ATTACHMENT D
Revised as of December 16, 1994

# APPLICATION, PRODUCT, AND ESTABLISHMENT FEES

## COMMON ISSUES AND THEIR RESOLUTION*

This document describes how FDA resolved some important fee assessment issues that arose during the preparation of product, establishment, application, and supplement invoices.

## A. Product Fees

### 1. Products with generic competition

#### a. Generally

The Prescription Drug User Fee Act of 1992 (the User Fee Act) contains an exception from product fees for products that are "the same product as a product approved under an application filed under section 505(b)(2) or 505(j)."[1] Products that are the same as products approved under full new drug applications (NDA's), i.e., those approved under 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 355(b)(1), do not qualify for the exclusion. "Same" means the same active ingredient, strength, potency, dosage form, and route of administration. The products need **not** have the same "Orange Book"[2] Therapeutic Equivalence code to be considered the same.

The ownership of the 505(b)(2) or 505(j) application is not a determining factor. It is the existence of an approved § 505(b)(2) or (j) application that triggers the exemption, whether or not the (b)(2) or (j) application is owned by the same NDA or product license application (PLA) holder as the 505(b)(1) application.

The marketing status of the 505(b)(2) or 505(j) application also is not a determining factor. If the 505(b)(2) or (j) application has been approved and not withdrawn, the first approved product is excluded from fees even if the generic product is not presently marketed. Tentative approvals of a 505(j) application are not considered approvals.

*Shading indicates revisions since 7/16/93 revision.

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[1] 21 U.S.C. § 379h (a)(3)(B).

[2] U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Management, "Approved Drug Products with Therapeutic Equivalence Evaluations," 13th Edition, 1993.

Note: the product fee exclusion lists that were previously mailed to NDA or PLA holders on February 1 and 17, 1993, listed "paper" NDA's as an exclusion (explanation P-2), without regard to the date on which such approval was granted. However, paper NDA's that were approved before 1984 (when section (b)(2) was added to the statute) are not eligible for exclusion from product fees.

b. Antibiotics

Innovator antibiotic drug products (that is, the initial certification or initial approval of an antibiotic drug under section 507 of the Federal Food, Drug, and Cosmetic Act) are subject to product fees. Generic antibiotic drug products (those that are not the first approval of a particular antibiotic drug) are not subject to product fees.

Innovator antibiotic drug products must continue to pay product fees even after subsequent generic antibiotic drug products are approved. The User Fee Act does not exclude from product fees innovator drugs approved under section 507, following approval of a generic version of the drug. Invoices for innovator antibiotic products for which there are generic competitors will be addressed in a separate reconciliation effort, in the next cycle of invoices.

Bulk antibiotic drugs are not subject to product fees because they are not products in finished dosage form (see section B.3, below).

2. Listed Products and Products no longer marketed

To be subject to product fees, a "prescription drug product" must be the subject of an approved "human drug application" and must be listed under section 510 of the Federal Food, Drug, and Cosmetic Act. Under section 510 and 21 CFR 207, firms that own or operate establishments engaged in the manufacture of pharmaceuticals are required to register all such establishments with the Food and Drug Administration, update their registration annually, file a list of all drugs processed for commercial distribution at their establishments, and update the drug list in June and December of each year. For the purposes of assessing product fees, the agency considers a product to be listed under section 510 on the date of receipt of the initial submission of information for the intended purpose of listing the product, whether or not the agency finds the information submitted is complete or requests the submission of additional information. The agency considers a product to be de-listed on the date of receipt of the submission

deleting the product from Drug Listing. A product is subject to fees if it is listed under section 510, whether or not it is marketed.

3. Products transferred to another NDA or PLA holder

An NDA or PLA holder generally is liable for a product fee in any fiscal year in which the criteria for the fee are met (e.g., when a new product is approved or if a previously approved product continues to be marketed). If a product is transferred from one NDA or PLA holder to another during the fiscal year, the first NDA or PLA holder will be charged the fee in that fiscal year, and the new NDA or PLA holder will be charged the product fee in the next and subsequent years.

4. Products manufactured in the U.S. but only marketed abroad

If a product is approved under an NDA or PLA and listed under section 510 of the FD&C Act, it is subject to product fees, even if it is marketed only outside of the United States (if other criteria are met). The FD&C Act listing provision does not exclude from the listing requirements United States firms that manufacture for export only. Section 510(j) requires that every person who registers under section 510(b) list the drugs it manufactures "for commercial distribution," including commercial distribution to a foreign country.

5. Blood Collection Containers

Blood collection containers are not subject to user fees.

6. Products made available for emergency use only

Products made available for emergency use only are subject to user fees if they are approved products, are not the same as products approved under 505(j) or 505(b)(2), and are subject to listing under section 510 of the FD&C Act.

7. Prescription Drug Products

Some prescription drug products, such as injections, are normally administered by a physician in the physician's office, and normally, no prescription is written for these products. Nevertheless, if the approval (NDA or PLA) specifies that the product may be dispensed only under prescription pursuant to section 503(b) of the FD&C Act, it is a prescription drug product subject to product fees.

8. Product Fee Triggers

If the other product fee criteria are met, an original application or supplement with or without clinical data pending after September 1, 1992 would trigger product fees for all prescription drugs listed under section 510.

9. Different strengths or potencies

Products that differ in strength or potency are subject to separate product fees. Products of the same strength or potency packaged in different container sizes are not subject to separate fees. The primary determining criterion is strength or potency, which is identified by the product field, the middle segment of the National Drug Code (NDC). However, where distinct differences exist between products of the same potency (e.g., Tuberculin Purified Protein Derivative (PPD), Tine Test versus Tuberculin PPD for intradermal injection, or oral contraceptives products in 21 and 28 day regimens), FDA will also consider the product portion of the NDC. In such cases, if the product codes are different, normally a separate fee will be assessed for each product.

10. DESI Products

Products that are currently undergoing DESI review but have not yet been found to be effective do not qualify for user fees. The standard for approval of new drugs established in the 1962 amendments to the FD&C Act requires demonstration of both safety and effectiveness. Approvals for such products prior to 1962 were on the basis of safety only. Therefore, they are not considered to be prescription drug products approved under section 505(b)(1) until their review under DESI is completed.

11. Large Volume Parenterals (LVP's)

LVP's approved before September 1, 1992, are not subject to product fees. Parenteral products sold in powders for reconstitution do not qualify for the exclusion for LVP's and are subject to fees. The legislative history (Senate Joint Statement) defines LVP's as "single dose sterile fluids." Products used for irrigation can be considered LVP's under the Act.

12. Prescription Products Composed Wholly or Partly of Insulin: "Human drug application" is defined in the PDUFA as an application for approval of a new drug submitted under section 505(b)(1) and certain applications submitted under

section 505(b)(2). The agency has determined that applications for insulin products are submitted and approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act in addition to being subject to the certification requirements of section 506. Therefore, the agency will assess 1) application fees for human drug applications for all insulin products (whether they are for prescription or over-the-counter (OTC) sale), 2) establishment fees for manufacturing facilities of prescription insulin products, and 3) product fees for prescription insulin products. PDUFA does not authorize the assessment of product fees for OTC products nor for establishments that only manufacture OTC products.

**B. Establishment Fees**

1. Establishment Fee Triggers

If the other establishment fee criteria are met, an original application or supplement (with or without clinical data) that is pending after September 1, 1992, would trigger establishment fees for all qualifying establishments.

2. Parent/subsidiary and joint venture relationships

A person who had an application or supplement pending after September 1, 1992, and who owns and manages an establishment that manufactures at least one prescription drug product as defined in the User Fee Act must pay establishment fees for its establishment. The person need not be the holder of the approved NDA or PLA for the product manufactured at the establishment.

3. Finished dosage form

Unless a product is manufactured in finished dosage form at an establishment, the establishment is not subject to an establishment fee. "Finished dosage form" means in a form approved for administration to a patient without further manufacturing. Thus, if a product is sterilized by filtration and placed into vials by a "contract manufacturer" that has no pending NDA's or PLA's or supplements after September 1, 1992, then no establishment fee is due for either the contract manufacturer or the facility that performs the rest of the manufacturing steps.

4. Foreign Manufacturing Facilities

If a prescription drug product as defined in the User Fee Act is manufactured in a foreign plant for foreign marketing under an approved NDA, the foreign establishment would be subject to establishment fees if it were owned by an NDA or PLA holder that had a pending NDA, PLA, or supplement after September 1, 1992.

**C. Application Fees**

1. Resubmitted Applications

Applications or supplements withdrawn or refused for filing before September 1, 1992, and resubmitted after September 1, 1992, are treated as new original or supplemental applications and will be assessed fees.

2. Type 6 NDA's

Type 6 NDA's are defined in Center for Drug Evaluation and Research Staff Manual Guide 4820.3 (January 22, 1992) as, "A drug product that duplicates a drug product (same active moiety, same salt, same formulation, or same combination) already approved or marketed in the U.S. by the same or another firm except that it provides for a new indication." Type 6 NDA's will be treated as efficacy supplements for purposes of assessing user fees. Therefore, if they contain clinical data, they will be assessed the fee for supplements containing clinical data. If they do not contain clinical data, they will not be assessed a fee.