26

Guidance for Industry and Reviewers

Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Procedural 1

Revised, May 1998

Guidance for Industry and Reviewers

Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
The Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Procedural 1

Revised, May 1998

Table of Contents

I. INTRODUCTION 1

II. SUMMARY OF SECTION 125 OF THE FDAMA 1

III. POLICIES 2

A. Definitions 2

B. Application Numbering Conventions 2

C. Applications Subject to Section 125 Exemptions 3

D. Action Letters 5

E. Monographs 5

F. Bulk Drug Applications (Pending and Approved) 5

GUIDANCE FOR INDUSTRY AND REVIEWERS[1]

Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act

I. INTRODUCTION

Section 125 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act), signed into law by President Clinton on November 21, 1997, repealed section 507 of the Federal Food, Drug, and Cosmetic Act (the Act). As a result of the repeal of section 507, which took effect immediately, several of the Agency's administrative processes for reviewing and approving antibiotic drug applications must be changed. This document is intended to clarify, on an interim basis, the administrative processes that will be followed in implementing section 125 of the Modernization Act. In the current revision, the Agency clarifies the procedures applicable to bulk drug substances for products previously regulated under section 507.

II. SUMMARY OF SECTION 125 OF THE FDAMA

Prior to the enactment of the Modernization Act, the Agency approved antibiotic drug marketing applications under section 507 of the Act. In addition, section 507 required the Agency to publish regulations (antibiotic monographs) that set forth standards of identity, strength, quality, and purity for each marketed antibiotic drug.

As a result of the repeal of section 507, the Agency's legal obligation to publish antibiotic monographs has been eliminated from the Act. Moreover, all antibiotic drug applications will now be filed, reviewed, and approved under section 505 of the Act, as are all other new drugs.

Section 125 of the Modernization Act specifically provides that:

1. All full applications approved under section 507 on or before November 20, 1997, are now deemed to have been submitted and filed under section 505(b) and approved for safety and effectiveness under section 505(c).

2. All abbreviated applications approved under section 507 on or before November 20, 1997, are now deemed to have been filed and approved under section 505(j). (The status of antibiotic bulk drug applications that were submitted or approved under former section

---

[1]This guidance has been prepared by the Antibiotic Working Group of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the implementation of the repeal of section 507 of the Federal Food, Drug, and Cosmetic Act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

507 is discussed in section III.F., below.)

3. All applications for drugs that contain an antibiotic that was the subject of any marketing application ***received by the Secretary*** on or before November 20, 1997, (hereafter referred to as an "old" antibiotic) are exempt from the patent listing, patent certification, and exclusivity provisions in section 505. (See section III.C, below.) The effects of this exemption provision include the following:

   a. Antibiotic drug marketing applications that were pending in FDA on or before November 20, 1997, need not be updated with the patent information required under section 505(b)(1) and would not be eligible to claim exclusivity under sections 505(c) or 505(j).

   b. Already approved antibiotic drug marketing applications need not be updated with patent information and cannot seek exclusivity under sections 505(c) or 505(j).

   c. New applications (those received on or after November 21, 1997) under section 505(b) or 505(j) for drugs that contain "old" antibiotics need not include patent information and are not eligible for exclusivity under sections 505(c) or 505(j).

   d. An application received on or after November 21, 1997, that does not contain an "old" antibiotic would be required to file patent information and could seek exclusivity, as appropriate, under sections 505(c) or 505(j).

   e. An abbreviated application under section 505(j) or an application under section 505(b)(2) that refers to a drug that does not contain an "old" antibiotic would be required to include appropriate patent certifications and may be subject to the exclusivity provisions in sections 505(c) or (j), as appropriate.

4. Finally, section 125 preserves for all products containing an antibiotic drug the special export status that has been allowed over the years for antibiotic drugs.

III. POLICIES

A. Definitions

For purposes of section 125 of the Modernization Act, the "date of the enactment of this Act" is November 21, 1997. *Before the date of the enactment of this Act* means on or before November 20, 1997.

B. Application Numbering Conventions

Because of the exemptions that apply to *old* antibiotics, we will continue to maintain our numbering system for new drug applications to allow us to distinguish between applications that contain *old* antibiotics and all other applications. Beginning November 21, 1997, we will apply our NDA numbering system as follows:

1. All applications (except bulk drug applications) assigned a series 50,000 or series 60,000 NDA number on or before November 20, 1997, will keep that number. As discussed above, the exemption provisions in section 125 that exempt applications for drugs that contain "old" antibiotic drugs from the patent listing, patent certification, and exclusivity provisions in section 505 of the Act apply to these applications. For bulk drug applications assigned series 60,000 numbers on or before November 20, 1997, see section III.F, below.

2. Series 50,000 numbers will be assigned to all marketing applications submitted under 505(b) on or after November 21, 1997, to which the section 125 exemptions apply.

3. Series 60,000 numbers will be assigned to all marketing applications submitted under 505(j) on or after November 21, 1997, to which the section 125 exemptions apply.

4. Series 20,000 numbers will be assigned to all marketing applications submitted under 505(b) on or after November 21, 1997, to which the section 125 exemptions do not apply.

5. Series 70,000 or 40,000 numbers will be assigned to all marketing applications submitted under 505(j) on or after November 21, 1997, to which the section 125 exemptions do not apply.

Example. The marketing application (NDA) for azithromycin was submitted to FDA (i.e., the Secretary) before November 21, 1997. If, on or after November 21, 1997, another NDA is submitted for a new dosage form or a new indication for azithromycin, this newly submitted NDA would be assigned a series 50,000 number because the drug (i.e., azithromycin) that is the subject of the new NDA was originally received by the Secretary (see section C.2., below) prior to November 21, 1997.

C. Applications Subject to Section 125 Exemptions

Section 125 of the Modernization Act exempts from the patent listing, patent certification, and sections 505(c) and (j) marketing exclusivity provisions, marketing applications for drugs that contain *old* antibiotics. (See section 125(d)(2) of the Modernization Act for a list of the specific provisions in section 505 of the Act that do not apply to applications that contain *old* antibiotics.) For purposes of implementing this provision, consider these

points in deciding whether an application is subject to the exemption.

1. The drug that is the subject of the application must contain (in whole or as part of a combination) an *antibiotic drug*. As was the case prior to the repeal of section 507, an *antibiotic drug* is:

   any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for use by man containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including the chemically synthesized equivalent of any such substance) or any derivative thereof. (See new section 201(jj) of the Act.)

2. The antibiotic drug that is contained in the application must have been the subject of a marketing application that was *received **by the Secretary*** on or before November 20, 1997. For purposes of section 125 of the Modernization Act, this would include any antibiotic application (including an old Form 5 or Form 6 application) that was:

   a. Received by FDA (as evidenced by an Agency date stamp) on or before November 20, 1997.

   b. Filed or approved on or before November 20, 1997.

   c. Received on or before November 20, 1997, and is presently under review.

   d. The subject of an action letter on or before November 20, 1997 (e.g., AE, NA, or WD), and is now *back with the company*.

   e. Received on or before November 20, 1997, filed, reviewed, approved, and then withdrawn from the market (either for safety or other reasons).

   f. Received on or before November 20, 1997, and then withdrawn prior to filing and has not been further submitted.

   g. Received on or before November 20, 1997, and subsequently refused filing and has not been further submitted.

   h. Received on or before November 20, 1997, and was unacceptable for filing under PDUFA for failure to submit the appropriate user fee and has not been further submitted.

   For purposes of section 125 of the Modernization Act *received by the Secretary* does ***not*** mean (1) canceled applications (i.e., administrative errors) or (2)

applications for which only a *presubmission* was received without a full submission ever having been received subsequently by the Agency. (See also 21 CFR 314.101(d).)

3. Other factors, such as the extent to which derivatives of the active moiety of an *old* antibiotic are also considered to be *old* antibiotics, are beyond the scope of this administrative guidance and may be addressed as part of an Agency rulemaking proceeding.[2]

D. Action Letters

Beginning November 21, 1997, the action letter templates for 507 drugs will no longer be used. Section 507 no longer provides a statutory basis for approval of a drug product. All action letters must use the 505(b) or 505(j) templates, even for drugs that originally were submitted under section 507, but are the subject of Agency action on or after November 21, 1997.

For action letters on marketing applications to which the section 125 exemptions apply, the following sentence should be added after the initial reference to section 505: "We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997."

E. Monographs

On and after November 21, 1997, FDA will no longer publish or maintain antibiotic monographs in the Code of Federal Regulations (CFR). Products approved under section 505 do not require such monographs. The Agency recently published a direct final rule to remove the antibiotic monographs from the CFR (63 FR 26066, May 12, 1998).

F. Bulk Drug Applications (Pending and Approved)

Prior to the repeal, the Agency consistently read section 507 to require that bulk antibiotic drug substances must be either batch certified or exempted from batch certification through the approval of an antibiotic drug application. Applications for bulk antibiotic drugs were previously assigned 60,000 application numbers. The Agency, however, has not required the filing or approval of such an application under section 505 for bulk drug substances used in the manufacture of non-antibiotic new drug products. Rather, in accordance with 21 CFR 314.420, information about drug substances, drug substance intermediates, and materials used in their preparation or in the preparation of new drug

---

[2] Section 125 of the Modernization Act also authorizes the Secretary to publish the established name of each antibiotic drug that is subject to the section 125 exemption (i.e., each "old" antibiotic drug). The Agency has not yet decided how it will implement this authority.

products may be filed and maintained as Type II Drug Master Files (DMFs). Alternatively, drug substance information may be filed as part of the marketing application for the finished dosage form of the drug.

In light of the repeal of section 507 and the Agency's longstanding regulatory approach to handling bulk drug substances under section 505, the Agency intends to administratively convert all antibiotic bulk drug substance applications ("bulk applications") into DMFs.

Action — After August 31, 1998, all unapproved bulk applications that were pending in CDER as of November 21, 1997, will be administratively converted into DMFs. Likewise, after August 31, 1998, FDA will begin administratively converting all approved bulk applications into DMFs. Any bulk application received by CDER after November 21, 1997, will be returned to the applicant. The agency has not approved any bulk applications since the repeal of section 507 went into effect on November 21, 1997.

Following issuance of this revised guidance, the Agency will provide written notice to each sponsor of a bulk application of the Agency's intention to convert the application into a DMF. Following the conversion of each application, the Agency will notify the sponsor of the newly assigned DMF reference number.

The Agency does not intend at this time to require sponsors of converted bulk applications to submit new letters of authorization for each of the dosage form manufacturers who may reference the DMF. Similarly, the Agency does not expect to require dosage form manufacturers to amend their marketing applications to reference the newly assigned DMF number. However, following conversion of a bulk application, any new letters of authorization or other correspondence relating to the bulk substance will be expected to reference the new DMF number, in accordance with 21 CFR 314.420(b).

Sponsors of bulk applications need not take any action for their applications to be converted. The Agency expects most, if not all, bulk applications will be handled under this process. However, if a sponsor does not wish to maintain a DMF for a particular bulk drug substance, the information in the bulk application may be merged into one or more dosage form applications, or the Agency may cancel and retire the application in accordance with Agency record keeping practices. The Agency also would consider requests for more expeditious conversion of bulk applications to DMFs from sponsors who would like their applications converted before August 31, 1998. Sponsors interested in one of these alternatives should contact Jerry Phillips, Director, Division of Labeling and Program Support, CDER, at 301-827-5846, before August 31, 1998.