

RESTRICTED MARKETING UNDER ACCELERATED APPROVAL

Preamble to Final Rule and Regulations

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**Department of
Health and Human
Services**

Food and Drug Administration

**21 CFR Parts 314 and 601
New Drug, Antibiotic, and Biological Drug
Product Regulations; Accelerated
Approval; Final Rule**

PREAMBLE ONLY

DEPARTMENT OF HEALTH AND
HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 91N-0278]

RIN 0905-AD65

New Drug, Antibiotic, and Biological
Drug Product Regulations; Accelerated
ApprovalAGENCY: Food and Drug Administration,
HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations under which the agency will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provisions for any necessary continued study of the drugs' clinical benefits after approval or with restrictions on use, if necessary. These new procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic benefit compared to existing treatment.

Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence from adequate and well-controlled studies of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under these procedures will have met the requisite standards for safety and effectiveness under the Federal Food, Drug, and Cosmetic Act (the act) or the Public Health Service Act (the PHS Act) and, thus, will have full approval for marketing.

EFFECTIVE DATE: January 11, 1993.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of April 15, 1992 (57 FR 13234), FDA published proposed procedures under which the

agency would accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. FDA provided 60 days for public comment, and, upon request, in the Federal Register of June 18, 1992 (57 FR 27202), extended the comment period for an additional 30 days until July 15, 1992. The final rule incorporates all of the provisions of the proposed rule and provides additional clarification regarding both timing and content of the submissions of promotional materials and regarding the nature of required postmarketing studies. The agency has added a new provision clarifying when certain postmarketing requirements of the rule will be terminated.

Highlights of the final rule are summarized below, followed by a summary and discussion of the comments.

II. Highlights of the Final Rule

This final rule establishes procedures under parts 314 and 601 (21 CFR parts 314 and 601) under which FDA will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. These procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic advantage over existing treatment. The preamble of the proposed rule (57 FR 13234) provides a description of other mechanisms available to facilitate access, speed development, and expedite review of therapeutic products (e.g., treatment investigational new drug applications (IND's), subpart E, parallel track). Where appropriate, these mechanisms can be utilized in concert with accelerated approval. The major provisions of the final rule are as follows:

A. Scope

The new procedures apply to certain new drug, antibiotic, and biological products used in the treatment of serious or life-threatening diseases, where the products provide meaningful therapeutic advantage over existing treatment (21 CFR 314.500 and 601.40).

B. Criteria for Approval

Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under this final rule will have met the requisite standards for safety and effectiveness under the act or the PHS Act and, thus, will have full approval for marketing (21 CFR 314.510, 314.520, 601.41, and 601.42). Ordinarily, products used to treat serious or life-threatening illnesses, for which approval is based on a surrogate endpoint that is recognized as validated by definitive studies, will be considered for approval under the traditional process rather than under accelerated approval.

C. Postmarketing Studies

Where a drug's approval under these provisions is based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, the applicant will be required to conduct clinical studies necessary to verify and describe the drug's clinical benefit and to resolve remaining uncertainty as to the relation of the surrogate endpoint upon which approval was based to clinical benefit, or the observed clinical benefit to ultimate outcome. The requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval; it is expected that the studies will usually be underway at the time of approval. The proposed regulations have been revised to clarify that required postmarketing studies must also be adequate and well-controlled (21 CFR 314.510 and 601.41).

D. Restrictions on Use After Marketing

FDA may grant marketing approval of a drug or biological product shown to be effective where safe use can only be assured if distribution or use is restricted. Under this final rule, FDA may: (1) Restrict distribution to certain facilities or to physicians with special training or experience, or (2) condition distribution on the performance of

specified medical procedures. The restrictions on use will be tailored to the specific safety issue raised by the particular drug or biological product and agreed to by the applicant at the time of approval (21 CFR 314.520 and 601.42). FDA expects that the imposition of these restrictions on distribution will be rare.

E. Promotional Materials

The final rule requires submission of planned promotional materials, including promotional labeling and advertisements, both prior to approval (reflecting the initial campaign), and following approval, unless informed by the agency that such submission is no longer necessary, at least 30 days before the intended time of initial dissemination of the promotional labeling or initial publication of the advertisement (21 CFR 314.550 and 601.45).

F. Withdrawal of Approval

The final rule establishes an expedited procedure for the withdrawal of approval if: (1) Postmarketing clinical studies fail to verify clinical benefit; (2) the applicant fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug or biological product; (4) the applicant fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug or biological product is not shown to be safe or effective under its conditions of use (21 CFR 314.530 and 601.43).

G. Termination of Requirements

In response to comments, the final rule provides that the requirements set forth in §§ 314.520, 314.530, and 314.550 for new drugs and antibiotics and §§ 601.42, 601.43, and 601.45 for biological products ordinarily will terminate when FDA determines that the results of required postmarketing studies have demonstrated that the drug or biological product has clinical benefit, or, where restrictions on distribution or use have been imposed, when FDA determines that safe use of the drug or biological product can be ensured without such restrictions, e.g., through appropriate labeling. FDA will notify the applicant when these requirements no longer apply (21 CFR 314.560 and 601.46).

III. Effective Date

This regulation will become effective on January 11, 1993.

IV. Comments on the Proposed Rule

FDA received 54 comments on the proposed rule. The comments came from individuals, specific disease organizations, universities, pharmaceutical manufacturers, trade associations, health professionals, and professional societies. The comments reflect broad support and acceptance of the goal of expediting the approval of drugs intended for the treatment of serious and life-threatening illnesses. A number of comments asked that the proposal be finalized expeditiously without change. Many comments posed specific questions and raised important concerns.

A. General Comments

1. One comment suggested that the term "conditional approval" was less confusing and ambiguous than the term "accelerated approval." The comment also referred to the statement in the proposal that "Drugs * * * approved under this proposal will have met the requisite standards * * * under the (act)" and argued that because postmarketing conditions may be imposed, this statement can only be read to say that the requisite standards under the act can only be met by a lower standard of evidence in hand, combined with assurance that further evidence will be obtained.

Another comment expressed concern that the proposal appears to establish a standard for the evaluation of drug product effectiveness that is inconsistent with the substantial evidence requirement of section 505(d) of the act (21 U.S.C. 355(d)), which means "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 of use prescribed, recommended, or suggested in the labeling or proposed labeling * * *." The comment argued that, with few exceptions, the agency has consistently interpreted the "substantial evidence" requirement as an instruction that determinations of effectiveness be based on data unambiguously reflecting the clinical status of subjects evaluated under controlled conditions in bona fide clinical experiments. In the absence of compelling empirical evidence documenting that a drug-induced change in a surrogate measure reliably and consistently predicts improved

clinical outcome, a surrogate indicator is no more than a hypothetical construct. The comment asserted that the proposed rule's endorsement of the use of unvalidated surrogate endpoints, therefore, appears to represent a significant departure from traditional agency interpretations of "substantial evidence" within the meaning of the act because it allows belief rather than evidence to serve as the basis for a conclusion about the effectiveness of a new drug.

Three comments asserted that the new regulations are not needed to approve drugs intended to treat serious or life-threatening illnesses. Two comments cited FDA's approval, without new regulations, of didanosine (formerly called ddi) and zalcitabine (formerly called ddc) in combination with zidovudine (formerly called AZT) based on a surrogate marker, i.e., an increase in CD4 cell counts and the "subpart E" procedures at 21 CFR part 312, which address the need for expediting the development, evaluation, and marketing of new therapies intended to treat life-threatening or severely debilitating illnesses as examples of existing mechanisms for the expedited approval of important new drugs. One comment argued that the act requires that drugs be shown to be "safe" and "effective," and proof of effectiveness is not limited by the act to demonstration of an effect on "survival or irreversible morbidity," as the proposed rule seems to assume. The comment further argued that FDA has considerable statutory discretion to define what type of data constitutes proof of effectiveness, and demonstration of an effect on a surrogate marker is one type of such proof.

The agency believes that what the procedures are called is much less important than what the procedures are. The shorthand term selected by the agency reflects the intent of the rule, especially that part related to use of surrogate markers, which is to make drugs that provide meaningful improvement over existing therapies for serious illnesses widely available (through marketing) at the earliest time consistent with the law. The essence of the proposal is thus acceleration, not the imposition of conditions. Approval under these procedures is dependent on compliance with certain additional requirements, such as timely completion of studies to document the expected clinical benefit. The evidence available at the time of approval under this rule will meet the statutory standard, in that there must be evidence from adequate and well-controlled studies showing that the drug will have

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[50 FR 7493, Feb. 22, 1985, as amended at 55 FR 11581, Mar. 29, 1990; 56 FR 3776, Jan. 31, 1991]

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

SOURCE: 57 FR 58958, Dec. 11, 1992, unless otherwise noted.

§ 314.500 Scope.

This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

[57 FR 58958, Dec. 11, 1992, as amended at 64 FR 402, Jan. 5, 1999]

EFFECTIVE DATE NOTE: At 64 FR 402, Jan. 5, 1999, § 314.500 was amended by removing the phrase "and antibiotic", effective May 20, 1999.

§ 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies

must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

§ 314.530 Withdrawal procedures.

(a) For new drugs approved under §§ 314.510 and 314.520, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 314.510 or § 314.520. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

§ 314.540

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(c) Submission of data and information.

(1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the FEDERAL REGISTER in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

[57 FR 58958, Dec. 11, 1992, as amended at 64 FR 402, Jan. 5, 1999]

EFFECTIVE DATE NOTE: At 64 FR 402, Jan. 5, 1999, § 314.530 was amended by removing the

phrase "and antibiotics" from paragraph (a), effective May 20, 1999.

§ 314.540 Postmarketing safety reporting.

Drug products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.550 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 314.560 Termination of requirements.

If FDA determines after approval that the requirements established in § 314.520, § 314.530, or § 314.550 are no longer necessary for the safe and effective use of a drug product, it will so notify the applicant. Ordinarily, for drug products approved under § 314.510, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the drug product's clinical benefit and the drug product would be appropriate for approval under traditional procedures. For drug products approved under § 314.520, the restrictions would no longer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.