agency will refuse to file an application if any of the following applies:

(1) The drug product that is the subject of the submission is already coverd by an approved application.

(2) The submission purports to be an abbreviated application under § 314.55, but the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under § 314.55(b). FDA will file a copy of the application as a citizen petition under § 10.30 seeking a finding under § 314.55 that an abbreviated application is acceptable for the drug product, and so notify the applicant in writing.

(3) The drug product is subject to licensing by FDA under the Public Health Service Act (58 Stat. 632 as amended (42 U.S.C. 201 et seq.)) and Subchapter F of Chapter I of Title 21 of the Code of Federal Regulations.

(f) (1) Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either (i) approve the application or (ii) issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an application in response to an approvable letter or a not approvable letter.

(2) This paragraph does not apply to applications that have been withdrawn from FDA review by the applicant.

§ 314.102 Communication between FDA and applicants.

(a) *General principles.* During the course of reviewing an application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most

appropriate to discuss the particular issue at hand. Communications shall be appropriately documented in the application in accordance with § 10.65. Further details on the procedures for communication between FDA and applicants are contained in a staff manual guide that is publicly available.

(b) *Notification of easily correctable deficiencies.* FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application needed to facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application by agency managers as well as reviewing staff. Instead, these major scientific issues will ordinarily be addressed in an action letter.

(c) *Ninety-day conference.* Approximately 90 days after the agency receives the application, FDA will provide applicants with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to inform applicants of the general progress and status of their applications, and to advise applicants of deficiencies which have been identified by that time and which have not already been communicated. This meeting will be available on applications for all new chemical entities and major new indications of marketed drugs. Such meetings will be held at the applicant's option, and may be held by telephone if mutually agreed upon.

(d) *End-of-review conference.* At the conclusion of FDA's review of an application, as designated by the issuance of an approvable or not approvable letter, FDA will provide applicants with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to discuss what further steps need to be taken by the applicant before the application can be approved. This meeting will be available on all applications, with priority given to applications for new chemical entities and major new indications for marketed drugs. Requests for such meetings shall be directed to the director of the division responsible for reviewing the application.

(e) *Other meetings.* Other meetings between FDA and applicants may be held, with advance notice, to discuss scientific, medical, and other issues that arise during the review process. Requests for meetings shall be directed to the director of the division responsible for reviewing the application. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times. However, "drop-in" visits (i.e., an unannounced and unscheduled visit by a company representative) are discouraged except for urgent matters, such as to discuss an important new safety issue.

§ 314.103 Dispute resolution.

(a) *General.* The Food and Drug Administration is committed to resolving differences between applicants and FDA reviewing divisions with respect to technical requirements for applications as quickly and amicably as possible through the cooperative exchange of information and views.

(b) *Administrative and procedural issues.* When administrative or procedural disputes arise, the applicant should first attempt to resolve the matter with the division responsible for reviewing the application, beginning with the consumer safety officer assigned to the application. If resolution is not achieved, the applicant may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings, obtaining timely replies to inquiries, and obtaining timely completion of pending reviews. Further details on this procedure are contained in a staff manual guide that is publicly available under FDA's public information regulations in Part 20.

(c) *Scientific and medical disputes.* (1) Because major scientific issues are ordinarily communicated to applicants in an approvable or not approvable letter pursuant to § 314.110 or § 314.120, respectively, the "end-of-review conference" described in § 314.102(d) will provide a timely forum for discussing and resolving, if possible, scientific and medical issues on which the applicant disagrees with the agency. In addition, the "ninety-day conference" described in § 314.102(c) will provide a timely forum for discussing and resolving, if possible, issues identified by that date.

(2) When scientific or medical disputes arise at other times during the review process, applicants should discuss the matter directly with the responsible reviewing officials. If necessary, applicants may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Ordinarily, such meetings would be held first with the Division Director, then with the Office Director, and finally with the Center Director if the matter is still unresolved. Requests for such meetings shall be directed to the director of the division responsible for reviewing the application. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may also bring their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of is standing advisory committees for its consideration and recommendations.

§ 314.104 Drugs with potential for abuse.

The Food and Drug Administration will inform the Drug Enforcement Administration under section 201(f) of the Controlled Substances Act (21 U.S.C. 801) when an application is submitted for a drug that appears to have an abuse potential.

§ 314.105 Approval of an application.

(a) The Food and Drug Administration will approve an application and send the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the application apply. The date of the agency's approval letter is the date of approval of the application. When FDA sends an applicant an approval letter for an antibiotic, it will promulgate a regulation under § 314.300 providing for certification of the drug, if necessary. A new drug product or antibiotic may not be marketed until an approval letter is issued. Marketing of an antibiotic need not await the promulgation of a regulation under § 314.300.

(b) FDA will approve an application and issue the applicant an approval

letter (rather than an approvable letter under § 314.110) on the basis of draft labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

(c) FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to them and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet them. FDA makes its views on drug products and classes of drugs available through guidelines, recommendations, and other statements of policy.

§ 314.106 Foreign data.

(a) *General.* The acceptance of foreign data in an application generally is governed by § 312.20.

(b) *As sole basis for marketing approval.* An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if: (1) The foreign data are applicable to the U.S. population and U.S. medical practice; (2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria will result in the application not being approvable based on the foreign data alone. FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.

(c) *Consultation between FDA and applicants.* Applicants are encouraged to meet with agency officials in a "presubmission" meeting when approval based solely on foreign data will be sought.

§ 314.110 Approvable letter to the applicant.

In selected circumstances it is useful at the end of the review period for the Food and Drug Administration to indicate to the applicant that the application is basically approvable providing certain issues are resolved. An approvable letter may be issued in such circumstances. FDA will send the applicant an approvable letter if the application substantially meets the requirements of this part and the agency believes that it can approve the application if specific additional information or material is submitted or specific conditions (for example, certain changes in labeling) are agreed to by the applicant. The approvable letter will describe the information or material FDA requires or the conditions the applicant is asked to meet. As a practical matter, the approvable letter will serve in most instances as a mechanism for resolving outstanding issues on drugs that are about to be approved and marketed. Within 10 days after the date of the approvable letter, the applicant shall either:

(a) Amend the application or notify FDA of an intent to file an amendment. The filing of an amendment or notice of intent to file an amendment constitutes an agreement by the applicant to extend the review period for 45 days after the date FDA receives the amendment. The extension is to permit the agency to review the amendment.

(b) Withdraw the application. FDA will consider the applicant's failure to respond within 10 days to an approvable letter to be a request by the applicant to withdraw the application under § 314.65. A decision to withdraw an application is without prejudice to a refiling.

(c) For a new drug, ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) of the act. The applicant shall submit the request to the Division of Regulatory Affairs (HFN-360), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Within 60 days of the date of the approvable letter, or within a different time period to which FDA and the applicant agree, the agency will either approve the application under § 314.105 or refuse to approve the application under § 314.125 and give the applicant written notice of an opportunity for a hearing under § 314.200 and section 505(c)(2) of the act on the question of whether there are grounds for denying approval of the application under section 505(d) of the act.

(d) For an antibiotic, file a petition or notify FDA of an intent to file a petition proposing the issuance, amendment, or repeal of a regulation under § 314.300 and section 507(f) of the act.

(e) Notify FDA that the applicant agrees to an extension of the review period under section 505(c) of the act, so that the applicant can determine whether to respond further under paragraph (a), (b), (c), or (d) of this section. The applicant's notice is required to state the length of the extension. FDA will honor any reasonable request for such an extension. FDA will consider the applicant's failure to respond further within the extended review period to be a request to withdraw the application under § 314.65. A decision to withdraw an application is without prejudice to a refiling.

§ 314.120 Not approvable letter to the applicant.

The Food and Drug Administration will send the applicant a not approvable letter if the agency believes that the application may not be approved for one of the reasons given in § 314.125. The not approvable letter will describe the deficiencies in the application. Within 10 days after the date of the not approvable letter, the applicant shall either:

(a) Amend the application or notify FDA of an intent to file an amendment. The filing of an amendment or a notice of intent to file an amendment constitutes an agreement by the applicant to extend the review period under § 314.60.

(b) Withdraw the application. FDA will consider the applicant's failure to respond within 10 days to a not approvable letter to be a request by the applicant to withdraw the application under § 314.65. A decision to withdraw the application is without prejudice to refiling.

(c) For a new drug, ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) of the act. The applicant shall submit the request to the Division of Regulatory Affairs (HFN-360), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Within 60 days of the date of the not approvable letter, or within a different time period to which FDA and the applicant agree, the agency will either approve the application under § 314.105 or refuse to approve the application under § 314.125 and give the applicant written notice of an opportunity for a hearing under § 314.200 and section 505(c)(2) of the act on the question of whether there are grounds for denying approval of the

application under section 505(d) of the act.

(d) For an antibiotic, file a petition or notify FDA of an intent to file a petition proposing the issuance, amendment, or repeal of a regulation under § 314.300 and section 507(f) of the act.

(e) Notify FDA that the applicant agrees to an extension of the review period under section 505(c) of the act, so that the applicant can determine whether to respond further under paragraph (a), (b), (c), or (d) of this section. The applicant's notice is required to state the length of the extension. FDA will honor any reasonable request for such an extension. FDA will consider the applicant's failure to respond further within the extended review period to be a request to withdraw the application under § 314.65. A decision to withdraw an application is without prejudice to a refiling.

§ 314.125 Refusal to approve an application.

(a) The Food and Drug Administration will refuse to approve the application and for a new drug give the applicant written notice of an opportunity for a hearing under § 314.200 on the question of whether there are grounds for denying approval of the application under section 505(d) of the act, or for an antibiotic publish a proposed regulation based on an acceptable petition under § 314.300, if:

(1) FDA sends the applicant an approvable or a not approvable letter under § 314.110 or § 314.120;

(2) The applicant requests an opportunity for hearing for a new drug on the question of whether the application is approvable or files a petition for an antibiotic proposing the issuance, amendment, or repeal of a regulation; and

(3) FDA finds that any of the reasons given in paragraph (b) of this section apply.

(b) FDA may refuse to approve an application for any of the following reasons:

(1) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

(2) The investigations required under section 505(b) or 507 of the act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.

(4) There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

(6) The proposed labeling is false or misleading in any particular.

(7) The application contains an untrue statement of a material fact.

(8) The drug product's proposed labeling does not comply with the requirements for labels and labeling in Part 201.

(9) The application does not contain bioavailability or bioequivalence data required under Part 320.

(10) A reason given in a letter refusing to file the application under § 314.101(d), if the deficiency is not corrected.

(11) The drug will be manufactured or processed in whole or in part in an establishment that is not registered and not exempt from registration under section 510 of the act and Part 207.

(12) The applicant does not permit a properly authorized officer or employee of the Department of Health and Human Services an adequate opportunity to inspect the facilities, controls, and any records relevant to the application.

(13) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in Parts 210 and 211.

(14) The application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source.

(15) A nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations in Part 58 and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(16) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in Part 56 or informed consent regulations in Part 50, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

§ 314.126 Adequate and well-controlled studies.

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of sections 505 and 507 of the act. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs and antibiotics. Therefore, the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

(b) An adequate and well-controlled study has the following characteristics:

(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.

(2) The study uses a design that permits a valid comparison with a control to provide a quantitative

assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized:

(i) *Placebo concurrent control.* The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.

(ii) *Dose-comparison concurrent control.* At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

(iii) *No treatment concurrent control.* Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

(iv) *Active treatment concurrent control.* The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

(v) *Historical control.* The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.

(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug. The protocol for the study and the report of its results should describe how subjects were assigned to groups. Ordinarily, in a concurrently controlled study, assignment is by randomization, with or without stratification.

(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.

(6) The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.

(7) There is an analysis of the results of the study adequate to assess the effects of the drug. The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed.

(c) The Director of the Center for Drugs and Biologics may, on the Director's own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in paragraph (b) of this section with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study. A petition for a waiver is required to set forth clearly and concisely the specific criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been employed, and what results have been obtained. The petition is also required to state why the clinical investigations so conducted will yield, or have yielded, substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(d) For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

§ 314.150 Withdrawal of approval of an application.

(a) The Food and Drug Administration will notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application under section 505(e) of the act and under the procedure in § 314.200, or, for an antibiotic, rescind a certification or release, or amend or repeal a regulation providing for certification under section 507 of the act under the procedure in § 314.300, if any of the following applies:

(1) The Secretary of Health and Human Services has suspended the approval of the application for a new drug on a finding that there is an imminent hazard to the public health. FDA will promptly afford the applicant an expedited hearing following summary suspension on a finding of imminent hazard to health.

(2) FDA finds:

(i) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the

conditions of use upon the basis of which the application was approved; or

(ii) That new evidence of clinical experience, not contained in the application or not available to FDA until after the application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application was approved, evaluated together with the evidence available when the application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or

(iii) Upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in § 314.126, that the drug will have the effect it is purported or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or

(iv) That the application contains any untrue statement of a material fact.

(b) FDA may notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application under section 505(e) of the act and under the procedure in § 314.200, or, for an antibiotic, rescind a certification or release, or amend or repeal a regulation providing for certification under section 507 of the act and the procedure in § 314.300, if the agency finds:

(1) That the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain required records or to make required reports under section 505(j) or 507(g) of the act and §§ 314.80 and 314.81, or that the applicant has refused to permit access to, or copying or verification of, its records.

(2) That on the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the agency.

(3) That on the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the labeling of the drug, based on a fair evaluation of all material facts, is false or misleading in any particular; and the labeling was not corrected by the applicant within a reasonable time after receipt of written notice from the agency.

(4) That the applicant has failed to comply with the notice requirements of section 510(j)(2) of the act.

(5) That the applicant has failed to submit bioavailability or bioequivalence data required under Part 320.

(6) The application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source.

(7) That any nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its labeling was not conducted in compliance with the good laboratory practice regulations in Part 58 and no reason for the noncompliance was provided or, if it was, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(8) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in Part 56 or informed consent regulations in Part 50, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(c) FDA will withdraw approval of an application if the applicant requests its withdrawal because the drug subject to the application is no longer being marketed, provided none of the conditions listed in paragraphs (a) and (b) of this section apply to the drug. FDA will consider a written request for withdrawal under this paragraph to be a waiver of an opportunity for hearing otherwise provided for in this section. Withdrawal of approval of an application under this paragraph is without prejudice to refiling.

(d) FDA may notify an applicant that it believes a potential problem associated with a drug is sufficiently serious that the drug should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided for under this section, to permit FDA to withdraw approval of the application for the product, and to remove voluntarily the product from the market. If the applicant agrees, the agency will not make a finding under paragraph (b) of this section, but will withdraw approval of the application in a notice published in the **Federal Register** that contains a brief summary of the agency's and the applicant's views of the reasons for withdrawal.

§ 314.152 Notice of withdrawal of approval of an application for a new drug.

If the Food and Drug Administration withdraws approval of an application for a new drug, FDA will publish a notice in the **Federal Register** announcing the withdrawal of approval.

§ 314.160 Approval of an application for which approval was previously refused, suspended, or withdrawn.

Upon the Food and Drug Administration's own initiative or upon request of an applicant, FDA may, on the basis of new data, approve an application which it had previously refused, suspended, or withdrawn approval. FDA will publish a notice in the **Federal Register** announcing the approval.

§ 314.170 Adulteration and misbranding of an approved drug.

All drugs, including those the Food and Drug Administration approves, or provides for certification of, under sections 505, 506, and 507 of the act and this part, are subject to the adulteration and misbranding provisions in sections 501, 502, and 503 of the act. FDA is authorized to regulate approved new drugs and approved antibiotic drugs by regulations issued through informal rulemaking under sections 501, 502, and 503 of the act.

Subpart D—Hearing Procedures for New Drugs

§ 314.200 Notice of opportunity for hearing; notice of participation and request for hearing; grant or denial of hearing.

(a) *Notice of opportunity for hearing.* The Director of the Center for Drugs and Biologics, Food and Drug Administration, will give the applicant, and all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, notice and an opportunity for a hearing on the Center's proposal to refuse to approve an application or to withdraw the approval of an application. The notice will state the reasons for the action and the proposed grounds for the order.

(1) The notice may be general (that is, simply summarizing in a general way

the information resulting in the notice) or specific (that is, either referring to specific requirements in the statute and regulations with which there is a lack of compliance, or providing a detailed description and analysis of the specific facts resulting in the notice).

(2) FDA will publish the notice in the **Federal Register** and will state that the applicant, and other persons subject to the notice under § 310.6, who wishes to participate in a hearing, has 30 days after the date of publication of the notice to file a written notice of participation and request for hearing. The applicant, or other persons subject to the notice under § 310.6, who fails to file a written notice of participation and request for hearing within 30 days, waives the opportunity for a hearing.

(3) It is the responsibility of every manufacturer and distributor of a drug product to review every notice of opportunity for a hearing published in the **Federal Register** to determine whether it covers any drug product that person manufactures or distributes. Any person may request an opinion of the applicability of a notice to a specific product that may be identical, related, or similar to a product listed in a notice by writing to the Division of Drug Labeling Compliance (HFN–310), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. A person shall request an opinion within 30 days of the date of publication of the notice to be eligible for an opportunity for a hearing under the notice. If a person requests an opinion, that person's time for filing an appearance and request for a hearing and supporting studies and analyses begins on the date the person receives the opinion from FDA.

(b) FDA will provide the notice of opportunity for a hearing to applicants and to other persons subject to the notice under § 310.6, as follows:

(1) To any person who has submitted an application, by delivering the notice in person or by sending it by registered or certified mail to the last address shown in the application.

(2) To any person who has not submitted an application but who is subject to the notice under § 310.6, by publication of the notice in the **Federal Register**.

(c) (1) *Notice of participation and request for a hearing, and submission of studies and comments.* The applicant, or any other person subject to the notice under § 310.6, who wishes to participate in a hearing, shall file with the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, Rockville, MD 20857, (i) within 30 days after the date of the publication of the notice (or of the date of receipt of an opinion requested under paragraph (a)(3) of this section) a written notice of participation and request for a hearing and (ii) within 60 days after the date of publication of the notice, unless a different period of time is specified in the notice of opportunity for a hearing, the studies on which the person relies to justify a hearing as specified in paragraph (d) of this section. The applicant, or other person, may incorporate by reference the raw data underlying a study if the data were previously submitted to FDA as part of an application or other report.

(2) FDA will not consider data or analyses submitted after 60 days in determining whether a hearing is warranted unless they are derived from well-controlled studies begun before the date of the notice of opportunity for hearing and the results of the studies were not available within 60 days after the date of publication of the notice. Nevertheless, FDA may consider other studies on the basis of a showing by the person requesting a hearing of inadvertent omission and hardship. The person requesting a hearing shall list in the request for hearing all studies in progress, the results of which the person intends later to submit in support of the request for a hearing. The person shall submit under paragraph (c)(1)(ii) of this section a copy of the complete protocol, a list of the participating investigators, and a brief status report of the studies.

(3) Any other interested person who is not subject to the notice of opportunity for a hearing may also submit comments on the proposal to withdraw approval of the application. The comments are required to be submitted within the time and under the conditions specified in this section.

(d) The person requesting a hearing is required to submit under paragraph (c)(1)(ii) of this section the studies (including all protocols and underlying raw data) on which the person relies to justify a hearing with respect to the drug product. Except, a person who requests a hearing on the refusal to approve an application is not required to submit additional studies and analyses if the studies upon which the person relies have been submitted in the application and in the format and containing the summaries required under § 314.50.

(1) If the grounds for FDA's proposed action concern the effectiveness of the drug, each request for hearing is required to be supported only by adequate and well-controlled clinical studies meeting all of the precise requirements of § 314.126 and, for combination drug products, § 300.50, or by other studies not meeting those requirements for which a waiver has been previously granted by FDA under § 314.126. Each person requesting a hearing shall submit all adequate and well-controlled clinical studies on the drug product, including any unfavorable analyses, views, or judgments with respect to the studies. No other data, information, or studies may be submitted.

(2) The submission is required to include a factual analysis of all the studies submitted. If the grounds for FDA's proposed action concern the effectiveness of the drug, the analysis is required to specify how each study accords, on a point-by-point basis, with each criterion required for an adequate well-controlled clinical investigation established under § 314.126 and, if the product is a combination drug product, with each of the requirements for a combination drug established in § 300.50, or the study is required to be accompanied by an appropriate waiver previously granted by FDA. If a study concerns a drug or dosage form or condition of use or mode of administration other than the one in question, that fact is required to be clearly stated. Any study conducted on the final marketed form of the drug product is required to be clearly identified.

(3) Each person requesting a hearing shall submit an analysis of the data upon which the person relies, except that the required information relating either to safety or to effectiveness may be omitted if the notice of opportunity for hearing does not raise any issue with respect to that aspect of the drug; information on compliance with § 300.50 may be omitted if the drug product is not a combination drug product. FDA can most efficiently consider submissions made in the following format.

I. Safety data.

A. Animal safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

B. Human safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

II. Effectiveness data.

A. Individual active components: Controlled studies, with an analysis showing clearly how each study satisfies, on a point-by-point basis, each of the criteria required by § 314.126.

B. Combinations of individual active components.

1. Controlled studies with an analysis showing clearly how each study satisfies on a point-by-point basis, each of the criteria required by § 314.126.

2. An analysis showing clearly how each requirement of § 300.50 has been satisfied.

III. A summary of the data and views setting forth the medical rationale and purpose for the drug and its ingredients and the scientific basis for the conclusion that the drug and its ingredients have been proven safe and/or effective for the intended use. If there is an absence of controlled studies in the material submitted or the requirements of any element of § 300.50 or § 314.126 have not been fully met, that fact is required to be stated clearly and a waiver obtained under § 314.126 is required to be submitted.

IV. A statement signed by the person responsible for such submission that it includes in full (or incorporates by reference as permitted in § 314.200(c)(2)) all studies and information specified in § 314.200(d).

(Warning: A willfully false statement is a criminal offense, 18 U.S.C. 1001.)

(e) *Contentions that a drug product is not subject to the new drug requirements.* A notice of opportunity for a hearing encompasses all issues relating to the legal status of each drug product subject to it, including identical, related, and similar drug products as defined in § 310.6. A notice of appearance and request for a hearing under paragraph (c)(1)(i) of this section is required to contain any contention that the product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act, or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act or under section 107(c) of the Drug Amendments of 1962, or for any other reason. Each contention is required to be supported by a submission under paragraph (c)(1)(ii) of this section and the Commissioner of Food and Drugs will make an administrative determination on each contention. The failure of any person subject to a notice of opportunity for a hearing, including any person who manufactures or distributes an identical, related, or similar drug product as defined in § 310.6, to submit a notice of participation and request for hearing or to raise all such contentions constitutes a waiver of any contentions not raised.

(1) A contention that a drug product is generally recognized as safe and effective within the meaning of section 201(p) of the act is required to be supported by submission of the same quantity and quality of scientific evidence that is required to obtain approval of an application for the product, unless FDA has waived a requirement for effectiveness (under § 314.126) or safety, or both. The submission should be in the format and with the analyses required under paragraph (d) of this section. A person who fails to submit the required scientific evidence required under paragraph (d) waives the contention. General recognition of safety and effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.

(2) A contention that a drug product is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962, is required to be supported by evidence of past and present quantitative formulas, labeling, and evidence of marketing. A person who makes such a contention should submit the formulas, labeling, and evidence of marketing in the following format.

I. Formulation.

A. A copy of each pertinent document or record to establish the exact quantitative formulation of the drug (both active and inactive ingredients) on the date of initial marketing of the drug.

B. A statement whether such formulation has at any subsequent time been changed in any manner. If any such change has been made, the exact date, nature, and rational for each change in formulation, including any deletion or change in the concentration of any active ingredient and/or inactive ingredient, should be stated, together with a copy of each pertinent document or record to establish the date and nature of each such change, including, but not limited to, the formula which resulted from each such change. If no such change has been made, a copy of representative documents or records showing the formula at representative points in time should be submitted to support the statement.

II. Labeling.

A. A copy of each pertinent document or record to establish the identity of each item of written, printed, or graphic matter used as labeling on the date the drug was initially marketed.

B. A statement whether such labeling has at any subsequent time been discontinued or changed in any manner. If such discontinuance or change has been made, the exact date, nature, and rationale for each discontinuance or change and a copy of each pertinent document or record to establish each such discontinuance or change should be submitted, including, but not limited to, the labeling which resulted from each such discontinuance or change. If no such discontinuance or change has been made, a copy of representative documents or records showing labeling at representative points in time should be submitted to support the statement.

III. Marketing.

A. A copy of each pertinent document or record to establish the exact date the drug was initially marketed.

B. A statement whether such marketing has at any subsequent time been discontinued. If such marketing has been discontinued, the exact date of each such discontinuance should be submitted, together with a copy of each pertinent document or record to establish each such date.

IV. Verification.

A statement signed by the person responsible for such submission, that all appropriate records have been searched and to the best of that person's knowledge and belief it includes a true and accurate presentation of the facts.

(Warning: A willfully false statement is a criminal offense, 18 U.S.C. 1001.)

(3) The Food and Drug Administration will not find a drug product, including any active ingredient, which is identical, related, or similar, as described in § 310.6, to a drug product, including any active ingredient for which an application is or at any time has been effective or deemed approved, or approved under section 505 of the act, to be exempt from part or all of the new drug provisions of the act.

(4) A contention that a drug product is not a new drug for any other reason is required to be supported by submission of the factual records, data, and information that are necessary and appropriate to support the contention.

(5) It is the responsibility of every person who manufactures or distributes a drug product in reliance upon a "grandfather" provision of the act to maintain files that contain the data and information necessary fully to document and support that status.

(f) *Separation of functions.* Separation of functions commences upon receipt of a request for hearing. The Director of the Center for Drugs and Biologics, Food and Drug Administration, will prepare an analysis of the request and a proposed order ruling on the matter. The analysis and proposed order, the request for hearing, and any proposed order denying a hearing and response under paragraph (g) (2) or (3) of this section will be submitted to the Office of the Commissioner of Food and Drugs for

review and decision. When the Center for Drugs and Biologics recommends denial of a hearing on all issues on which a hearing is requested, no representative of the Center will participate or advise in the review and decision by the Commissioner. When the Center for Drugs and Biologics recommends that a hearing be granted on one or more issues on which a hearing is requested, separation of functions terminates as to those issues, and representatives of the Center may participate or advise in the review and decision by the Commissioner on those issues. The Commissioner may modify the text of the issues, but may not deny a hearing on those issues. Separation of functions continues with respect to issues on which the Center for Drugs and Biologics has recommended denial of a hearing. The Commissioner will neither evaluate nor rule on the Center's recommendation on such issues and such issues will not be included in the notice of hearing. Participants in the hearing may make a motion to the presiding officer for the inclusion of any such issue in the hearing. The ruling on such a motion is subject to review in accordance with § 12.35(b). Failure to so move constitutes a waiver of the right to a hearing on such an issue. Separation of functions on all issues resumes upon issuance of a notice of hearing. The Office of the General Counsel, Department of Health and Human Services, will observe the same separation of functions.

(g) *Summary judgment.* A person who requests a hearing may not rely upon allegations or denials but is required to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing with respect to a particular drug product specified in the request for hearing.

(1) Where a specific notice of opportunity for hearing (as defined in paragraph (a)(1) of this section) is used, the Commissioner will enter summary judgment against a person who requests a hearing, making findings and conclusions, denying a hearing, if it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application; for example, no adequate and well-controlled clinical investigations meeting each of the precise elements of § 314.126 and, for a combination drug product, § 300.50, showing effectiveness have been identified. Any order entering summary judgment is required to set forth the Commissioner's findings and conclusions in detail and is required to specify why each study submitted fails to meet the requirements of the statute and regulations or why the request for hearing does not raise a genuine and substantial issue of fact.

(2) When following a general notice of opportunity for a hearing (as defined in paragraph (a)(1) of this section) the Director of the Center for Drugs and Biologics concludes that summary judgment against a person requesting a hearing should be considered, the Director will serve upon the person requesting a hearing by registered mail a proposed order denying a hearing. This person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(3) When following a general or specific notice of opportunity for a hearing a person requesting a hearing submits data or information of a type required by the statute and regulations, and the Director of the Center for Drugs and Biologics concludes that summary judgment against the person should be considered, the Director will serve upon the person by registered mail a proposed order denying a hearing. The person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(4) If review of the data, information, and analyses submitted show that the grounds cited in the notice are not valid, for example, that substantial evidence of effectiveness exists, the Commissioner will enter summary judgment for the person requesting the hearing, and rescind the notice of opportunity for hearing.

(5) If the Commissioner grants a hearing, it will begin within 90 days after the expiration of the time for requesting the hearing unless the parties otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

(6) The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact or if the Commissioner concludes that a hearing would otherwise be in the public interest.

(7) If the manufacturer or distributor of an identical, related, or similar drug product requests and is granted a hearing, the hearing may consider whether the product is in fact identical, related, or similar to the drug product named in the notice of opportunity for a hearing.

(8) A request for a hearing, and any subsequent grant or denial of a hearing, applies only to the drug products named in such documents.

(h) FDA will issue a notice withdrawing approval and declaring all products unlawful for drug products subject to a notice of opportunity for a hearing, including any identical, related, or similar drug product under § 310.6, for which an opportunity for a hearing is waived or for which a hearing is denied. The Commissioner may defer or stay the action pending a ruling on any related request for a hearing or pending any related hearing or other administrative or judicial proceeding.

§ 314.201 Procedure for hearings.

Parts 10 through 16 apply to hearings relating to new drugs under section 505 (d) and (e) of the act.

§ 314.235 Judicial review.

(a) The Commissioner of Food and Drugs will certify the transcript and record. In any case in which the Commissioner enters an order without a hearing under §314.200(g), the record certified by the Commissioner is required to include the requests for hearing together with the data and information submitted and the Commissioner's findings and conclusion.

(b) A manufacturer or distributor of an identical, related, or similar drug product under § 310.6 may seek judicial review of an order withdrawing approval of a new drug application, whether or not a hearing has been held, in a United States court of appeals under section 505(h) of the act.

Subpart E—Administrative Procedures for Antibiotics

§ 314.300 Procedure for the issuance, amendment, or repeal of regulations.

(a) The procedures in Part 10 apply to the issuance, amendment, or repeal of regulations under section 507 of the act.

(b) (1) The Commissioner of Food and Drugs, on his or her own initiative or on the application or request of any interested person, may publish in the **Federal Register** a notice of proposed rulemaking and order to issue, amend, or repeal any regulation contemplated by section 507 of the act.

The notice and order may be general (that is, simply summarizing in a general way the information resulting in the notice and order) or specific (that is, either referring to specific requirements in the statute and regulations with which there is a lack of compliance, or

providing a detailed description and analysis of the specific facts resulting in the notice and order).

(2) The Food and Drug Administration will give interested persons an opportunity to submit written comments and to request an informal conference on the proposal, unless the notice and opportunity for comment and informal conference have already been provided in connection with the announcement of the reports of the National Academy of Sciences/National Research Council, Drug Efficacy Study Group, to persons who will be adversely affected, or as provided in §§ 10.40(e) and 12.20(c)(2). A person is required to request an informal conference within 30 days of the notice of proposed rulemaking unless otherwise specified in the notice. If an informal conference is requested and granted, those persons participating in the conference may submit comments, within 30 days of the conference, unless otherwise specified in the proposal.

(3) It is the responsibility of every manufacturer and distributor of an antibiotic drug product to review every proposal published in the **Federal Register** to determine whether it covers any drug product that person manufactures or distributes.

(4) After considering the written comments, the results of any conference, and the data available, the Commissioner will publish an order in the **Federal Register** acting on the proposal, with an opportunity for any person who will be adversely affected to file objections, to request a hearing, and to show reasonable grounds for the hearing. Any person who wishes to participate in a hearing, shall file with the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, (i) within 30 days after the date of the publication of the order a written notice of participation and request for a hearing and (ii) within 60 days after the date of publication of the order, unless a different period of time is specified in the order, the studies on which the person relies to justify a hearing as specified in paragraph (b)(6) of this section. The person may incorporate by reference the raw data underlying a study if the data were previously submitted to FDA as part of an application or other report.

(5) FDA will not consider data or analysis submitted after 60 days in determining whether a hearing is warranted unless they are derived from well-controlled studies begun before the date of the order and the results of the studies were not available within 60 days after the date of publication of the order. Nevertheless, FDA may consider other studies on the basis of a showing by the person requesting a hearing of inadvertent omission and hardship. The person requesting a hearing shall list in the request for hearing all studies in progress, the results of which the person intends later to submit in support of the request for hearing. The person shall submit under paragraph (b)(4)(ii) of this section a copy of the complete protocol, a list of the participating investigators, and a brief status report of the studies.

(6) The person requesting a hearing is required to submit as required under § 314.200(c)(1)(ii) the studies (including all protocols and underlying raw data) on which the person relies to justify a hearing with respect to the drug product. Except, a person who requests a hearing on a proposal is not required to submit additional studies and analyses if the studies upon which the person relies have been submitted in an application and in the format and containing the summaries required under § 314.50.

(i) If the grounds for DFA proposed action concern the effectiveness of the drug, each request for hearing is required to be supported only by adequate and well-controlled clinical studies meeting all of the precise requirements of § 314.126 and, for combination drug products, § 300.50, or by other studies not meeting those requirements for which a waiver has been previously granted by FDA under § 314.126. Each person requesting a hearing shall submit all adequate and well-controlled clinical studies on the drug product, any unfavorable analyses, views, or judgements with respect to the studies. No other data, information, or studies may be submitted.

(ii) The submission is required to include a factual analyses of all the studies submitted. If the grounds for FDA proposed action concern the effectiveness of the drug, the analysis is required to specify how each study accords, on a point-by-point basis, with each criterion required for an adequate well-controlled clinical investigation established under § 314.126 and, if the product is a combination drug product, with each of the requirements for a combination drug established in § 300.50, or the study is required to be accompanied by an appropriate waiver previously granted by FDA. If a study concerns a drug entity or dosage form or condition of use or mode of administration other than the one in question, that fact is required to be clearly stated. Any study conducted on the final marketed form of the drug product is required to be clearly identified.

(iii) Each person requesting a hearing shall submit an analysis of the data upon which the person relies, except that the required information relating either to safety or to effectiveness may be omitted if the notice of opportunity for hearing does not raise any issue with respect to that aspect of the drug; information on compliance with § 300.50 may be omitted if the drug product is not a combination drug product. FDA can most efficiently consider submissions made in the following format.

I. Safety data.

A. Animal safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

B. Human safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

II. Effectiveness data.

A. Individual active components: Controlled studies, with an analysis showing clearly how each study satisfies, on a point-by-point basis, each of the criteria required by § 314.126.

B. Combinations of individual active components.

1. Controlled studies with an analysis showing clearly how each study satisfies on a point-by-point basis, each of the criteria required by § 314.126.

2. An analysis showing clearly how each requirement of § 300.50 has been satisfied.

III. A summary of the data and views setting forth the medical rationale and purpose for the drug and its ingredients and the scientific basis for the conclusion that the drug and its ingredients have been proven safe and/or effective for the intended use. If there is an absence of controlled studies in the material submitted or the requirements of any element of § 300.50 or § 314.126 have not been fully met, that fact is required to be stated clearly and a waiver obtained under § 314.126 is required to be submitted.

IV. A statement signed by the person responsible for such submission that it includes in full (or incorporates by reference as permitted in § 314.200(c)(2)) all studies and information specified in § 314.200(d).

(**Warning**: A willfully false statement is a criminal offense, 18 U.S.C. 1001.)

(7) *Separation of functions.* Separation of functions commences upon receipt of a request for hearing. The Director of the Center for Drugs and Biologics will prepare an analysis of the request and a proposed order ruling on the matter. The analysis and proposed order, the request for hearing, and any proposed order denying a hearing and response under paragraph (b)(8) (ii) or (iii) of this section will be submitted to the Office of the Commissioner for review and decision. When the Center for Drugs and Biologics recommends denial of a hearing on all issues on which a hearing is requested, no representative of the Center will participate or advise in the review and decision by the Commissioner. When the Center for Drugs and Biologics recommends that a hearing be granted on one or more issues on which a hearing is requested, separation of functions terminates as to those issues, and representatives of the Center may participate or advise in the review and decision by the Commissioner on those issues. The Commissioner may modify the text of the issues, but may not deny a hearing on those issues. Separation of functions continues with respect to issues on which the Center for Drugs and Biologics has recommended denial of a hearing. The Commissioner will neither evaluate nor rule on the Center's recommendation on such issues and such issues will not be included in the notice of hearing. Participants in the hearing may make a motion to the presiding officer for the inclusion of any such issue in the hearing. The ruling on such a motion is subject to review in accordance with § 12.35(b). Failure to so move constitutes a waiver of the right to a hearing on such an issue. Separation of functions on all issues resumes upon issuance of a notice of hearing. The Office of the General Counsel, Department of Health and Human Services, will observe the same separation of functions.

(8) *Summary judgment.* A person who requests a hearing may not rely upon allegations or denials but is required to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing with respect to a particular drug product specified in the request for hearing.

(i) Where a specific notice of opportunity for hearing (as defined in paragraph (b)(1) of this section) is used, the Commissioner will enter summary judgment against a person who requests a hearing, making findings and conclusions, denying a hearing, if it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application; for example, no adequate and well-controlled clinical investigations meeting each of the precise elements of § 314.126 and, for a combination drug product, § 300.50, showing effectiveness have been identified. Any order entering summary judgment is required to set forth the Commissioner's findings and conclusions in detail and is required to specify why each study submitted fails to meet the requirements of the statute and regulations or why the request for hearing does not raise a genuine and substantial issue of fact.

(ii) When following a general notice of opportunity for a hearing (as defined in paragraph (b)(1) of this section) the Director of the Center for Drugs and Biologics concludes that summary judgment against a person requesting a hearing should be considered, the Director will serve upon the person requesting a hearing by registered mail a proposed order denying a hearing. This person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(iii) When following a general or specific notice of opportunity for a hearing a person requesting a hearing submits data or information of a type required by the statute and regulations, and the Director of the Center for Drugs and Biologics concludes that summary judgment against the person should be considered, the Director will serve upon the person by registered mail a proposed order denying a hearing. The person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(iv) If review of the data, information, and analyses submitted show that the basis for the order is not valid, for example, that substantial evidence of effectiveness exists, the Commissioner will enter summary judgment for the person requesting the hearing, and revoke the order. If a hearing is not requested, the order will become effective as published.

(v) If the Commissioner grants a hearing, it will be conducted under Part 12.

(vi) The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact or if the Commissioner concludes that a hearing would otherwise be in the public interest.

(9) The repeal of any regulation constitutes a revocation of all outstanding certificates based upon such regulation. However, the Commissioner may, in his or her discretion, defer or stay such action pending a ruling on any related request for a hearing or pending any related hearing or other administrative or judicial proceeding.

(c) Whenever any interested person submits an application or request under section 507 of the act and Part 314 and FDA sends the person an approvable letter under § 314.110 or a not approvable letter under § 314.120, the person may file a petition proposing the issuance, amendment, or repeal of the regulation under the provisions of section 507(f) of the act and Part 10. The Commissioner shall cause the regulations proposed in the petition to be published in the **Federal Register** within 60 days of the receipt of an acceptable petition and further proceedings shall be in accord with the provisions of sections 507(f) and 701 (f) and (g) of the act and Part 10.

(d) (1) FDA will no promulgate a regulation providing for the certification of any batch of any drug composed wholly or in part of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof, intended for human use and no existing regulation will be continued in effect unless it is established by substantial evidence that the drug will have such characteristics of identity, strength, quality, and purity necessary to adequately ensure safety and efficacy of use. "Substantial evidence" has been defined by Congress to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions prescribed, recommended, or suggested in the labeling or proposed labeling thereof." This definition is made applicable to a number of antibiotic drugs by section 507(h) of the act and it is the test of efficacy that FDA will apply in promulgating, amending, or repealing regulations for all antibiotics under section 507(a) of the act as well.

(2) The scientific essentials of an adequate and well-controlled clinical investigation are described in § 314.126.

Subpart F—Miscellaneous Provisions

§ 314.410 Imports and exports of new drugs and antibiotics.

(a) *Imports.* (1) A new drug or an antibiotic may be imported into the United States if: (i) It is the subject of an approved application under this part or, in the case of an antibiotic not exempt from certification under Part 433, it is also certified or released; or (ii) it complies with the regulations pertaining to investigational new drugs under Part 312; and it complies with the general regulations pertaining to imports under Subpart E of Part 1.

(2) A drug substance intended for use in the manufacture, processing, or repacking of a new drug may be imported into the United States if it complies with the labeling exemption in § 201.122 pertaining to shipments of drug substances in domestic commerce.

(b) *Exports.* (1) A new drug or an antibiotic may be exported if it is the subject of an approved application under this part, and, in the case of an antibiotic, it is certified or released, or it complies with the regulations pertaining to investigational new drugs under Part 312.

(2) A new drug substance that is covered by an application approved under this part for use in the manufacture of an approved drug product may be exported by the applicant or any person listed as a supplier in the approved application, provided the drug substance intended for export meets the specifications of, and is shipped with a copy of the labeling required for, the approved drug product.

(3) An antibiotic drug product or drug substance that is subject to certification under section 507 of the act, but which has not been certified or released, may be exported under section 801(d) of the act if it meets the following conditions:

(i) It meets the specifications of the foreign purchaser;

(ii) It is not in conflict with the laws of the country to which it is intended for export;

(iii) It is labeled on the outside of the shipping package that it is intended for export; and

(iv) It is not sold or offered for sale in the United States.

§ 314.420 Drug master files.

(a) A drug master file is a submission of information to the Food and Drug Administration by a person (the drug master file holder) who intends it to be used for one of the following purposes: To permit the holder to incorporate the information by reference when the holder submits an investigational new drug application under Part 312 or submits an application or an abbreviated application or an amendment or supplement to them under this part, or to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person. FDA ordinarily neither independently reviews drug master files nor approves or disapproves submissions to a drug master file. Instead, the agency customarily reviews the information only in the context of an application under Part 312 or this part. A drug master file may contain information of the kind required for any submission to the agency, including information about the following:

(1) Facilities and operating procedures used to manufacture a drug substance or drug product;

(2) Drug substances or components used in the manufacture of a drug product, or drug products;

(3) Packaging materials;

(4) Components used in drug products, including colors, flavors, and essences; or

(5) Preclinical or clinical data.

(b) An investigational new drug application or an application, abbreviated application, amendment, or supplement may incorporate by reference all or part of the contents of any drug master file in support of the submission if the holder authorizes the incorporation in writing. Each incorporation by reference is required to describe the incorporated material by name, reference number, volume, and page number of the drug master file.

(c) A drug master file is required to be submitted in three copies. The agency has prepared under § 10.90(b) a guideline that provides information about how to prepare a well-organized drug master file. If the drug master file holder adds, changes, or deletes any information in the file, the holder shall notify in writing, each person authorized to reference that information. Any addition, change, or deletion of information in a drug master file (except the list required under paragraph (d) of this section) is required to be submitted in three copies and to describe by name, reference number, volume, and page number the information affected in the drug master file.

(d) The drug master file is required to contain a complete list of each person currently authorized to incorporate by reference any information in the file, identifying by name, reference number, volume, and page number the information that each person is authorized to incorporate. If the holder restricts the authorization to particular drug products, the list is required to include the name of each drug product and the application number, if known, to which the authorization applies.

(e) The public availability of data and information in a drug master file, including the availability of data and information in the file to a person authorized to reference the file, is determined under Part 20 and § 314.430.

§ 314.430 Availability for public disclosure of data and information in an application.

(a) The Food and Drug Administration will determine the public availability of any part of an application under this section and Part 20. For purposes of this section, the application includes all data and information submitted with or incorporated by reference in the application, including investigational new drug applications, drug master files under § 314.420, supplements submitted under § 314.70, reports under § 314.80, and other submissions. For purposes of this section, safety and effectiveness data include all studies and tests of a drug on animals and humans and all studies and tests of the drug for identity, stability, purity, potency, and bioavailability.

(b) FDA will not publicly disclose the existence of an application before an approvable letter is sent to the applicant under § 314.110, unless the existence of the application has been previously publicly disclosed or acknowledged. The Center for Drugs and Biologics will maintain and make available for public disclosure a list of applications for which the agency has sent an approvable letter to the applicant.

(c) If the existence of an unapproved application has not been publicly disclosed or acknowledged, no data or information in the application is available for public disclosure.

(d) If the existence of an application has been publicly disclosed or acknowledged before the agency sends an approval letter to the applicant, no data or information contained in the application is available for public disclosure before the agency sends an approval letter, but the Commissioner may, in his or her discretion, disclose a summary of selected portions of the safety and effectiveness data that are appropriate for public consideration of a specific pending issue, for example, for consideration of an issue at an open session of an FDA advisory committee.

(e) After FDA sends an approval letter to the applicant, the following data and information in the application are immediately available for public disclosure, unless the applicant shows that extraordinary circumstances exist. A list of approved applications is publicly available from the Government Printing Office, Washington, DC 20402. The list is updated monthly.

(1) [Reserved]

(2) If the application applies to a new drug, all safety and effectiveness data previously disclosed to the public as set forth in § 20.81 and a summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the application. The summaries do not constitute the full reports of investigations under section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) on which the safety or effectiveness of the drug may be approved. The summaries consist of the following:

(i) For an application approved before July 1, 1975, internal agency records that describe safety and effectiveness data and information, for example, a summary of the basis for approval or internal reviews of the data and information, after deletion of the following:

(*a*) Names and any information that would identify patients or test subjects or investigators.

(*b*) Any inappropriate gratuitous comments unnecessary to an objective analysis of the data and information.

(ii) For an application approved on or after July 1, 1975, a Summary Basis of Approval (SBA) document that contains a summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process. The SBA is prepared in one of the following ways:

(*a*) Before approval of the application, the applicant may prepare a draft SBA which the Center for Drugs and Biologics will review and may revise. The draft may be submitted with the application or as an amendment.

(*b*) The Center for Drugs and Biologics may prepare the SBA.

(3) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61.

(4) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information after deletion of the following:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(5) A list of all active ingredients and any inactive ingredients previously disclosed to the public as set forth in § 20.81.

(6) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61.

(7) All correspondence and written summaries of oral discussions between FDA and the applicant relating to the application, under the provisions of Part 20.

(8) All records showing the testing of an action on a particular lot of a certifiable antibiotic by FDA.

(f) All safety and effectiveness data and information which have been submitted in an application and which have not previously been disclosed to the public are available to the public, upon request, at the time any one of the following events occurs unless extraordinary circumstances are shown:

(1) No work is being or will be undertaken to have the application approved.

(2) A final determination is made that the application is not approvable and all legal appeals have been exhausted.

(3) Approval of the application is withdrawn and all legal appeals have been exhausted.

(4) A final determination has been made that the drug is not a new drug.

(5) For applications submitted under section 505(b) of the act, the effective date of the approval of the first application submitted under section 505(j) of the act which refers to such drug, or the date on which the approval of an application under section 505(j) which refers to such drug could be made effective if such an application had been submitted.

(6) For applications submitted under sections 505(j), 506, and 507 of the act, when FDA sends an approval letter to the applicant.

(g) The following data and information in an application are not available for public disclosure unless they have been previously disclosed to the public as set forth in § 20.81 or they relate to a product or ingredient that has been abandoned and they do not represent a trade secret or confidential commercial or financial information under § 20.61:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales distribution, and similar data and information, except that any compilation of that data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(h) The compilations of information specified in § 20.117 are available for public disclosure.

§ 314.440 Addresses for applications.

(a) Applicants shall send applications and other correspondence relating to matters covered by this part, except for products listed in paragraph (b) of this section, to the Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, and directed to the appropriate office identified below:

(1) An application under § 314.50 submitted for filing should be directed to the Document and Records Section (HFN–106). Applicants may obtain folders for binding applications from that office. After FDA has filed the application, the agency will inform the applicant which one of the divisions in the Office of New Drug Evaluation is responsible for the application. Amendments, supplements, resubmissions, requests for waivers, and other correspondence about an application that has been filed should be directed to the appropriate division.

(2) An abbreviated application under § 314.55, and amendments, supplements, resubmissions, and other correspondence about an abbreviated application should be directed to the Division of Generic Drugs (HFN–230). Applicants may obtain folders for binding abbreviated applications from that office.

(3) A request for an opportunity for a hearing under § 314.110 or § 314.120 on the question of whether there are grounds for denying approval of an application, except an application under paragraph (b) of this section, should be directed to the Division of Regulatory Affairs (HFN–360).

(b) Applicants shall send applications and other correspondence relating to matters covered by this part for the drug products listed below to the Office of Biologics Research and Review (HFN–825), Center for Drugs and Biologics, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, except applicants shall send a request for an opportunity for a hearing under § 314.110 or § 314.120 on the question of whether these are grounds for denying

approval of an application to the Director, Office of Biologics Research and Review (HFN–800), at the same address.

(1) Ingredients packaged together with containers intended for the collection, processing, or storage of blood and blood components.

(2) Urokinase products.

(3) Plasma volume expanders and hydroxyethyl starch for leukapheresis.

§ 314.445 Guidelines.

(a) The Food and Drug Administration prepares guidelines under § 10.90(b) to help persons comply with requirements in this part.

(b) The Center for Drugs and Biologics will maintain and make publicly available a list of guidelines that apply to the Center's regulations. The list states how a person can obtain a copy of each guideline. A request for a copy of the list should be directed to the Office of Consumer and Professional Affairs (HFN–10), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND NOT MISBRANDED

9. Part 330 is amended in § 330.10 by revising paragraph (c), to read as follows:

§ 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.

* * * * *

(c) Information and data submitted under this section shall include, with respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

PART 430—ANTIBIOTIC DRUGS; GENERAL

10. Part 430 is amended:

a. By revising Subpart B to read as follows:

Subpart B—Antibiotic Drugs Affected by the Drug Amendments of 1962

§ 430.10 Certification or release of antibiotic drugs affected by the drug amendments of 1962.

(a) Before the 1962 amendments to it, the Federal Food, Drug, and Cosmetic Act only permitted the Food and Drug Administration to provide for the certification of batches of antibiotic drugs containing penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin, or any derivative of them. FDA certified those drugs under regulations promulgated on the basis of scientific proof of the drugs' safety and effectiveness. Most drugs containing an antibiotic other than one of those listed were subject to the new drug provisions of the act, which required that an applicant show that the drug was safe and obtain FDA approval of a new drug application before marketing it. An affirmative showing of effectiveness was not then required to obtain approval. Some antibiotic drugs that were not subject to certification, however, were also not subject to the new drug provisions of the act under informal FDA opinions that the drug was "not a new drug" or "no longer a new drug." FDA revoked those opinions under § 310.100 of this chapter.

(b) The 1962 amendments amended section 507 of the act to require the certification, release without certification, or exemption from certification, of all antibiotic drugs on the basis of scientific proof of safety and effectiveness. The amendments provided that FDA implement them for antibiotic drugs that were marketed on April 30, 1963 and were not subject to the certification provisions on that date. FDA is implementing the amendments with respect to antibiotic drugs formerly subject to the new drug provisions of the act through its Drug Efficacy Study Implementation (DESI) program under which the agency is evaluating those antibiotic drugs for efficacy. Until FDA completes that evaluation it will permit continued marketing of those antibiotic drugs under paragraph (c) of this section. The agency is also implementing the 1962 amendments with respect to antibiotic drugs formerly not subject to either the certification or new drug provisions of the act and the agency is evaluating those antibiotic drugs for both safety and efficacy. Until FDA completes that evaluation, it will permit continued marketing of those antibiotic drugs under paragraph (d) of this section.

(c) Unless exempted from certification, FDA will certify or release antibiotic drugs which on April 30, 1963 were the subject of an approved new drug application under section 505 of the act, under regulations providing for certification of the drugs. Although the initial regulation for each of these drugs established under section 507(h) of the act was not conditioned upon an affirmative finding of the effectiveness of the drug, FDA is proceeding under its DESI program to amend or repeal those regulations to provide for certification of those drugs only if they had been shown to be both safe and effective.

(d) Unless exempted from certification, FDA will release without certification an antibiotic drug that was marketed on April 30, 1963, but not subject to certification, and not subject to an approved new drug application on that date, unless FDA has made a determination that the drug has not been shown to be safe or lacks substantial evidence of effectiveness under the DESI program. FDA is proceeding under its DESI program to establish regulations under section 507 to provide for certification of those drugs only if they have been shown to be safe and effective.

§ 430.20 [Removed]

b. By removing § 430.20 *Procedure for the issuance, amendment, or repeal of regulations.*

PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS

11. Part 431 is amended:

§ 431.1 [Amended]

a. In § 431.1 *Requests for certification, check tests and assays, and working standards; information and samples required* by removing and reserving paragraph (b).

§ 431.16 [Removed]

b. By removing § 431.16 *Changes in facilities or controls; changes in mailing or promotional pieces.*

c. By revising § 431.17, to read as follows:

§ 431.17 Request to provide for certification of an antibiotic drug.

A request under section 507 of the Federal Food, Drug, and Cosmetic Act to provide for certification of an antibiotic drug is required to comply with the procedures and meet the requirements applicable to the submission to the Food and Drug Administration and review by the agency of applications and abbreviated applications, and amendments and supplements to them, under Part 314 of this chapter.

§ 431.50 [Amended]

d. In § 431.50 *Forms for certification or exemption of antibiotic drugs* by removing the entries for Form 5 and Form 6.

§ 431.60 [Removed]

e. By removing § 431.60 *Records and reports concerning experience with*

antibiotic drugs for human use for which a certificate or release has been issued.

§ 431.70 [Amended]

f. In § 431.70 *Confidentiality of data and information in an investigational new drug notice for an antibiotic drug,* paragraphs (b) and (c) are amended by changing the references "§ 431.71" to "§ 314.430 of this chapter".

§ 431.71 [Removed]

g. By removing §431.71 *Confidentiality of data and information in an antibiotic drug file.*

PART 433—EXEMPTIONS FROM ANTIBIOTIC CERTIFICATION AND LABELING REQUIREMENTS

§ 433.25 [Removed]

12. Part 433 is amended by removing § 433.25 *Antibiotic drugs intended for export.*

PART 510—NEW ANIMAL DRUGS

§ 510.3 [Amended]

8. Part 510 is amended:

a. In § 510.3 *Definitions and interpretations* in paragraph (1) by removing the words "and § 310.9 of this chapter".

b. In § 510.95 by revising the first sentence, to read as follows:

§ 510.95 Designated journals.

The following journals are available to the Food and Drug Administration and thus permit waiving of the submission of reprints and summaries covering reports contained in these journals to the extent that such requirements are waived in the regulations in this part:

* * * * *

PART 511—NEW ANIMAL DRUGS FOR INVESTIGATIONAL USE

13. Part 511 is amended in § 511.1 by revising paragraph (b)(4)(ii), to read as follows:

§ 511.1 New animal drugs for investigational use exempt from section 512 (a) of the act.

* * * * *

(b) * * *

(4) * * *

(ii) All labeling and other pertinent information to be supplied to the investigators. When such pertinent information includes nonclinical laboratory studies, the information shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

PART 514—NEW ANIMAL DRUG APPLICATIONS

14. Part 514 is amended:

a. In § 514.1 by revising paragraph (b)(12)(iii), to read as follows:

§ 514.1 Applications.

* * * * *

(b) * * *

(12) * * *

(iii) Will respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

b. In § 514.8 by revising paragraph (l), to read as follows:

§ 514.8 Supplemental new animal drug applications.

* * * * *

(l) A supplemental application that contains nonclinical laboratory studies shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

c. In § 514.15 by revising paragraph (c), to read as follows:

§ 514.15 Untrue statements in applications.

* * * * *

(c) Any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, and the application fails to include a brief statement of the reason for the noncompliance.

d. In § 514.110 by revising paragraph (b)(8), to read as follows:

§ 514.110 Reasons for refusing to file applications.

* * * * *

(b) * * *

(8) It fails to include, with respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reasons for the noncompliance.

* * * * *

e. In § 514.111 by revising paragraph (a)(11), to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(11) Any nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

* * * * *

f. In § 514.115 by revising paragraph (b)(4), to read as follows:

§ 514.115 Withdrawal of approval of applications.

* * * * *

(b) * * *

(4) That any nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

* * * * *

PART 570—FOOD ADDITIVES

15. Part 570 is amended in § 570.35 by revising paragraph (c)(1)(vi), to read as follows:

§ 570.35 Affirmation of generally recognized as safe (GRAS) status.

* * * * *

(c) * * *

(1) * * *

(vi) If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set

forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

PART 571—FOOD ADDITIVE PETITIONS

16. Part 571 is amended:

a. In § 571.1 by revising paragraph (k), to read as follows:

§ 571.1 Petitions.

* * * * *

(k) If nonclinical laboratory studies are involved, petitions filed with the Commissioner under section 409(b) of the act shall include, with respect to each study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

b. In § 571.6 by revising the last sentence of the section to read as follows:

§ 571.6 Amendment of petition.

* * * If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each such study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason or the noncompliance.

PART 601—LICENSING

17. Part 601 is amended in § 601.2 by revising the first sentence of paragraph (a), to read as follows:

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Office of Biologics Research and Review, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.104 or § 56.105, and was conducted in compliance with requirements for informed consent set forth in Part 50 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures, and containers proposed to be used for the product.

* * *

* * * * *

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

18. Part 812 is amended in § 812.27 by revising paragraph (b)(3), to read as follows:

§ 812.27 Report of prior investigations.

* * * * *

(b) * * *

(3) If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice regulations in Part 58, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.

PART 1003—NOTIFICATION OF DEFECTS OR FAILURE TO COMPLY

19. Part 1003 is amended in § 1003.31 by revising paragraph (b), to read as follows:

§ 1003.31 Granting the exemption.

* * * * *

(b) Such views and evidence shall be confined to matters relevant to whether the defect in the product or its failure to comply with an applicable Federal standard is such as to create a significant risk of injury, including genetic injury, to any person and shall be presented in writing unless the Secretary determines that an oral presentation is desirable. Where such evidence includes nonclinical laboratory studies, the data submitted shall include, with respect to each such study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. When such evidence includes clinical investigations involving human subjects, the data submitted shall include, with respect to each clinical investigation either a statement that each investigation was conducted in compliance with the requirements set forth in Part 56 of this chapter, or a statement that the investigation is not subject to such requirements in accordance with § 56.104 or § 56.105, and a statement that each investigation was conducted in compliance with the requirements set forth in Part 50 of this chapter.

* * * * *

PART 1010—PERFORMANCE STANDARDS FOR ELECTRONIC PRODUCTS: GENERAL

20. Part 1010 is amended:

a. In § 1010.4 by revising paragraph (b)(1)(ix), to read as follows:

§ 1010.4 Variances.

* * * * *

(b) * * *

(1) * * *

(ix) With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

b. In § 1010.5 by revising paragraph (c)(13), to read as follows:

§ 1010.5 Exemptions for products intended for United States Government use.

* * * * *

(c) * * *

(13) With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

Effective date. These regulations are effective May 23, 1985, except § 314.80 is effective August 22, 1985.

(Secs. 409, 501, 502, 503, 505, 506, 507, 512–516, 520, 701, 706, 52 Stat. 1049–1053 as amended, 1055, 1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 82 Stat. 343–351, 90 Stat. 540–560 (21 U.S.C. 348, 351, 352, 353, 355, 356, 357, 360b–360f, 371, 376); sec. 215, 301, 351, 354–360F, 58 Stat. 609, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 241, 262, 263b–263n)

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

Dated: December 7, 1984.

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