

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 314

[Docket No. 99N-3088]

RIN 0910-AB33

**Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

DMB

Display Date	1-21-00
Publication Date	1-24-00
Certifier	SNReese

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**SUMMARY:** The Food and Drug Administration (FDA) is proposing regulations to exempt marketing applications for certain antibiotic drug products from regulatory provisions governing marketing exclusivity and patents. The proposal would apply to marketing applications for drug products containing an antibiotic drug that was the subject of a marketing application received by FDA before November 21, 1997, the effective date of the Food and Drug Administration Modernization Act of 1997 (Modernization Act). This action is intended to bring the agency's regulations into conformance with certain transitional provisions of the Modernization Act. FDA is including in the proposed regulation a list of the active moieties of antibiotic drugs that were the subjects of marketing applications received by FDA before November 21, 1997.

**DATES:** Written comments by (*insert date 90 days after date of publication in the Federal Register*).

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

NPR-1

**FOR FURTHER INFORMATION CONTACT:** Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

**SUPPLEMENTARY INFORMATION:**

**I. The Modernization Act**

On November 21, 1997, the President signed the Modernization Act (Public Law 105-115). Section 125(b) of the Modernization Act repealed section 507 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 357 (1996)). Section 507 was the section of the act under which the agency certified antibiotic drugs. Section 125(b) of the Modernization Act also made conforming amendments to the act.

In the **Federal Register** of May 12, 1998 (63 FR 26066), and January 5, 1999 (64 FR 396), the agency issued conforming amendments to its regulations to remove provisions governing certification of antibiotic drugs (21 CFR parts 430 to 460) and to make other changes needed to reflect the repeal of section 507 of the act.

Section 125(d)(1) of the Modernization Act provides that marketing applications for antibiotic drugs that were approved under former section 507 of the act will be considered to have been submitted and approved under the new drug application (NDA) submission and approval provisions found at section 505(b) and (c) of the act (21 U.S.C. 355(b) and (c)). If the marketing application was an approved abbreviated antibiotic drug application, it will be considered to have been submitted and approved under the abbreviated new drug application (ANDA) provisions found in section 505(j) of the act.

The Modernization Act also exempts certain antibiotic-related drug marketing applications from the marketing exclusivity and patent provisions found in section 505 of the act.<sup>1</sup> Under former section 507 of the act, antibiotic drug applications were not subject to the patent listing and

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<sup>1</sup> The Modernization Act does not affect whatever rights patent holders may have regarding patent term extensions under 35 U.S.C. 156 for patents claiming antibiotic drug products.

exclusivity provisions in section 505 of the act. Section 125 of the Modernization Act preserves this distinction with an expansive line. Section 125 exempts those applications that contain an antibiotic drug that was the subject of a marketing application received by FDA under former section 507 of the act before November 21, 1997 (prerepeal antibiotic drugs). Drugs that were approved and marketed under former section 507 of the act, as well as those that were the subject of applications that may have been withdrawn, not filed, or refused approval under section 507 of the act are excluded from the patent listing and exclusivity provisions.

Specifically, section 125(d)(2) of the Modernization Act provides that marketing applications for drug products that contain prerepeal antibiotic drugs are not subject to the following provisions of section 505 of the act:

- The third and fourth sentences of section 505(b)(1) (requiring submission of patent information in NDA's).
- Section 505(b)(2)(A) (requiring that 505(b)(2) applications contain patent certifications).
- Section 505(b)(2)(B) (requiring that applications submitted under section 505(b)(2) of the act (505(b)(2) applications) contain a statement about relevant method of use patents).
- Section 505(b)(3) (requiring applicants submitting 505(b)(2) applications (505(b)(2) applicants) to provide notice to the patent owner and NDA holder of the certification of invalidity or noninfringement of a patent).
- Section 505(c)(2) (requiring submission of patent information if that information becomes available after an NDA is submitted).
- Section 505(c)(3) (providing for delayed effective dates of approval of 505(b)(2) applications under patent provisions of the act).
- Section 505(d)(6) (allowing FDA to refuse to approve an application that does not contain required patent information).
- Section 505(e)(4) (requiring FDA to withdraw approval of an application if the applicant refuses to submit required patent information).

- Section 505(j)(2)(A)(vii) and (j)(2)(A)(viii) (requiring ANDA's to contain patent certifications or other patent information).
- Section 505(j)(2)(B) (requiring ANDA applicants to provide notice to the patent owner and NDA holder of the certification of invalidity or noninfringement of a patent).
- Section 505(j)(5)(B) (providing for delayed effective dates of approval of ANDA's under patent provisions of the act).<sup>2</sup>
- Section 505(j)(5)(D) (describing submission of and effective dates of approval of ANDA's under marketing exclusivity provisions of the act).

Section 125(d)(3) of the Modernization Act authorizes FDA to make available to the public the established name of each antibiotic drug that was the subject of a marketing application received by FDA under former section 507 of the act before November 21, 1997.

## II. Description of the Rule

### *A. List of Regulatory Provisions That Are Not Applicable*

This proposed rule would exempt from the regulatory requirements that correspond to the statutory requirements described above, applications or abbreviated applications in which the drug product that is the subject of the application contains a pre-repeal antibiotic drug. Specifically, under the proposed rule, the following provisions found in part 314 (21 CFR part 314) would not apply to marketing applications for drug products that contain pre-repeal antibiotic drugs:

- Sections 314.50(h) and 314.53 (relating to submission of patent information in NDA's).
- Section 314.50(i) (relating to patent certifications and statements about relevant method of use patents in 505(b)(2) applications).
- Section 314.52 (relating to notices to the patent owner and NDA holder of certification of invalidity or noninfringement of a patent by 505(b)(2) applicants).

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<sup>2</sup>The Modernization Act added a new section 505(j)(3) to the act. This resulted in the renumbering of sections 505(j)(3) through (j)(8) as sections 505(j)(4) through (j)(9), respectively.

- Section 314.94(a)(12) (relating to patent certifications and statements about relevant method of use patents in ANDA's).
- Section 314.95 (relating to notices to the patent owner and NDA holder of certification of invalidity or noninfringement of a patent by ANDA applicants).
- Section 314.107(b) through (f) (relating to delayed effective dates of approval of ANDA's and 505(b)(2) applications under patent provisions of the act).
- Section 314.108(b) (relating to submission of and effective dates of approval of ANDA's and 505(b)(2) applications under marketing exclusivity provisions of the act).
- Section 314.125(b)(18) (relating to refusal to approve an NDA that does not contain required patent information).
- Section 314.150(a)(2)(v) (relating to withdrawal of approval of an NDA if the applicant refuses to submit required patent information).

The brief parenthetical descriptions of the various provisions of part 314 in this section and in the codified portion of this proposed rule (as well as the similar descriptions of provisions of section 505 of the act given in section I of this document) are provided merely as aids to the reader in understanding the scope of the proposed rule. They are not intended to have any regulatory significance and should not be understood to be statements of agency policy regarding the provisions they describe.

#### *B. List of Pre-Repeal of Antibiotic Drugs*

In applying section 125(d)(2) of the Modernization Act, the agency must determine whether a drug that is the subject of an NDA or ANDA contains a pre-repeal antibiotic drug. As described in section I, the Modernization Act specifies patent listing and exclusivity provisions that will not apply when the drug that is the subject of any application contains an antibiotic drug, and the antibiotic drug was the subject of any application received under section 507 of the act prior to November 21, 1997. Section 125(d)(3) of the Modernization Act also authorizes FDA to publish

the established name of each antibiotic drug that was the subject of any application for marketing received by FDA under former section 507 of the act.

The term “antibiotic drug,” as used in section 125(d) of the Modernization Act, is defined as:

\* \* \* 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 human use 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 a chemically synthesized equivalent of any such substance) or any derivative thereof.

21 U.S.C. 321(jj)

Thus, the term “antibiotic drug” includes not only the “chemical substance which is produced by a micro-organism,” and which “has the capacity to inhibit or destroy micro-organisms,” but also “any derivative” of any such substance, such as a salt or ester of the substance.

For this reason, and the reasons discussed below, the determination under section 125(d) of the Modernization Act of whether a drug contains a pre-repeal antibiotic depends on whether the drug that is the subject of a marketing application contains an active moiety that can be found in a pre-repeal antibiotic drug.

An active moiety is the molecule or ion responsible for physiological or pharmacological action, excluding appended portions that would cause the drug to be an ester, salt, or other noncovalent derivative of the molecule (see § 314.108(a)). FDA has consistently looked at active moieties to determine if the exclusivity protection granted to a drug product would allow a subsequent ANDA or application described in section 505(b)(2) of the act to be submitted or approved.

The agency’s primary regulation governing marketing exclusivity is found at § 314.108. This regulation, which was proposed in the **Federal Register** of July 10, 1989 (54 FR 28872), and made final in the **Federal Register** of October 3, 1994 (59 FR 50338), incorporated an

interpretation of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) (the Hatch-Waxman Amendments) that had been adopted by the agency shortly after the enactment of the Hatch-Waxman Amendments on September 24, 1984. The Hatch-Waxman Amendments established the exclusivity and patent provisions that are addressed by the exemptions described in section 125(d)(2) of the Modernization Act, and are the subject of this rulemaking. In interpreting the exclusivity provisions in the Hatch-Waxman Amendments, the agency concluded that Congress did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds. (See, e.g., Congressional Record H9124 (September 6, 1984) (statement of Representative Waxman); H. Rept. 857, Part I, 98th Cong., 2d sess. 38 (1984).) Therefore, the agency determined that it is appropriate to assess whether the drug seeking exclusivity is a new chemical entity, that is, a drug that does not contain any previously approved active moiety.

This approach is also consistent with FDA’s drug classification system, which assesses and classifies NDA’s based upon the characteristics of the active ingredient or ingredients of the product. (See 54 FR 28872 at 28897.)

The language of section 125(d)(2) of the Modernization Act likewise supports the conclusion that Congress did not intend to confer exclusivity on, or require patent listing for, products that represent minor or incremental variations on pre-repeal antibiotic drugs. As discussed above, Congress in section 125(d)(2) of the Modernization Act chose to exclude all drugs containing pre-repeal “antibiotic drugs,” a term that by definition includes the active drug substance and “any derivative thereof” (see section 201(jj) of the act (21 U.S.C. 321(jj))).

Accordingly, the agency is proposing to implement section 125(d)(2) of the Modernization Act by relying on a comparison of active moieties to determine whether the drug that is the subject of an NDA contains a pre-repeal antibiotic drug. NDA’s for products that contain, for example, a salt of a pre-repeal antibiotic drug, or that propose such things as a new manufacturing process,

new dosage form, or new use of a pre-repeal antibiotic drug, will be subject to the exceptions listed in section 125(d)(2) of the Modernization Act and proposed § 314.109(a).

To help interested persons determine which drug products would be exempt from the marketing exclusivity and patent provisions described above, FDA will maintain in the Code of Federal Regulations a list of the names of each pre-repeal active moiety. A proposed version of that list is included as § 314.109(b).

The list will provide all of the information required for an interested person to determine whether a marketing application is for a drug that contains a pre-repeal antibiotic drug. The list is intended to be comprehensive, but the inadvertent omission of an active moiety found in a pre-repeal antibiotic drug will not affect the regulatory status of a marketing application for a drug that contains that active moiety; the application will still be exempt from the statutory and regulatory requirements regarding marketing exclusivity and patents described above. A person who believes that a drug has been improperly included or omitted from the list should submit to the Dockets Management Branch (address above) written comments suggesting amendments to the list, along with any information that supports the suggested amendments. Comments should be identified with the docket number found in brackets in the heading of this document.

### **III. Environmental Impact**

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

### **IV. Analysis of Impacts**

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches

that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of \$100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. Because, the proposed rule is a significant regulatory action as defined by the Executive Order and it was subject to review under the Executive Order.

The Regulatory Flexibility Act requires that if a rule has a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options to minimize the economic impact on small entities. The agency certifies, for the reasons discussed below, that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The Unfunded Mandates Reform Act requires an agency to prepare a budgetary impact statement before issuing any rule likely to result in a Federal mandate that may result in expenditures by State, local, and tribal governments or the private sector of \$100 million (adjusted annually for inflation) in any one year. Exempting applications for certain antibiotic drugs from regulatory provisions dealing with marketing exclusivity and patent information will not result in any increased expenditures by State, local, and tribal governments or the private sector. Because this proposed rule will not result in an expenditure of \$100 million or more by any governmental entity or the private sector, no budgetary impact statement is required.

This proposed rule is intended to bring FDA's regulations governing the new drug approval process into conformance with the transitional provisions found in section 125(d)(2) of the Modernization Act. This proposed rule is not intended to create any rights or responsibilities that are not found in the statute. For these reasons, the agency believes that this proposed rule is necessary and that it is consistent with the principles of Executive Order 12866; that it is not

a significant regulatory action under that Executive Order; that it will not have a significant economic impact on a substantial number of small entities; and that it is not likely to result in an annual expenditure in excess of \$100 million.

## **V. Paperwork Reduction Act of 1995**

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

## **VI. Request for Comments**

Interested persons may, on or before (*insert date 90 days after date of publication in the Federal Register*), submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

## **List of Subjects in 21 CFR Part 314**

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 314 be amended as follows:

## **PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG**

1. The authority citation for 21 CFR part 314 is revised to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 371, 374, 379e; sec. 125(d), Pub. L. 105–115, 111 Stat. 2296.

2. Add § 314.109 to subpart D to read as follows:

**§ 314.109 Marketing exclusivity and patent provisions not applicable to certain antibiotic-related drug marketing applications.**

(a) The following regulatory provisions do not apply to any application or abbreviated application in which the drug that is the subject of the application or abbreviated application contains an antibiotic drug that has the same active moiety (as defined in § 314.108(a)) as an antibiotic drug that was the subject of a marketing application received by FDA under former section 507 of the act (21 U.S.C. 357 (1996)) before November 21, 1997:

(1) Sections 314.50(h) and 314.53 (relating to submission of patent information in applications).

(2) Section 314.50(i) (relating to patent certifications and statements about relevant method of use patents in 505(b)(2) applications).

(3) Section 314.52 (relating to notices of certification of invalidity or noninfringement of a patent by 505(b)(2) applicants).

(4) Section 314.94(a)(12) (relating to patent certifications and statements about relevant method of use patents in 505(j) applications).

(5) Section 314.95 (relating to notices of certification of invalidity or noninfringement of a patent by 505(j) applicants).

(6) Section 314.107(b) through (f) (relating to delayed effective dates of approval of 505(j) applications and 505(b)(2) applications under patent provisions of the act).

(7) Section 314.108(b) (relating to submission of and effective dates of approval of 505(j) applications and 505(b)(2) applications under marketing exclusivity provisions of the act).

(8) Section 314.125(b)(18) (relating to refusal to approve an application that does not contain required patent information).

(9) Section 314.150(a)(2)(v) (relating to withdrawal of approval of an application if the applicant refuses to submit required patent information).

(b) The following are the active moieties of antibiotic drugs that were the subject of marketing applications received by FDA under former section 507 of the act before November 21, 1997. The list is intended to be comprehensive, but the inadvertent omission of an active moiety will not affect the regulatory status of a marketing application for a drug product that contains that active moiety.

Almecillin

Amdinocillin

Amikacin

Amoxicillin

Amphotycin

Amphotericin B

Ampicillin

Azacitidine

Azaserine

Azithromycin

Azlocillin

Aztreonam

Bacampicillin

Bacitracin

Benzyl penicilloyl-polylysine

Bleomycin

Candicidin

Capreomycin

Carbenicillin

Cefaclor

Cefadroxil

Cefamandole

Cefazolin

Cefdinir

Cefepime

Cefixime

Cefmenoxime

Cefmetazole

Cefodizime

Cefonicid

Cefoperazone

Ceforanide

Cefotaxime

Cefotetan

Cefotiam

Cefoxitin

Cefpiramide

Cefpodoxime

Cefprozil

Cefsulodin

Ceftazidime

Ceftibuten

Ceftizoxime

Ceftriaxone

Cefuroxime

Cephacetrile

Cephalexin

Cephaloglycin

Cephaloridine

Cephalothin  
Cephapirin  
Cephradine  
Chloramphenicol  
Chlortetracycline  
Cilastatin  
Clarithromycin  
Clavulanate/clavulanic acid  
Clindamycin  
Clioquinol  
Cloxacillin  
Colistimethate  
Colistin  
Cyclacillin  
Cycloserine  
Cyclosporine  
Dactinomycin  
Dalfopristin  
Daunorubicin  
Demeclocycline  
Detorubicin  
Dicloxacillin  
Dihydrostreptomycin  
Dirithromycin  
Doxorubicin  
Doxycycline  
Epirubicin

Erythromycin  
Flouxacillin  
Fosfomicin  
Fusidate/fusidic acid  
Gentamicin  
Gramicidin  
Griseofulvin  
Hetacillin  
Idarubicin  
Imipenem  
Ivermectin  
Kanamycin  
Lincomycin  
Loracarbef  
Meclocycline  
Meropenem  
Methacycline  
Methicillin  
Mezlocillin  
Minocycline  
Mitomycin  
Moxalactam  
Mupirocin  
Mycophenolate/mycophenolic acid  
Nafcillin  
Natamycin  
Neomycin

Netilmicin  
Niphimycin  
Novobiocin  
Nystatin  
Oleandomycin  
Oxacillin  
Oxytetracycline  
Paromomycin  
Penicillamine  
Penicillin G  
Penicillin V  
Phenethicillin  
Piperacillin  
Plicamycin  
Polymyxin B  
Quinupristin  
Rifabutin  
Rifampin  
Rifamycin  
Rolitetracycline  
Sisomicin  
Spectinomycin  
Streptomycin  
Streptozocin  
Sulbactam  
Sultamicillin  
Tacrolimus

Tazobactam

Teicoplanin

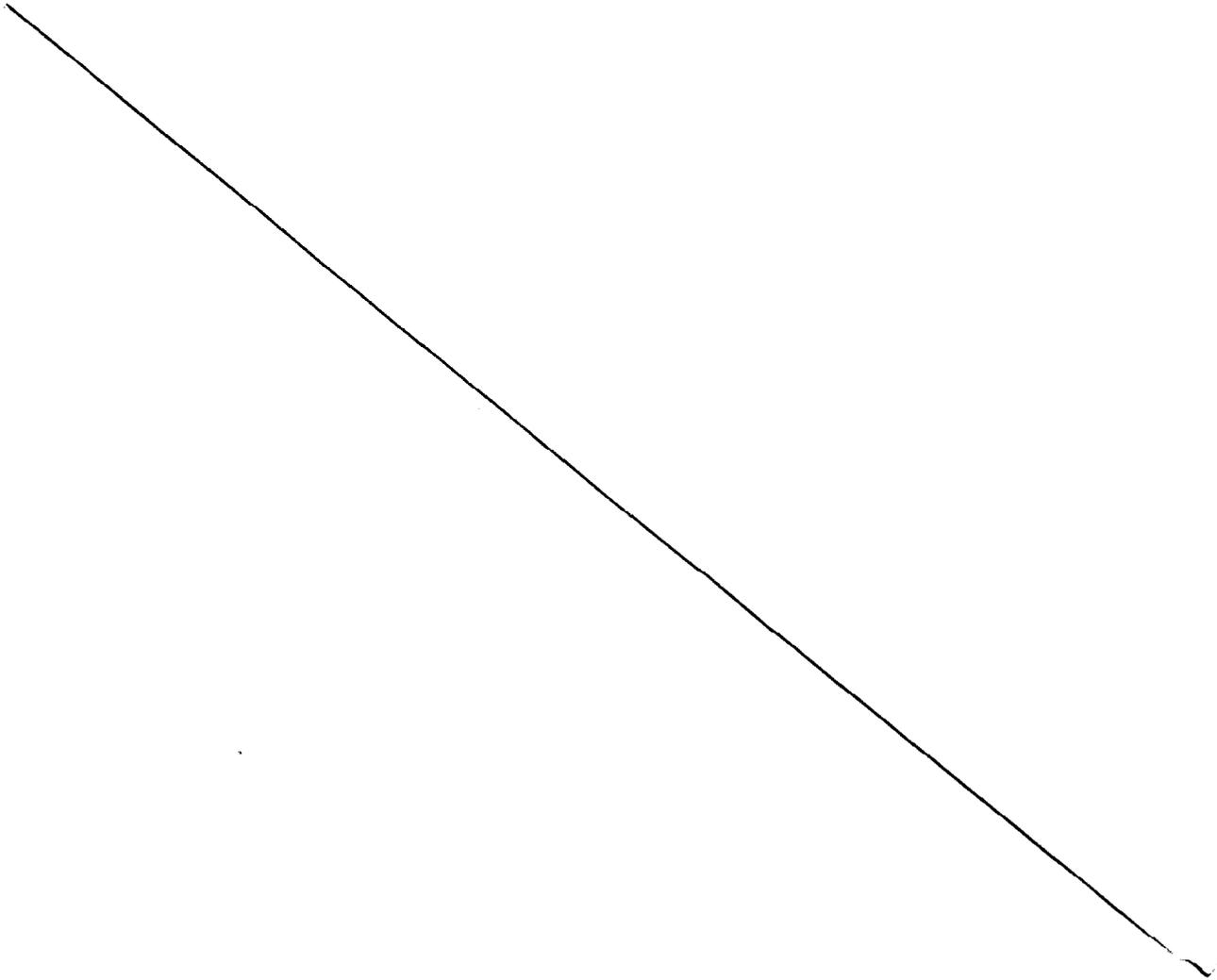
Tetracycline

Ticarcillin

Tobramycin

Troleandomycin

Tyrothricin

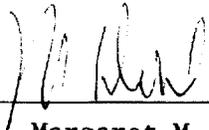


Vancomycin

Vidarabine

Viomycin

Dated: 10/5/99  
October 5, 1999



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Margaret M. Dotzel  
Acting Associate Commissioner for Policy

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