

August 22, 2019

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-P-1679; Supplemental Information in Further Support of Braeburn, Inc.’s Citizen Petition and in Response to the July 24, 2019 Comments Submitted by Indivior Inc.

Dear Sir or Madam:

On behalf of Braeburn, Inc. (“Braeburn”), and in accordance with 21 C.F.R. § 10.30(g), the undersigned hereby submits supplemental information in support of Braeburn’s petition and in response to the comments submitted on July 24, 2019 by Indivior, Inc. (“Indivior”). This submission provides further support for Braeburn’s position that Sublocade™ (buprenorphine extended-release) injection was never eligible for orphan drug designation (“ODD”) because Indivior, Inc. (“Indivior”) failed to submit a new ODD request for that specific “drug” as required by the Orphan Drug Act and Food and Drug Administration (“FDA”) regulations.

Under both the Orphan Drug Act and FDA’s implementing regulations, a “drug” cannot be designated as an orphan drug unless the sponsor submits a request for ODD before the submission of a marketing application. 21 U.S.C. § 360bb(a)(1); 21 C.F.R. § 316.20(a). Under the statute, FDA is authorized to grant ODD only in response to a “request.” 21 U.S.C. § 360bb(a)(1). Likewise, FDA’s regulations define “orphan-drug designation” as “FDA’s act of granting *a request* for designation under section 526 of the act.” 21 C.F.R. § 316.3(b)(11) (emphasis added). In other words, if there is no request, there can be no designation.

Indivior concedes it never submitted a request for designation for Sublocade. Indivior Comments, p. 29 (July 24, 2019) (“Ind.”). The company argues, however, that a new request was not required because ODD attaches to the active moiety, not the specific drug product. Ind., p. 24. Because Sublocade contains the same active moiety as Subutex, it allegedly is automatically covered by FDA’s 1994 ODD determination for Subutex. Indivior contends that this is “the direct result of the Agency’s longstanding orphan-drug regulations, which for decades have established the relevant ‘drug’ for orphan-drug designation purposes as the active moiety and not any particular NDA product that contains it.” Ind., p. 24.

Not surprisingly, Indivior never cites a single FDA regulation to support its position that the regulations define “drug” as “active moiety.” Ind., pp. 23-26. That is because FDA’s “longstanding orphan-drug regulations” do precisely the opposite: they clearly and unambiguously *preclude* treating the relevant “drug” for ODD purposes as the active moiety. *See, e.g.*, 21 C.F.R.

§ 316.3(b)(14)(i). Instead, the regulations require FDA to treat the relevant drug for ODD purposes as the specific “drug product” for which an ODD request was submitted. In this case, the only such “drug” is Subutex, not Sublocade.

FDA’s regulations do not define the term “drug,” but other regulatory provisions clarify its meaning and make clear that it *cannot* mean “active moiety.” First, FDA’s long-standing regulations define the term “same drug,” in relevant part, to mean “a drug that *contains* the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug” 21 C.F.R. § 316.3(b)(14)(i) (emphasis added). If a “drug” is something that “contains” an active moiety, it cannot be defined as an active moiety itself. Active moieties do not “contain” active moieties; rather, *drug products* contain active moieties. Therefore, the regulations make clear that the term “drug” cannot mean “active moiety” and must instead mean “drug product.”

In a highly similar situation, FDA concluded that an interpretation of the term “drug” that failed to account for the word “contains” was contrary to the clear language of the relevant statutory provision.¹ In that case, FDA was called upon to interpret the term “drug” in section 125(d)(2) of the Food and Drug Administration Modernization Act of 1997 (“FDAMA”), which provided an exception from certain Hatch-Waxman provisions for any marketing application “in which the drug that is the subject of the application contains an antibiotic drug.” Pub. L. No. 105-115 (1997). The petitioner argued that the reference to antibiotic “drug” meant antibiotic “drug product.” FDA, however, rejected this interpretation as contrary to the plain language of the statute. Focusing on the word “contains,” FDA explained that the petitioner’s interpretation did “not make sense on its face” because “drug products do not contain drug products; rather, drug products contain drug substances.”² In this case, the same reasoning applies: because active moieties do not “contain” active moieties, the term “drug” cannot mean active moiety. Indivior’s interpretation of “drug” to mean “active moiety” thus is nonsensical on its face and contrary to the plain language of the regulations.

Second, Indivior’s interpretation conflicts with FDA’s clinical superiority regulations. According to the regulation defining the term “same drug,” “if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.” 21 C.F.R. § 316.3(b)(14)(i). The regulations further provide that one drug is “clinically superior” to an “approved drug” if it is shown to have greater effectiveness, greater safety, or makes a major contribution to patient care. 21 C.F.R. § 316.3(b)(3). But if “drug” means “active moiety,” as Indivior contends, this provision would be rendered meaningless because an active moiety cannot be clinically superior to the same active moiety, even the same active moiety manufactured by a different sponsor. This provision (and the definition of “same drug”) makes sense only if the term “drug” is interpreted to mean “drug product.” This, in fact, is consistent with FDA longstanding interpretation of the regulations, as detailed in Braeburn’s prior submissions. For example, FDA treated Nutropin Depot and Tyvaso as distinct “drugs” requiring separate ODD requests because

¹ FDA Restasis Petition Response, Docket No. FDA-2003-P-0116 (Dec. 18, 2003) (Exhibit 1).

² FDA Restasis Petition Response, p. 39.

they were, in fact, different drug products than the relevant previously approved and orphan-designated drug products (Nutropin and Remodulin, respectively).³

Indivior's argument that Sublocade is exempt from the requirement to submit a new ODD request because it is the "same drug" as Subutex thus is misplaced. While the regulatory concept of "same drug" performs many different functions under the orphan drug regulations – such as prohibiting approval of certain drugs during the seven-year exclusivity period – it does not perform the one function Indivior identifies. Specifically, the regulations nowhere state that a "drug" (*i.e.*, drug product) is exempt from the otherwise applicable statutory and regulatory requirement to submit a *request* for designation as a prerequisite to receiving ODD if it is the "same drug" as a previously approved drug. 21 U.S.C. § 360bb(a)(1); 21 C.F.R. § 316.20(a). Quite the contrary, "same drug" status operates to impose *additional requirements* on ODD applicants beyond the otherwise applicable baseline requirements. Specifically, a drug that is "otherwise the same" as a previously approved drug must provide a "plausible hypothesis" of clinical superiority *in addition to* establishing eligibility as a *bona fide* orphan drug by satisfying either the Patient Population Prong or the Cost Recovery Prong. 21 C.F.R. § 316.20(a).

In sum, because Sublocade is a distinct drug (drug product) from Subutex under FDA's clear and unambiguous regulations, it was not eligible for ODD unless Indivior submitted a separate request to FDA prior to submission of its New Drug Application. Indivior concedes that it did not do so. Moreover, Sublocade is not exempt from the requirement to submit a new ODD request simply because it is considered to be the "same drug" as Subutex. Rather Sublocade's "same drug" status only means that Indivior was required to provide a "plausible hypothesis" that Sublocade is clinically superior to Subutex. Because Indivior failed to submit a designation request for Sublocade, it was not eligible under the statute or FDA regulations to receive ODD, and that ODD thus must be revoked now. 21 C.F.R. § 316.29.

Thank you for your consideration of these supplemental comments, and please do not hesitate to contact me directly if you have any questions.

Sincerely,



Scott M. Lassman
Counsel to Braeburn, Inc.

cc: Dr. Janet Maynard, Director, Office of Orphan Product Development
Elizabeth Dickinson, Office of Chief Counsel
Sharon Hertz, M.D., Director, DAAAP

³ Defining "drug" to mean "drug product" does not mean that "same drug" should be defined as "same drug product." This is because "same drug" is a separately defined term in the regulations that means, in essence, a "different drug product that contains the same active moiety as a previously approved drug product."

EXHIBIT 1

HFA-305

DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
Rockville MD 20857

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Re: 2003P-0275/CP1 & PSA1

Dear Mr. Mahn, Mr. Mauk, Ms. Vicente, Mr. Beers, and Mr. Bagley:

This letter responds to your citizen petition (petition), submitted on behalf of Allergan Inc. (Allergan), dated June 13, 2003.¹ You request that the Food and Drug Administration (FDA) reclassify cyclosporine as a "non-antibiotic drug" and remove it from the proposed list of drugs that are ineligible for marketing exclusivity and patent listing pursuant to section 125(d) of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) (Public Law 105-115) (petition at 1). In the alternative, you request that FDA find that Restasis (cyclosporine ophthalmic emulsion) 0.05% is not an antibiotic drug product that falls under the transition provisions of section 125(d) of the Modernization Act and grant Restasis three-year marketing exclusivity and patent listing rights under section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355) (petition at 1). This letter also responds to your petition for stay of action (petition for stay) dated August 1, 2003.²

DECISION SUMMARY

In summary, the Agency denies your request that we reclassify cyclosporine as a nonantibiotic drug substance. Restasis (and all drug products containing cyclosporine) are antibiotic drugs. The statutory definition of antibiotic drug turns on the nature of the drug substance; the definition does not reference a particular quantity of the drug substance, nor a particular indication. The Agency's interpretation is supported by the plain language of former section 507 of the Act and current 201(jj) of the Act, and legislative intent; and it is also consistent with FDA's past practice. Cyclosporine is an antibiotic drug substance that was the subject of an application received by FDA before

¹ Fish & Richardson P.C. submitted the June 13, 2003 citizen petition, and an amendment to the citizen petition dated August 1, 2003. Arnold & Porter submitted to the docket, on behalf of Allergan, two declarations by cover letter dated October 24, 2003.

² The August 1, 2003 petition for stay also repeats your request that FDA list patents for Restasis in the *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly referred to as the *Orange Book*.

2003P-0275

PDN 1

November 21, 1997. Restasis is an antibiotic drug that falls under section 125(d)(2), and, consequently, Restasis is not eligible for Hatch-Waxman benefits. This conclusion is supported by the plain language of section 125(d)(2) and legislative intent. Further, your claim of detrimental reliance is not persuasive. Finally, the Agency denies your petition for stay of action.

OVERVIEW

Because your underlying goal is the eligibility of Restasis for Hatch-Waxman benefits, it is important to consider your requests — for reclassification of cyclosporine as a nonantibiotic drug substance and removal of cyclosporine from the proposed list of antibiotic drugs that were the subjects of marketing applications received by FDA before November 21, 1997 — in that light. To this end, the fundamental question is whether Restasis falls under section 125(d)(2).

In your petition, you advance the main arguments set forth below in support of your position that Restasis is eligible for Hatch-Waxman benefits:

- (1) Cyclosporine was improperly classified as an antibiotic drug under former section 507 of the Act;
- (2) Restasis and cyclosporine are not "antibiotic drugs" under former section 507 of the Act and current section 201(jj) of the Act because they are not indicated for antimicrobial or anti-infective use, despite the fact that Restasis satisfies the literal definition of section 201(jj) of the Act;
- (3) Even assuming Restasis is an antibiotic drug under section 201(jj) of the Act, Restasis should be eligible for Hatch-Waxman benefits; and
- (4) In any event because Allergan relied on the Agency's representations that Restasis was not an antibiotic drug, Restasis should be eligible for Hatch-Waxman benefits.

Part I of this response sets forth some background information on general definitions, regulatory history, and the facts relevant to this matter. Part II sets forth the Agency's interpretation of the statutory definition of antibiotic drug under former section 507 of the Act, which is essentially the same as current section 201(jj) of the Act. Part III explains why the classification of drug products containing cyclosporine as antibiotic drugs under former section 507 and current section 201(jj) of the Act was, and continues to be, proper. Part IV explains that the classification of Restasis as an antibiotic drug is compelled by the plain language of section 201(jj) of the Act, legislative intent, and FDA's consistent practice with respect to other drugs. Part V explains that because cyclosporine is an antibiotic drug substance that was the subject of an application received by FDA before November 21, 1997, cyclosporine was properly included on the proposed list of antibiotic drugs subject to section 125(d)(2). Part VI explains that because Restasis is an antibiotic drug that falls under section 125(d)(2), Restasis is not eligible for Hatch-Waxman benefits. Part VII explains why your claim that you detrimentally relied on FDA's representations and therefore you should nonetheless be

eligible for Hatch-Waxman benefits is not persuasive. Part VIII denies your petition for stay. Part IX sets forth the Agency's summary conclusion.

DISCUSSION

I. BACKGROUND

A. General Definitions

For the purposes of this petition response only, to prevent confusion we set forth some terms below:

- *antibacterial* means having the capacity to inhibit or destroy bacteria.
- *antifungal* means having the capacity to inhibit or destroy fungi.
- *anti-infective* means capable of killing infectious agents or preventing them from spreading or causing infection.
- *antimicrobial* means having the capacity to inhibit or destroy micro-organisms.
- *micro-organisms* include bacteria, fungi, viruses, and other microscopic organisms.
- *in vitro* means in a test tube or other artificial environment.
- *in vivo* means within the living body.

Also, for the purposes of this petition response:

- We use the terms *active ingredient*, *drug substance*, and *chemical substance* interchangeably. Under 21 CFR 314.3(b)(2003), "[d]rug 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 or any function of the human body, but does not include intermediates used in the synthesis of such ingredient."
- We sometimes use the term *antibiotic drug substance* for brevity to refer to "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)."
- We sometimes use the term *Hatch-Waxman benefits* to refer to the provisions of section 505 of the Act that provide, for example, for new drug exclusivity, patent listing, patent certification, and 30 month stays on approval of abbreviated new drug applications (ANDAs).

B. Summary of Regulatory Background

1. Historical Differences Between Statutory Schemes for Generic Antibiotic Drugs and Generic Nonantibiotic Drugs.

Before the enactment of the Modernization Act in 1997, antibiotic drug applications were submitted under section 507 of the Act, whereas nonantibiotic drug applications were submitted under section 505 of the Act. These different approval schemes resulted in differences in the availability of generic antibiotic drugs and generic nonantibiotic drugs - which translated into a fundamental difference in the amount of competition the sponsors of innovator drugs faced.

Before the enactment of the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Pub. L. No. 98-417, 98 Stat. 1585 (1984), sponsors of nonantibiotic drugs were required to submit scientific data demonstrating the safety and effectiveness of nonantibiotic drugs. The Agency also required sponsors of generic nonantibiotic drugs to submit safety and efficacy data. As a result, there were few generic nonantibiotic drugs approved between 1962 and 1984.³

There were, however, many generic antibiotic drugs available due to the difference in the statutory schemes.⁴ Section 507 of the Act required the Agency to publish regulations (antibiotic monographs) setting forth standards of identity, strength, quality, and purity for each approved antibiotic drug. That is, the Agency created a monograph system, which streamlined the approval and entry of generic antibiotic drugs into the market place.⁵ As a result, unlike sponsors of generic nonantibiotic drugs, sponsors of generic antibiotic drugs did not have to submit the underlying safety and efficacy data to receive approval.⁶ Accordingly, generic antibiotic drugs were widely available.⁷

The 1984 Hatch-Waxman Amendments created an abbreviated approval process for generic nonantibiotic drugs whereby generic nonantibiotic drugs could rely on the Agency's finding of safety and effectiveness for the innovator drug. This ANDA process shortens the time and effort needed for approval by, among other things, allowing the sponsor to demonstrate that its drug product is bioequivalent to the innovator drug, rather than reproduce the safety and effectiveness data for the innovator drug. *See Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990). The timing of approval of an ANDA depends in part on statutory patent listing, patent certification, and exclusivity protections that were added to the Act.

The Hatch-Waxman Amendments reflect the "fundamental difference" between the approval processes for antibiotic drugs and nonantibiotic drugs.⁸ Hence, the Hatch-Waxman Amendments provided sponsors of innovator nonantibiotic drugs with marketing exclusivity and patent listing provisions as a quid pro quo for the abbreviated

³ See Hearings of the Committee on Labor and Human Resources United States Senate, 105th Cong. 1 Sess. 228 March 19 and April 11, 1997.

⁴ *Id.*

⁵ *Id.*

⁶ See generally *Glaxo, Inc. v. Heckler*, 623 F. Supp. 69, 71 (E.D.N.C. 1985).

⁷ Note that antibiotic drugs may be protected by patent. To avoid infringing a patent, the sponsor of a generic antibiotic drug may wait until patent expiration before marketing its approved antibiotic drug or the scope of patent protection may be decided in patent infringement litigation.

⁸ See Hearings of the Committee on Labor and Human Resources United States Senate, 105th Cong. 1 Sess. 228 March 19 and April 11, 1997.

approval mechanism for sponsors of generic nonantibiotic drugs.⁹ In the case of innovator antibiotic drugs, however, sponsors had nothing to trade for marketing exclusivity and patent listing because the Agency historically approved antibiotic drug applications submitted pursuant to section 507 through a streamlined monograph system.¹⁰ Therefore, antibiotic drugs were not entitled to any patent listing, patent certification, or exclusivity protections that were added by the Hatch-Waxman Amendments. *See Glaxo, Inc. v. Heckler*, 623 F. Supp. 69 (E.D.N.C. 1985).

In 1997, the Modernization Act, among other things, repealed section 507 of the Act and required all applications for antibiotic drugs to be submitted under section 505 of the Act. *See Section 125(d)(1)*. The Modernization Act included a transition provision declaring that an application approved under section 507 of the Act before enactment of the Modernization Act must be considered to be an application submitted, filed, and approved under section 505 of the Act (transition provision). *See section 125(d)(1)*. Congress created an exception to this transition provision in section 125(d)(2). Section 125(d)(2) exempted certain applications for antibiotic drugs from those provisions of 505 that provide, for example, for new drug exclusivity, patent listing, patent certification, and 30 month stays on approval of ANDAs (*i.e.*, Hatch-Waxman benefits). *See section 125(d)(2)*. Specifically, section 125(d)(2) exempts an application from Hatch-Waxman benefits when "the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application" received by FDA under section 507 of the Act before the enactment of the Modernization Act (*i.e.*, November 21, 1997).

2. *History of Changes to Definition of Antibiotic Drug*

Like the statutory schemes for approval, the definition of "antibiotic drug" has also evolved over time. Section 507 of the Act was enacted in 1945 to provide for batch certification of antibiotic drugs. Batch certification of antibiotic drugs, under section 507 of the Act, was intended to ensure the strength, quality, and potency of successive batches of these drugs, which were at the time all produced by fermentation — a manufacturing process that could be unpredictable.

Initially, when section 507 of the Act was enacted in 1945, it applied only to penicillin or any derivative of penicillin. Other substance-specific antibiotic drugs were added to the statute as they were developed. Streptomycin was added in 1947; aureomycin, chloramphenicol, and bacitracin were added in 1949; chlortetracycline was substituted for aureomycin (a trade name for chlortetracycline) in 1953.

The more general statutory definition of "antibiotic drug" was added to the Act in the Drug Amendments of 1962 (Public Law 87-781), thereby obviating the need for a statutory change with each discovery of additional antibiotic drugs. With this addition, section 507 of the Act required FDA to promulgate regulations for batch certification of

⁹ *Id.*

¹⁰ *See Hearings of the Committee on Labor and Human Resources United States Senate, 105th Cong. 1 Sess. 228 March 19 and April 11, 1997.*

drugs for human use "composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or *any other antibiotic drug*, or any derivative thereof." (emphasis added). Section 507 then defined "antibiotic drug" as "any 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)."

In 1997, Congress enacted section 125 of the Modernization Act, which (among other things): (i) repealed section 507 of the Act, and (ii) added the antibiotic drug definition under section 201(jj) of the Act.

Section 201(jj) of the Act defines an "antibiotic drug" 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.

Current section 201(jj) of the Act and former section 507 of the Act are essentially the same. Both include the same named antibiotic drug substances (*i.e.*, penicillin, streptomycin, chlortetracycline, chloramphenicol, and bacitracin). Moreover, both include the identical language for the general definition (*i.e.*, a drug 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. . . ." (emphasis added)).

C. Factual Background

Allergan currently holds the approved new drug application (NDA) for Restasis (cyclosporine ophthalmic emulsion) 0.05%. Restasis is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca¹¹ (see Restasis package insert). Cyclosporine is the active ingredient in Restasis (petition at 1).

According to your petition, Allergan began development of Restasis on September 29, 1994, after it took over an investigational new drug application (IND) previously held by Sandoz (petition at 2). During the investigational phase, it appears that Allergan did not raise the issue of whether Restasis is an antibiotic drug with the Division of Anti-

¹¹ Specifically, Restasis is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

Inflammatory, Analgesics, and Ophthalmic Drug Products (Division). On February 24, 1999, Allergan submitted the Restasis NDA, under section 505 of the Act (petition at 1). The NDA was incorrectly given a "20 series" (non-old antibiotic drug)¹² NDA number (21-023), instead of a "50 series" (old antibiotic drug) NDA number. On December 23, 2002, FDA approved the Restasis NDA (petition at 2; *see also* approval letter dated December 23, 2002).

Allergan requested five years of exclusivity in its Restasis NDA submission (petition at 12). The Agency makes exclusivity determinations for applications at the time of approval or shortly thereafter, not at the time of submission. According to the petition, one week after approval, the Division's Project Manager for Allergan's Restasis NDA contacted Allergan by telephone to say that Allergan made a mistake on its exclusivity request, and Allergan could be eligible for three years of exclusivity, not five years of exclusivity as Allergan originally requested (petition at 12). Soon after, FDA determined that Restasis was subject to section 125(d)(2) of the Modernization Act and that Restasis would not be eligible for exclusivity; and that the Restasis NDA had incorrectly been assigned a 20 series NDA number, instead of a 50 series NDA number.

According to the petition, the Division's Project Manager for Allergan's Restasis NDA contacted Allergan on January 21, 2003, and told Allergan that Restasis was not eligible for exclusivity (petition at 12). This information was memorialized in a follow-up letter to Allergan dated March 3, 2003. At no time did FDA ever list any patents or exclusivities in the *Orange Book* for Restasis.¹³

The Agency has a long history of regulating human drugs containing the drug substance cyclosporine as antibiotic drugs under former section 507 of the Act. Restasis is a drug intended for human use containing cyclosporine, which is produced by a micro-organism and has the capacity to inhibit or destroy micro-organisms in dilute solution. Therefore, Restasis is an antibiotic drug under the section 201(jj) of the Act.

¹² To distinguish between applications for antibiotic drugs that are exempt from Hatch-Waxman benefits under section 125(d)(2) and all other applications, the agency has assigned NDA numbers (in relevant part) as follows:

- (1) the "20 series" corresponds to all marketing applications submitted under section 505(b) of the Act, on or after November 21, 1997, to which section 125(d)(2) does not apply;
- (2) the "50 series" corresponds to all marketing applications submitted under section 505(b) of the Act, on or after November 21, 1997, to which section 125(d)(2) applies; all applications (with certain exceptions) assigned a "50 series" NDA number on or before November 21, 1997, will keep that number.

See Guidance for Industry and Reviewers; Repeal of Section 507 of the Federal, Food, Drug, and Cosmetic Act (May 1998)(Repeal of Section 507 Guidance) at 3.

¹³ Due to publication schedules, however, the NDA number for Restasis appears in the *Orange Book* (23rd Ed.) as NDA 21-023. The March 2003 Cumulative Supplement to the 23rd Edition of the *Orange Book* corrects this error, and lists the Restasis NDA number as NDA 50-790.

Allergan submitted a citizen petition dated June 13, 2003, among other things, asking the Agency to reclassify the active ingredient in Restasis (*i.e.*, cyclosporine) as a "non-antibiotic drug" (petition at 1).

II. THE AGENCY'S INTERPRETATION OF THE DEFINITION OF ANTIBIOTIC DRUG UNDER FORMER SECTION 507 (AND CURRENT SECTION 201 (jj)) OF THE ACT IS CORRECT.

The question of whether Allergan's Restasis is eligible for Hatch-Waxman benefits turns *in part* on whether the Agency received any application for an antibiotic drug (containing the drug substance cyclosporine) under section 507 of the Act before November 21, 1997. Before answering this question in the affirmative elsewhere in this response, we explain below the Agency's interpretation of the general statutory definition of antibiotic drug under former section 507 of the Act (and consequently, current section 201(jj) of the Act).¹⁴ To be classified as an antibiotic drug: (1) a human drug must contain *any quantity* of a *particular type* of drug substance; and (2) a human drug need *not* contain a particular quantity of the drug substance, *nor* have a particular intended use (*i.e.*, antimicrobial or anti-infective use). The plain language of former section 507 of the Act, with reference to the legislative history, supports this interpretation.

A. The plain language of section 507 of the Act supports FDA's interpretation of the general statutory definition of antibiotic drug.

Section 507 of the Act first sets forth a substance-specific list of antibiotic drugs, and then sets forth a more general definition of antibiotic drug. That is, section 507 of the Act states that by regulation the Agency must provide for batch certification of human drugs "composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or *any other antibiotic drug*, or any derivative thereof" (*emphasis added*). Section 507(a) of the Act then defines "antibiotic drug" as:

any 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) (*emphasis added*).

The plain language of this general statutory definition of "antibiotic drug" is most reasonably read to mean that a human drug containing *any quantity* of any chemical substance (*i.e.*, drug substance) having certain characteristics (*i.e.*, produced by a micro-organism and having the capacity to inhibit or destroy micro-organisms in dilute solution) is considered to be an antibiotic drug.

¹⁴ It is important to emphasize again that former section 507 of the Act and current section 201(jj) of the Act (*i.e.*, current statutory definition of antibiotic drug) are in relevant part essentially the same. Accordingly, the discussion in the text is applicable to section 201(jj) of the Act.

1. *The plain language of section 507 focused on the chemical substance.*¹⁵

Congress' emphasis on the chemical substance is evident in both the substance-specific list of antibiotic drugs and the more general statutory definition of antibiotic drug. In the substance-specific list of antibiotic drugs, Congress described these drugs as being composed "wholly or partly" of any kind of the following chemical substances: penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin. Congress' focus was on the chemical substance (*i.e.*, drug substance), not the particular dose or intended use.

Similarly, Congress enacted the more general statutory definition of antibiotic drug with the same emphasis, by defining antibiotic drug with respect to the properties of the chemical substance (*i.e.*, drug substance). That is, the more general statutory definition of antibiotic drug refers to "any quantity" of a chemical substance having certain characteristics (*i.e.*, produced by a micro-organism and having the capacity to inhibit or destroy micro-organisms in dilute solution). Furthermore, the parenthetical in the more general statutory definition of antibiotic drug refers to "any such substance," making it clear that the phrase preceding the parenthetical — "which has the capacity to inhibit or destroy micro-organisms in dilute solution" — refers to the "chemical substance," not to the "quantity." That is, a particular quantity of a drug substance is not required for a drug to be an antibiotic drug; rather, *any quantity* of a *particular type* of drug substance is required for a drug to be an antibiotic drug.¹⁶

2. *The plain language of section 507 does not include language pertaining to a particular dose or intended use.*

Neither section 507's substance-specific list of antibiotic drugs, nor its more general statutory definition of antibiotic drug includes any reference to the intended use of the drug (*e.g.*, to treat a specific disease or condition). In addition, the more general statutory definition of antibiotic drug plainly states, among other things, that if the chemical substance has the *capacity* to inhibit or destroy micro-organisms in dilute solution, it is an antibiotic drug. The statute does not state that the quantity of the chemical substance in a given drug product must inhibit or destroy micro-organisms for that drug product to be classified as an antibiotic drug.

Moreover, the Supreme Court has stated that "[w]hen 'Congress includes particular language in one section of a statute but omits it in another section of the same Act' we have recognized, 'it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.'" *See Clay v. United States*, 537 U.S. 522, 528

¹⁵ In deciding an issue of statutory interpretation, the first inquiry is "whether Congress has directly spoken to the question at issue. If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *See Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984).

¹⁶ The Supreme Court has noted that the term "any" is a broad term. *See, e.g., United States v. Gonzales*, 520 U.S. 1, 5 (1997) ("read naturally, the word "any" has an expansive meaning"); *see also General Electric Co. v. Whitman*, 257 F. Supp. 2d 8, 20-21 & fn. 5 (D.D.C. 2003).

(1983) (internal citations omitted). Congress could have added an intended use element to the statutory definition of antibiotic drug similar to that contained in the definitions of "drug," "device," and "cosmetic" under the Act, but Congress decided against it, despite its familiarity with the concept of intended use. One can readily comprehend Congress' decision not to incorporate an intended use element (*i.e.*, antimicrobial or anti-infective use) in the definition of antibiotic drug, because Congress intended to focus on the particular drug substance contained in the antibiotic drug. This concern was due in part to the nature of the manufacturing process, as discussed below.

Although the plain language of the statute does not refer to the drug product's particular dose or intended use, the statute clearly links the antibiotic drug definition to the specific properties of the chemical substance. Accordingly, the plain language of the more general statutory definition of antibiotic drug is most reasonably read to mean that any human drug containing *any quantity* of a drug substance having certain characteristics (*i.e.*, produced by a micro-organism and having the capacity to inhibit or destroy micro-organisms in dilute solution) is considered to be an antibiotic drug.

B. Legislative intent supports FDA's interpretation of the more general antibiotic drug definition under section 507 of the Act.

FDA's interpretation — that any human drug containing *any quantity* of a drug substance having certain characteristics is considered to be an antibiotic drug — is not only the most reasonable interpretation of the plain language of the statute, but it is also consistent with congressional intent. Congress' intent in enacting section 507 of the Act was to regulate drugs containing certain types of drug substances due in part to the nature of the manufacturing process, regardless of the particular dose or intended use of the drug.

1. Congress' intent was to focus on the drug substance and the nature of the manufacturing process, not a particular dose.

Section 507 was enacted on July 6, 1945 (Public Law 79-139) to provide, among other things, for batch certification of penicillin. Congress' focus was clearly on the drug substance and the process used to manufacture the drug substance. The House Report corresponding to the penicillin batch certification provision asserts that "[a] primary reason for the type of control proposed by this bill is the fact that penicillin is produced by a biological process and is subject to the vagaries inherent in all such processes. Furthermore, the potency of penicillin is determined by biological assay, which itself must be carefully controlled and checked to insure its accuracy." See House Report No. 702 79th Cong, 1st Sess. 2-3 (1945) ("Providing For Certification of Batches of Drugs Composed Wholly or Partly of Any Kind of Penicillin or Derivatives"; Committee on Interstate and Foreign Commerce) (emphasis added). Potency is generally a term that is used to describe the anti-microbial activity per unit quantity of the drug substance.¹⁷

¹⁷ 21 C.F.R § 430.6 defines "unit" as it applies to antibiotic substances. For example, "The term 'unit' applied to penicillin G means the penicillin activity (potency) contained in 0.600 microgram of the

Accordingly, Congress was primarily concerned with the nature of the drug substance, and the process by which it was produced.¹⁸

Congress' focus remained on the drug substance and the nature of the manufacturing process as new antibiotic drugs were added to the statute. The Senate Report No. 448 provides that "[p]enicillin, streptomycin, and these broad range antibiotics are all produced, with some modifications, by the same basic production method, except that Chloromycetin [chloramphenicol] is now produced by an even cheaper process, being produced synthetically. This basic method is the fermentation process."¹⁹ See Senate Report No. 448 (Report of the Committee on the Judiciary United States Senate made by its Subcommittee on Antitrust and Monopoly, 87th Cong 1st Sess. 82 (June 17, 1961).

penicillin G master standard" (See 21 CFR 430.6(a))(1985) (note this regulation was subsequently revoked).

¹⁸ Letters from other organizations and agencies also focused on the drug substance. Some excerpts are set forth below:

The Chairman of the Board of Trustees for the United States Pharmacopoeia, in supporting batch certification for penicillin, asserted that FDA "will be empowered to standardize, pretest, and certify all penicillin and penicillin-containing preparations before they are placed on the market." See House Report No. 702, 79th Cong. 1st Sess. 13 (1945) (letter from Chairman, Board of Trustees, United States Pharmacopoeia to Food and Drug Administration) (emphasis added).

The Federal Security Agency wrote: "[p]enicillin is produced by a biological process and is subject to the vagaries inherent in all such processes. Only a limited number of skilled manufacturers are now producing penicillin. Even they have occasional unexplainable mishaps in the manufacturing process which results in lack of the required potency or in contamination with pyrogens. . . . Penicillin is administered in cases of extreme illness. Sometimes the physician must wait as much as 12 hours before its effects become manifest in the patient. If the product administered is lacking in the expected potency, the patient may pass beyond human aid before the fault of the drug is recognized by the physician) [sic] A drug which has the required potency but is contaminated with toxic impurities may delay recovery if it does not cause a fatal ending." See House Report No. 702, 79th Cong. 1st Sess. 10 (1945) (letter from Federal Security Agency to Speaker of the House of Representatives).

The American Drug Manufacturers' Association wrote that certification "is offered as an extra measure of protection for a limited period of time due to the uncertainties which have appeared to exist in the assay of penicillin and the possibility that there may be initial uncertainties attendant upon the assay of new penicillin preparations, particularly in the case of companies who have not previously worked with penicillin. Penicillin is a chemical produced by a fermentation process." See House Report No. 702, 79th Cong. 1st Sess. 14 (1945) (letter from American Drug Manufacturers Association to Chairman, Interstate and Foreign Commerce Committee).

In all of these letters, the focus was on the drug substance itself and the process for producing the drug substance; the emphasis was not on a threshold quantity of the drug substance.

¹⁹ See also e.g., Hearings Before a Subcommittee of the Committee on Interstate and Foreign Commerce; House of Representatives, 81st Cong. 1st Sess. 3 (April 12, 1949) (Report of Federal Trade Commission made part of the record, stating "[a]ureomycin, chloramphenicol, and bacitracin are antibiotic drugs having exceptional value in the treatment of certain diseases of animals and man. It is important that these antibiotic drugs and their derivatives have the potency claimed for them. Since the manufacture of these preparations involves complicated technical procedures, it is in the interest of the public to have each batch of these antibiotic drugs and each derivative thereof certified as to identity, strength, quality, and purity, in order to insure safety and efficacy of use.").

Further evidence that Congress was concerned with the drug substance and the process for producing that substance stems from Congress' treatment of insulin products. Parallels may be drawn between the certification of antibiotics and the certification of insulin under former section 506 of the Act.²⁰ The provisions are roughly contemporaneous and both provided for FDA certification of therapeutic substances of biological, as opposed to synthetic chemical, origins. At the time, these natural products could not be purified at a high level. In addition, the manufacturing processes were inherently difficult to control. As a result, lot-to-lot consistency was difficult to achieve. A number of organizations noted the similarity of these drug substances thereby warranting certification of both antibiotic drugs and insulin.²¹

2. *Legislative intent demonstrates that Congress' focus was not on the antibiotic drug's particular end use.*
 - a. Congress' treatment of sulfonamides provides evidence that Congress' main concern was not drugs that have antimicrobial or anti-infective indications.

Congress' treatment of sulfonamides provides further evidence of Congress' intent to concentrate on drugs containing any quantity of a particular type of drug substance, rather than the particular intended use. Sulfonamide drugs were the first effective drugs to be employed systemically in human beings for the treatment of bacterial infections, several years before the development of penicillin. The considerable medical and public health importance and subsequent widespread use of these drugs were quickly reflected in the sharp decline in the morbidity and mortality figures for treatable diseases.²²

It is clear that Congress was well aware of the sulfonamides. The Elixir Sulfanilamide tragedy²³ received much scrutiny; it is generally considered to be one of the key events

²⁰ We note that section 506 of the Act was added to the Act on December 22, 1941 (55 Stat. 851), and the section was repealed by the Modernization Act in 1997.

²¹ The provisions relating to certification of insulin were cited by some organizations as "precedent for" pretesting and certification of penicillin. *See, e.g.*, House Report No. 702, 79th Cong. 1st Sess. 11 (1945) (letter from Federal Security Agency to Speaker of the House of Representatives); *See Hearings Before a Subcommittee of the Committee on Interstate and Foreign Commerce; House of Representatives*, 81st Cong. 1st Sess. 3 (April 12, 1949) (Report of Federal Security Agency that was made part of the record, stating insulin and certain antibiotics "are all highly efficacious for one or more serious diseases; they all present unusual difficulties in the process of manufacture and the methods of testing finished lots, and for this reason are prone to depart from standards of identity, strength, quality, and purity appropriate to insure the safety and efficacy of use.").

²² Gerald L. Mandel and William A. Petri, Jr., *Antimicrobial Agents: Sulfonamides, Trimethoprim-Sulfamethoxazole, Quinalones, and Agents for Urinary Tract Infections* in GOODMAN & GILLMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9TH ED. 1057 (Joel G. Hardman, et al. eds., 1996).

²³ Sulfanilamide was one of the earliest members of the sulfonamide class of drugs. The deaths of 107 people in 1937 were caused by diethylene glycol, an inactive ingredient in Elixir Sulfanilamide. *See CDR's Time Line: Chronology of Drug Regulation in the United States*, available at <http://www.fda.gov/cder/about/history/time1.htm> (last visited 12/11/03).

precipitating the enactment of the Act in 1938.²⁴ Sulfonamides and penicillin were used to treat a number of the same serious diseases. See House Report No. 702, 79th Cong 1st Sess. 10 (1945) (letter from Federal Security Agency to Speaker of the House of Representatives). However, sulfonamides were, and continue to be, produced by chemical synthesis rather than fermentation.

Although Congress enacted certification provisions for penicillin, Congress did not do so for sulfonamides. Accordingly, Congress was concerned with the nature of how the drug substance penicillin was produced, and not with a particular intended use (*e.g.*, antimicrobial or anti-infective use). If Congress wanted to focus only on the antimicrobial use, Congress could have made sulfonamides subject to the batch certification provision. Instead, Congress chose to focus on the properties of the drug substance and the nature of the manufacturing process.

- b. Congress specifically chose not to classify antibiotic drugs according to their intended use.

Congress' decision to depart from classifying "antibiotic drugs" based on "intended use" — a concept with which Congress was very familiar — demonstrates that Congress did not intend for a particular "intended use" of the antibiotic drug to be dispositive of its classification as an antibiotic drug under section 507 of the Act. The 1906 Act, for example, defined drugs to include only "medicines and preparations . . . and any substance or mixture of substances *intended to be used* for the cure, mitigation, or prevention of disease . . ." Pub. L. No. 59-384, § 6, 34 Stat. at 768 (emphasis added). In 1938, Congress expanded the definition of "drug" to include "*articles intended* to affect the structure or any function of the body." Pub. L. No. 75-717, 52 Stat. at 1041, as amended 201(g)(1)(c) of the Act (emphasis added). That is, Congress previously employed the intended use of products to establish regulatory categories in the Act. See, *e.g.*, section 201(g)(1) of the Act (definition of "drug"), and section 201(i) of the Act (definition of "cosmetic"), and 201(h) of the Act (definition of "device"). Yet, Congress departed from this "intended use" model, by defining antibiotic drug based on the presence of "any quantity" of a drug substance having certain characteristics.²⁵

²⁴ See 83 Cong. Rec. 2279 (1938) (Remarks of Mr. Coffee); Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* 88-93 (2003).

²⁵ At least one organization even recommended that Congress consider the issue of intended use. Despite this recommendation, Congress chose not to incorporate the element of antimicrobial or anti-infective use in the definition of antibiotic drug. The National Academy of Sciences — National Research Council recommended that "[t]he FDA should be given statutory authority to apply certification procedures to all antimicrobial agents used in the prophylaxis and treatment of infectious diseases. The Committee sees no reason for limiting certification to those antibiotic preparations which happen to have come on the market prior to 1950 . . ." See Hearings Before the Subcommittee on Antitrust and Monopoly of the Committee on the Judiciary United States Senate; Report of Special Committee Advisory to The Secretary of Health, Education, and Welfare to Review the Policies, Procedures, and Decisions of the Division of Antibiotics and the New Drug Branch of the Food and Drug Administration; National Academy of Sciences — National Research Council. 87th Cong 1st Sess. 460 (1961). In enacting the more general statutory definition of antibiotic drug, Congress did in fact give FDA the statutory authority to apply certification procedures to all antimicrobial agents. Congress did not limit certification to antibiotic preparations

Furthermore, when Congress was considering whether to add the more general statutory definition of antibiotic drug to the Act, Congress knew that there were other antibiotic drugs on the market that were not contained in the substance-specific list of antibiotic drugs and that (at the time) these other antibiotic drugs were outside the scope of section 507 of the Act. Congress specifically chose to sweep these other antibiotic drugs into the statutory definition of antibiotic drug under section 507 of the Act when it added the more general definition of antibiotic drug to the Act. Congress clearly intended to treat antibiotic drugs differently than other drugs.

Congress' intent to treat "antibiotic drugs" differently than "drugs" under the Act can be demonstrated by the discussion that took place during the Hearings on Drug Industry Act of 1962. Congressman Dingell raised the fact that five antibiotics were named in the statute, and since that time a number of other antibiotic drugs had come on the market.²⁶ The Congressman specifically asked the then-President of Eli Lilly Co. for confirmation as to whether these drugs were "just treated as ordinary drugs as opposed to antibiotics."²⁷ After getting confirmation that these other antibiotic drugs were being regulated as "ordinary drugs," the Congressman then indicated that the administration bill proposed to "expand the treatment of antibiotics to cover all of these."²⁸

The President of Eli Lilly, in expressing his opposition to the expansion of the statute, recognized, "that fermentation and the purification procedures were not at that time [*i.e.*, around the time of World War II] an exact science" and the proposal was not necessary because "fermentation has become a very much more exact science."²⁹ Congress obviously disagreed with this statement and expanded section 507(a) of the Act to include a more general statutory definition of antibiotic drug to encompass other antibiotic drugs not previously included in the substance-specific list.

C. FDA has applied the antibiotic drug definition consistently. Congress' 1997 enactment of the Modernization Act confirms that the Agency's interpretation of the general statutory definition of "antibiotic drug" under former section 507 (and current section 201(jj)) of the Act was, and continues to be, correct.

marketed before 1950. Congress extended the recommendation beyond the "treatment of infectious diseases" because Congress did not add this element in the statutory definition.

²⁶ See Drug Industry Act; House of Representatives, Committee on Interstate and Foreign Commerce, at 189 (August 20, 1962); see also Drug Industry Act; House of Representatives, Committee on Interstate and Foreign Commerce, at 414 (August 21, 1962) (Statement of Dr. Robert J. Feeney, Director of Commercial Development of Charles Pfizer & Co., Inc.; Accompanied by Charles F. Hagan, Legal Division; stating that the requirement for certification of penicillin was supported as a temporary measure when "production and control procedures were in a crude stage of development" and certification was no longer necessary). However, Congress chose to continue certification.

²⁷ See Drug Industry Act; House of Representatives, Committee on Interstate and Foreign Commerce, at 189 (August 20, 1962).

²⁸ *Id.*

²⁹ *Id.*

In 1997, Congress enacted section 125 of the Modernization Act, which: (i) repealed section 507 of the Act, and (ii) added the antibiotic drug definition under section 201(jj) of the Act by first setting forth the substance-specific definition, and then second by referencing both the origin and the chemical characteristics of the drug substance.³⁰ Section 201(jj) of the Act and former section 507 of the Act are in relevant part essentially the same (*i.e.*, a drug 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. . . .") (emphasis added).

In enacting section 201(jj) of the Act, Congress once again chose not to include a particular intended use element in the statutory definition of antibiotic drug — even though FDA had a history of interpreting the statutory definition of antibiotic drug in accordance with the plain language of the statute that resulted in: (1) classification of drugs approved for nonantimicrobial uses as antibiotic drugs, and (2) classification of some drugs approved for antimicrobial uses as nonantibiotic drugs.

By 1997 FDA had approved as antibiotic drugs many drugs that were not approved for any antimicrobial use. Those antibiotic drugs were not among those named in the substance-specific list of antibiotic drugs; thus, it is readily apparent that FDA approved them as part of the more general antibiotic drug definition. Specifically, in the 1980s, FDA published a number of monographs in the *Code of Federal Regulations* to provide standards for certification of bulk antibiotics and their finished dosage forms for antibiotic drugs. FDA also published a number of monographs for antibiotic drugs that were approved for oncologic (nonantimicrobial) uses, for example, mitomycin, doxorubicin, bleomycin, and daunorubicin. These antibiotic drug substances were listed under the "[d]efinitions of antibiotic substances" set forth in 21 CFR 430.4(a)(1985). Before 1997, these antibiotic drugs containing these antibiotic drug substances (*e.g.*, mitomycin, doxorubicin, bleomycin and daunorubicin) were on the market.

By 1997 FDA had also approved the immunomodulator drugs (*e.g.*, drugs used to prevent organ rejection in transplant patients, not an antimicrobial use), and classified them as antibiotic drugs under section 507 of the Act. These drugs contained the antibiotic drug substances *cyclosporine*, tacrolimus, and mycophenolate. (*See* electronic *Orange Book*.) Further, the Agency in 1984 had added cyclosporine to the "[d]efinitions of antibiotic substances" in the final rule titled *Antibiotic Drugs; Cyclosporine*. *See* 49 Fed. Reg. 22631 (May 31, 1984) (21 CFR 430.4 (a)(51)).

Conversely, FDA had approved a number of antimicrobial drug products that were not considered to be antibiotic drugs because they did not meet the statutory definition of

³⁰ Section 201(jj) of the Act defines an "antibiotic drug" 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.

antibiotic drug. Examples of these drugs include the quinolone antibacterial products (e.g., ciprofloxacin, levofloxacin, and trovafloxacin mesylate) and most antiviral products that have been regulated under section 505 of the Act.

"Congress is assumed to know the judicial or administrative gloss given to particular statutory language, and therefore is assumed to have adopted the existing interpretation unless it affirmatively indicates otherwise." *See e.g., Pfizer, Inc. v. Food and Drug Administration*, 753 F. Supp., 171, 177 (D. Md. 1990) (citing *Cannon v. University of Chicago*, 441 U.S. 677, 696-698 (1979)); *see also United States v. Rutherford*, 442 U.S. 544, 553 fn. 10 (1979). The Agency's classification of these drugs was well known given that they were published in the *Code of Federal Regulations*. If Congress wanted to mandate that a drug could be classified as an antibiotic drug only if it were labeled for anti-infective or antimicrobial use, Congress certainly could have amended the definition when it enacted the Modernization Act in 1997 to clarify this intent. Congress did not do so. The definition remained focused on drugs containing any quantity of a drug substance with certain properties.

In summary, to be classified as an antibiotic drug: (1) a human drug must contain *any quantity* of a *particular type* of drug substance; and (2) a human drug need *not* contain a particular quantity of the drug substance, *nor* be intended for a particular use (*i.e.*, antimicrobial or anti-infective use). The plain meaning of former section 507 (and current section 201(jj)) of the Act supports this interpretation. The legislative history of section 507 of the Act, and construction of the antibiotic drug statutory definition with respect to other provisions of the Act, also support this interpretation.

III. THE CLASSIFICATION OF DRUG PRODUCTS CONTAINING CYCLOSPORINE AS ANTIBIOTIC DRUGS UNDER FORMER SECTION 507 AND CURRENT SECTION 201(jj) OF THE ACT WAS, AND CONTINUES TO BE, PROPER.

You ask that the FDA reclassify cyclosporine "as a non-antibiotic drug" (petition at 1). The Agency denies your request. As discussed below, drug products containing cyclosporine were, and continue to be, properly classified as antibiotic drugs under former section 507 and current section 201(jj) of the Act.

A. Your rationale for why drug products containing cyclosporine should not be classified as antibiotic drugs is not persuasive.

- 1. You concede that FDA's interpretation of the statutory definition of antibiotic drug under former section 507 of the Act is the literal definition.**

You confirm that FDA's interpretation of the statutory definition of antibiotic drug under former section 507 of the Act is the literal meaning of the statute (petition at 3, 7). Specifically, you state that "[a]pplied literally, it [*i.e.*, the statutory definition of antibiotic drug] encompasses products that are neither approved nor marketed for antibiotic

indications. Indeed, it includes any drug product that contains even the smallest amount of *any* chemical substance produced by *any* microorganism as long as the substance has the capacity to inhibit or destroy *any other* microorganisms in a dilute solution" (emphasis in original petition; underlining changed to italics) (petition at 7). You also state that section 507 "contains essentially the same definition" found in section 201(jj) of the Act (petition at 7, fn. 15).

We agree that the statutory definition of antibiotic drug encompasses drugs that are not approved for antimicrobial or anti-infective indications, and that the definition of antibiotic drug includes human drugs that contain *any quantity* of a drug substance having certain characteristics (*i.e.*, produced by a micro-organism and having the capacity to inhibit or destroy micro-organisms in dilute solution). We also agree that in relevant part former section 507 and section 201(jj) of the Act are essentially the same.

You state in your petition that "cyclosporine has never been approved by the FDA or labeled for any antibiotic indications and should not be considered an antibiotic drug under the law" (petition at 6). You also state that no manufacturer has "ever sought an antibiotic indication" or "submitted data to the Agency to show that cyclosporine is "safe and effective" as an antibiotic drug (petition at 6-7). As such, you state that cyclosporine "should never have been regulated under section 507" of the Act (petition at 7).

We do not share your view that the statutory definition of antibiotic drug produces a "curious result," given the issues with which Congress was concerned when it enacted the definition. Moreover, the law dictates that the Agency cannot set aside the statutory definition of antibiotic drug and adopt a different definition, even if the Agency were to agree that the statutory definition is not ideal. Case law states that even though a statute may be "imperfect," an agency "has no power to correct the flaws it perceives in the statute it is empowered to administer." *See Board of Governors of the Fed. Reserve Sys. v. Dimension Fin. Corp.*, 474 U.S. 361, 374 (1985) (stating "[i]f the Bank Holding Company Act falls short of providing safeguards desirable or necessary to protect the public interest, that is a problem for Congress, and not the Board or the courts, to address"). Moreover, "[t]he process of effectuating congressional intent at times may yield anomalies," and "the explicit language of the statute" in application may produce "a curious result." *See Tri-Bio Labs., Inc., v. United States*, 836 F.2d 135, 143 (3d Cir. 1987) (citing *Board of Governors of the Fed. Reserve Sys.*). Here, the Agency's interpretation of the statute adheres to the plain language chosen by Congress and effectuates a congressional intent that is not anomalous.

2. *FDA will not ignore the plain language of the statute and the legislative history and adopt your approach to classifying antibiotic drugs.*

You ask that FDA set aside what you essentially concede to be the literal meaning of former section 507 and current section 201(jj) of the Act, and adopt instead what *you advocate* as a "common sense" or "accepted scientific meaning" definition of antibiotic drug.

Under the law, the Agency must apply the statutory definition of antibiotic drug under section 201(jj) of the Act. That is, the Agency cannot set aside the statutory definition in favor of what you are deeming a "common sense" or "accepted scientific meaning" definition just because the statute produces what *you* consider to be a less-than-perfect result. Moreover, the Agency's interpretation of the statutory definition is based precisely on the problem Congress intended to address. That is, Congress enacted a statutory definition of antibiotic drug that focuses on a particular type of drug substance. This focus was based in part on the nature of the manufacturing process. Accordingly, the Agency's interpretation makes perfect sense — both from a common sense and a scientific perspective.

- a. The Agency cannot set aside the statutory definition of antibiotic drug and adopt what you consider to be a "common sense" approach. Moreover, your approach does not address the problem Congress intended to address in enacting the statutory definition.

You state in your petition that "[c]ommon sense" dictates that antibiotic drugs must include certain essential elements (petition at 7-8).³¹ Specifically, you state in your petition that "[c]ommon sense" dictates that drugs regulated as antibiotics include the following elements:

- (1) "the drug must exhibit at least some therapeutic properties of an antibiotic;"
- (2) "[the drug] must contain at least one approved antibiotic indication; and"
- (3) "[the drug] must be labeled and marketed as an antibiotic" (petition at 7-8).³²

You are, in effect, asking FDA to engraft language into section 201(jj) that is not part of the statutory definition. Yet, in your petition, you do not provide support for these additional criteria based on the plain language of the Act or the legislative history. You merely state that cyclosporine has never been approved by the FDA or labeled for any antibiotic indications and should not be "considered an antibiotic drug under the law" (petition at 6).

As set forth in previous sections of this response, the statutory definition of antibiotic drug includes *no language whatsoever predicating classification of antibiotic drugs on*

³¹ You also make some vague, unsupported assertions that FDA has misclassified other drug products (petition at 8). You have not provided any evidence demonstrating that any of the drugs that you list are misclassified. In any event, we note that the agency makes scientific determinations with respect to classification of antibiotic drugs in a manner similar to other scientific determinations that fall within the agency's purview. That is, the agency's decision, which is informed by its experience and expertise, is necessarily based on a review of the available, relevant scientific data and information, including information submitted by the sponsor, at the time the decision is made. Accordingly, when available data demonstrate that a drug meets the statutory definition of antibiotic drug, that drug is classified as such.

³² We note that, in this response, we use the terms "antimicrobial indication" or "anti-infective indication," to refer to what you call "antibiotic indication." Further, the phrase "therapeutic properties of an antibiotic" is a misnomer. Antibiotic drugs can be classified as antibiotic drugs, regardless of indication.

antimicrobial or anti-infective indications or on labeling for antibiotic use. Instead, the statutory definition of antibiotic drug focuses on drugs containing "any quantity" of a drug substance with certain properties. The "agency, must give effect to the unambiguously expressed intent of Congress." *See Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 843 (1984).

Furthermore, Congress could have easily drafted statutory language consistent with the criteria you propose in your petition. Congress had previously used the intended use of products to establish regulatory categories in the Act. *See, e.g.*, sections 201(g)(1), 201(h), and 201(i) of the Act. Yet, Congress departed from this "intended use" model and defined antibiotic drug instead by focusing on the presence of "any quantity" of a drug substance having certain characteristics. The Agency's application of the plain language of the statutory definition of antibiotic drug resulted in the Agency: (1) classifying drugs approved for nonantimicrobial uses as antibiotic drugs, and (2) classifying drugs approved for antimicrobial uses as nonantibiotic drugs. Despite being aware of the Agency's interpretation and application of the statutory language, Congress chose not to add the elements described in your petition to the definition of antibiotic drug with the enactment of either the Drug Amendments of 1962 or the Modernization Act in 1997.

In addition, the elements you describe in your petition do not address Congress' main focus in enacting the statutory definition in the first place — that is, regulating drugs containing a particular type of drug substance, which was produced by an unpredictable manufacturing process. The Agency's interpretation, on the other hand, is consistent with Congress' goal.

Moreover, even assuming *arguendo* that your definition did reflect "common sense" — an assumption that is clearly unwarranted in light of the foregoing — the Supreme Court has explicitly stated that common sense definitions are not a substitute for statutory definitions. That is, in *Fox v. Standard Oil Co. of N.J.*, 294 U.S. 87, 95 (1935), the Court in rejecting a common sense definition stated, "definition by the average man or even by the ordinary dictionary with its studied enumeration of subtle shades of meaning is not a substitute for the definition set before us by the lawmakers with instructions to apply it to the exclusion of all others." Accordingly, the Agency cannot set aside the statutory definition of antibiotic drug (which itself is consistent with congressional purpose) to adopt the elements you propose.

- b. The Agency cannot set aside the statutory definition of antibiotic drug even if you deem the definition to be contrary to "any accepted scientific meaning" of the term.

You state that cyclosporine has always functioned therapeutically as an immunomodulator and that it suppresses the growth of T-Cells by blocking a specific chemical pathway (petition at 10). You also assert that "[g]iven its immunosuppressive properties, a doctor would never prescribe [cyclosporine] to combat infection" (petition at 10). You also provide a declaration from Dr. Cavanagh, whom you asked to comment on

clinical use of Restasis eye drops and on whether Restasis is used for treating eye infections. (see submission under cover letter dated October 24, 2003). You state that cyclosporine "has always functioned therapeutically as an immunomodulator" and, as such, it "operates as anti-antibiotic" (petition at 10)(emphasis in original). You acknowledge, however, that cyclosporine has been shown to inhibit fungi *in vitro* (petition at 9-10). Accordingly, you conclude that FDA's interpretation of "antibiotic drug" is contrary to the "accepted scientific meaning" of the term.

It is not unusual for terms to have multiple potential meanings. For example, the term "antibiotic drug" could be given a different meaning in a particular scientific or clinical setting. However, here, Congress enacted a statutory definition of antibiotic drug. The Agency must apply the statutory definition of antibiotic drug under former section 507 of the Act and current section 201(jj) of the Act. Moreover, the statutory definition was enacted to address a specific issue — drugs containing a particular type of drug substance, which was produced by an unpredictable manufacturing process. The Agency's classification of Restasis as an antibiotic is consistent with the Agency's classification of other immunomodulators as antibiotic drugs.³³ Accordingly, the statutory definition of antibiotic drug does not classify antibiotic drugs based on the indication.

Under the law, the statutory definition controls. See *United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 793 (1969).

3. *You concede that Congress has provided no guidance with respect to the terms "inhibit" and "dilute solution." Thus, Congress has provided FDA with a broad grant of discretion with respect to the type of information it may consider in determining whether a drug substance has the capacity to "inhibit" or destroy micro-organisms in "dilute solution."*

In your petition, you assert that the statutory definition of antibiotic drug provides no guidance with respect to the terms "inhibit" and "dilute solution" (petition at 7). You also state that "the statute's overbroad language forces upon FDA and drug manufacturers a regulatory scheme that may, in fact, have nothing whatsoever to do with any antibiotic therapy — an outcome plainly at odds with what Congress intended" (petition at 7).

Because Congress did not (as you also concede) provide any guidance with respect to the terms "inhibit" and "dilute solution," Congress clearly did not speak directly to the question of what these terms must mean. That is, Congress did not describe the type of information the Agency must consider in making its determination as to whether a drug substance has the capacity to "inhibit" or destroy micro-organisms in "dilute solution." Instead, Congress intended to provide FDA with a broad grant of discretion with respect

³³ We note that the Restasis package insert states, "cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known." Dr. Cavanagh's declaration (at 2) also states the exact mechanism of action is not known.

to the type of information the Agency may consider in concluding that a particular drug substance has the capacity to "inhibit" or destroy micro-organisms in "dilute solution."

- a. The word "inhibit," in the context of antimicrobial substances, has a well-established meaning. The Agency has reasonably interpreted the words "dilute solution."

The meaning of the word "inhibit" is well understood in the context of the statutory definition of antibiotic drug. An antibiotic drug substance must, among other things, have "the capacity to inhibit or destroy micro-organisms." The word inhibit, when used in the context of antimicrobial drug substances, is well-understood to mean the inhibition of the growth or replication of a micro-organism.

For example, the concept of antimicrobial inhibition is frequently encountered in the phrase *minimal inhibitory concentration* (frequently abbreviated as MIC), which means the lowest concentration of an antibiotic (or other antimicrobial substance) that inhibits the growth of a specific micro-organism (usually bacteria). (See, e.g., Dorland's definition of *minimal inhibitory concentration* listed under *concentration*.) The term minimal inhibitory concentration (or MIC) is used in the approved labeling of scores of antimicrobial drug products and is widely used in the literature.

In addition, the Agency has interpreted the words "dilute solution" to mean the concentration that correlates with levels expected to be found in human tissue (e.g., plasma) at any proposed or approved dose of a drug containing an antibiotic drug substance.

- b. Although you state that the statute's outcome is plainly at odds with what Congress intended when it adopted section 507 of the Act, you have not provided evidence to that effect.

You have not demonstrated that what you refer to as "overbroad language" leads to "an outcome plainly at odds with what Congress intended." As mentioned above, the Agency interprets the statutory definition of antibiotic drug to include any drug intended for human use containing *any quantity* of a drug substance having certain characteristics (*i.e.*, produced by a micro-organism and having the capacity to inhibit or destroy micro-organisms in dilute solution). This definition can include drugs that are approved for antimicrobial or anti-infective use, and drugs that are approved for nonantimicrobial uses. Moreover, some other drugs approved for antimicrobial use are not antibiotic drugs under the statutory definition.

You state in your petition that "Congressional intent for defining antibiotics under section 507 of the Act was to encourage the development of antibiotic drugs by standardizing the approval process for this *important class of chemical entities*" (petition at 7, fn. 16) (emphasis added). We note that it is not entirely clear whether your reference to the

"important class of chemical entities" is intended to confirm the Agency's interpretation of antibiotic drug as focusing on drug substances with certain properties.

In any event, your petition does not demonstrate that the Agency's interpretation is a "rare case" that sanctions departure from the plain language of the statute. *See Butler v. West*, 164 F.3d 634, at 641 (D.C. Cir. 1999). That is, you have not demonstrated that the "literal application" of the definition of "antibiotic drug" will produce a result "demonstrably at odds with the intentions of the drafters." *Id.* (emphasis added).

B. Your argument that cyclosporine was originally classified as an antibiotic drug by mistake is not persuasive.

In your petition you state that Sandoz' drug product containing cyclosporine was originally classified as an antibiotic drug by "mistake" because it met the "overbroad definition" in section 507 of the Act "based on early studies performed showing weak inhibition of fungi" (petition at 10). You also state that "because there was little difference in the approval processes for antibiotic and nonantibiotic drugs when CSA [cyclosporine] was first approved, no advantage was to be gained from one classification or another. As a result, CSA [cyclosporine] was inadvertently classified and accepted as an antibiotic in 1983" (petition at 10-11).³⁴ You state that for FDA to continue to classify cyclosporine drug products as antibiotic drugs would compound a "20-year-old mistake" (petition at 11).

First and foremost, you provide no new scientific evidence to dispute the classification of drug products containing cyclosporine as antibiotic drugs, under FDA's interpretation of the statute.³⁵ You merely contest the classification by improper reliance on the fact that drug products containing cyclosporine are immunomodulators and are not indicated for antimicrobial or anti-infective use. As discussed below, FDA's original classification of Sandoz's Sandimmune (containing cyclosporine) was not a mistake. This decision has been well-vetted by the Agency, and the classification is proper.³⁶

³⁴ We note that your assertion that there was "no advantage . . . to be gained from one classification or another" is inaccurate. As noted in the regulatory history section in Part I, there were differences in the approval processes in 1983 that could have affected competition.

³⁵ We note that you provide two expert declarations claiming to support your interpretation of the statute. (see submission under cover letter dated October 24, 2003):

- Dr. Tang-Liu comments on human tissue concentration of cyclosporine after recommended twice daily dosing of Restasis and in particular on the question of whether any such concentrations would reach the level of 0.1 micrograms per milliliter. However, to be classified as an antibiotic drug under the statute the drug must contain any quantity of a particular type of drug substance, *not* a particular quantity of a particular type of drug substance.
- Dr. Cavanagh comments on clinical use of Restasis eye drops and whether Restasis is used for treating eye infections. However, antibiotic drugs can be classified as such even if they are not indicated to treat infections.

Accordingly, these declarations are not relevant in determining the classification of Restasis as an antibiotic drug under the statute.

³⁶ The classification of cyclosporine as an antibiotic drug substance has been well-vetted by the agency. We have not been able to review the entire Sandimmune NDA file, which is located in FDA's archives and

1. *Drug products containing cyclosporine were originally classified as antibiotic drugs in 1983.*

Sandoz originally submitted two NDAs, both dated July 29, 1982, under section 505(b) of the Act, for the use of cyclosporine for prevention of organ rejection (heart, kidney, and liver) under the trade name Sandimmune. On November 14, 1983, FDA approved Sandimmune oral solution (NDA 50-574) and a Sandimmune injectable product (NDA 50-573), under section 507 of the Act.

2. *Upon request, FDA carefully reconsidered the classification of Sandimmune (containing the drug substance cyclosporine) as an antibiotic drug and upheld the classification.*

In October 1994 and on February 28, 1995, Sandoz apparently requested that its applications for Sandimmune and Neoral (both containing cyclosporine) be reclassified as nonantibiotic drugs. Dr. Murray M. Lumpkin, then Deputy Center Director (Review Management) for CDER, denied Sandoz's requests by letter dated April 19, 1995.³⁷ In this April 19, 1995 letter, Dr. Lumpkin explains that "cyclosporine can indeed inhibit or kill certain human pathogens *in vitro* at concentrations that are relevant to those found in the human body when cyclosporine is used as described in its approved or proposed labeling."³⁸

Dr. Lumpkin appended the microbiologist's report summarizing cyclosporine's antimicrobial activity to the April 19, 1995 letter. The December 15, 1994 memorandum from James Ramsey, Ph.D. to Dr. Lumpkin on the subject of "Cyclosporine-Request for Reclassification" (1994 Ramsey Memo) concludes that "[c]yclosporine should remain classified as an antibiotic drug." (*Id.* at 13).

The 1994 Ramsey Memo summarizes, among other things, one study³⁹ demonstrating an effect of cyclosporine on the growth of *Cryptococcus neoformans* strains 145A, ATCC

is not easily accessible in the time available for responding to your petition. We have requested that the NDA be retrieved from the archives in the event that it becomes necessary to review it. We believe that review of the entire NDA file is not necessary, however, given the information already available establishing that cyclosporine is produced by a micro-organism and that it has the capacity to inhibit or destroy micro-organisms in dilute solution.

³⁷ The April 19, 1995 letter asserts that both FDA and Sandoz agreed that "the manufacture of cyclosporine involves a fermentative process employing a microorganism" In that letter, Dr. Lumpkin makes clear that in making its decision (*i.e.*, that the cyclosporine products Sandimmune and Neoral were antibiotic drugs), the agency relied on the "ordinary meaning of the words in the statute" (*i.e.*, the statutory definition of antibiotic drug), with reference to Congressional intent. (*Id.* at 2).

³⁸ Dr. Ramsey's 1994 memo states that antifungal activity was demonstrated in both *in vitro* and animal tests. Dr. Lumpkin's April 19, 1995, letter makes reference to *in vitro* studies. Both concluded that cyclosporine has the capacity to inhibit or destroy micro-organisms in dilute solution.

³⁹ Mody, Christopher H., Galen B. Toews, and Mary F. Lipscomb. 1988. Cyclosporin [sic] A Inhibits the Growth of *Cryptococcus neoformans* in a Murine Model. *Infection and Immunity*. 56:7-12. The 1994 Ramsey Memo provides the following description of the study: For *in vitro* studies, *C. neoformans* was cultured for 48 hr in both neopeptone or yeast nitrogen base broth in the presence of cyclosporine at 0.1 or

36556, and H99 in cell culture and in mice. The 1994 Ramsey Memo asserts the following with respect to this study: "Results showed that for strains 145A, ATCC 36556 and H99, 0.1 μ g/ml cyclosporine inhibited growth approximately 95, 75, and 98%, respectively; whereas, at 1.0 μ g/ml, inhibition was 100% for all strains. Concentrations between 0.1 and 1.0 μ g/ml were not evaluated. Similar results were observed with both broth culture media utilized. Growth in media containing Cremaphor-EL and in media without additives was equivalent, suggesting that the pH differences in these cell cultures did not affect fungal growth. . . . These results establish that cyclosporine is fungicidal for *C. neoformans* *in vitro* with an MIC value of [</=] 1.0 μ g/ml" (*Id.* at 7-8). Furthermore, the 1994 Ramsey Memo states that "the MIC of cyclosporine against *C. neoformans*, determined *in vitro* and shown to be active in an infected animal model, is achievable in human plasma following administration of recommended doses of cyclosporine in transplant patient populations" (*Id.* at 9) (underlining replaced with italics).

The 1994 Ramsey Memo also summarizes another study,⁴⁰ which "determined the *in vitro* MIC and minimum fungicidal concentrations (MFC) of cyclosporine and Amphotericin B against the *Coccidioides immitis* strain *Silveria* and 10 clinical isolates. . ." (*Id.* 9-11) (underlining replaced with italics). The 1994 Ramsey Memo concludes, among other things, that "*in vitro* MIC values indicated that cyclosporine possessed antifungal activity against *C. immitis* greater than that observed for Amphotericin B, an antibiotic drug approved for the treatment of disseminated forms of coccidioidomycosis in human patients" (*Id.* at 10) (underlining replaced with italics).

In sum, Dr. Ramsey concluded cyclosporine has antifungal activity against the human pathogens *Cryptococcus neoformans* and *Coccidioides immitis* in dilute solution.⁴¹ The Agency has interpreted dilute solution to mean a concentration that correlates with levels expected to be found in human tissue (e.g., plasma) at any proposed or approved dose of a drug containing the antibiotic drug substance. At levels expected to be found in human tissue (e.g., plasma) following administration of a recommended dose of a drug containing cyclosporine, cyclosporine has been shown to have antifungal activity against *Cryptococcus neoformans* and *Coccidioides immitis* in both *in vitro* tests and *in vivo* animal tests.

1.0 μ g/ml. Growth of *C. neoformans* in broth cultures without additives or with Cremaphor-EL (the vehicle for Sandimmune IV) at a concentration equal to that present in the 1.0 μ g/ml cyclosporine broth cultures, served as controls. The pH of the culture media with Sandimmune IV, Cremaphor-EL, or without additives was 6.6, 6.7, and 6.2, respectively. Growth inhibition was determined by plating serial 10-fold dilutions of the 48 hr broth cultures onto agar medium and enumerating the number of colony forming units (CFU's) observed after an additional incubation for 48 hr. *Id.* at 7. (underlining replaced with italics).

⁴⁰ Hoeprich, Paul D. and Joanne M. Merry. 1987. Comparing Efficacy of Forphenicinol, Cyclosporine, and Amphotericin B in Experimental Murine Coccidioidomycosis. *Diagn. Microbiol. Infect. Dis.* 6:287-292.

⁴¹ Your petition acknowledges cyclosporine has antifungal activity. In your petition, you state, "[b]ased on such testing, CSA [cyclosporine] was shown to have very weak inhibition of growth for a very select group of fungi . . ." (petition at 9).

3. *FDA compared the classification of drugs containing cyclosporine as antibiotic drugs with the classification of drugs containing lovastatin as a nonantibiotic drugs, and upheld the classifications.*

Approximately two years after the Agency issued its decision with respect to the request for reclassification of Sandimmune and Neoral (both containing cyclosporine), Novartis (previously known as Sandoz) submitted another letter dated March 19, 1997, yet again requesting reconsideration of the antibiotic drug classifications. While Novartis maintained that it "continue[d] to believe that there is no valid scientific basis to classify cyclosporine as an antibiotic," it appears that Novartis provided no scientific rationale or scientific evidence to dispute that classification of drugs containing cyclosporine in the March 19, 1997 letter. Instead, Novartis alleged that the Agency classified a similarly-situated product, Mevacor (lovastatin), differently. Novartis specifically claimed that lovastatin and related drugs are similar to cyclosporine in fungal derivation and antifungal properties, and that there is no reason to treat cyclosporine and lovastatin differently under the Act. *Id.* at 2.

As requested, once again, the Agency revisited the classification of drug products containing cyclosporine as antibiotic drugs, this time in light of FDA's classification of Mevacor (lovastatin) as a nonantibiotic drug. The Agency did not consider Novartis' request lightly, as demonstrated by the 37-page memorandum (which cites in the text itself over 50 literature sources) from Dr. James Ramsey to Dr. Murray Lumpkin, dated August 1, 1997, on the subject of "Antimicrobial Activity of Lovastatin and Related Drugs" (1997 Ramsey Memo).

Mevacor, the first drug product containing lovastatin (an HMG-CoA reductase inhibitor) was approved in 1987 as a cholesterol-lowering agent. Lovastatin was originally isolated from the fungus *Penicillium citrinum*, but the first publications reporting lovastatin's antimicrobial activity appeared in 1988, a year after its approval.⁴² These publications provided no evidence that lovastatin has antimicrobial activity in humans. The Agency reviewed the literature to confirm that lovastatin has antimicrobial activity in animals. Because human data were not available, Dr. Ramsey reviewed the literature to compare the level of drug expected to be found in humans at approved doses to levels that were shown to inhibit or destroy micro-organisms in *in vitro* tests. It was estimated that, at concentrations found in humans treated at recommended doses as a cholesterol-lowering agent, lovastatin would not be expected to inhibit or destroy micro-organisms.⁴³

Not only did the Agency consider the classification of lovastatin per Novartis' request, but the Agency also considered in its analysis the classification of other related drugs, such as simvastatin. Simvastatin is another HMG-CoA reductase inhibitor that has

⁴² Note the current Mevacor (lovastatin) labeling states that it is a cholesterol lowering agent isolated from a strain of *Aspergillus terreus*.

⁴³ It should be noted that the concentration of lovastatin found in humans, when dosed according to labeling, is about 0.1 micromolar (μM), or about 4 parts per 10 million. A conservative estimate of the concentration of lovastatin needed to inhibit or destroy microorganisms is about 3- to 25-fold the actual concentration found in humans, or about 12 to 100 parts per 10 million. (See 1997 Ramsey Memo, at 27).

microbial origins and possesses antimicrobial activity. The literature on simvastatin was also reviewed and similar conclusions were drawn concerning its inability to inhibit or destroy micro-organisms at levels achieved with recommended doses as a cholesterol-lowering drug.

Cyclosporine is in many ways similar to lovastatin and simvastatin. However, there are important differences between cyclosporine and lovastatin/simvastatin that influence how cyclosporine is classified. Cyclosporine is produced by a micro-organism, and it has been shown to have antimicrobial activity. When the Agency reviewed the request for reclassification of cyclosporine, there were inadequate human data to show that cyclosporine had antimicrobial activity in humans; however, in evaluating the antifungal properties of cyclosporine in *animal models* as well as in *in vitro tests*, the Agency has concluded that cyclosporine has antifungal activity against the human pathogens *Cryptococcus neoformans* and *Coccidioides immitis* at levels that are found in human tissue (e.g., plasma) at a recommended dose of a drug product containing cyclosporine. Thus, cyclosporine, unlike lovastatin, has the capacity to inhibit or destroy micro-organisms in dilute solution. Cyclosporine is therefore an antibiotic drug substance.

FDA appropriately classified cyclosporine as an antibiotic drug substance. The classification of lovastatin as nonantibiotic drug substance is consistent with the classification of cyclosporine as an antibiotic drug substance. Accordingly, drugs containing cyclosporine remain classified as antibiotic drugs, and drugs containing lovastatin remain classified as nonantibiotic drugs.

4. *The Agency's consideration of in vitro studies, in vivo animal studies, and in vivo human studies is reasonable in determining whether an antibiotic drug substance, among other things, "has the capacity to inhibit or destroy micro-organisms in dilute solution."*

You state that cyclosporine was inadvertently classified as an antibiotic drug substance and that such a classification was a "20-year-old mistake" based on the early studies performed, showing the weak inhibition of certain fungi (petition at 10-11).

To the extent that your petition is challenging the data on which FDA relied in concluding that cyclosporine has the capacity to inhibit or destroy micro-organisms in dilute solution, in this section we briefly discuss the use of *in vitro* studies, *in vivo* animal studies, and *in vivo* human studies for making such determinations.

Congress has not prescribed the type of information the Agency may rely upon in making a determination as to whether a chemical substance (*i.e.*, drug substance) has the capacity to inhibit or destroy micro-organisms in dilute solution. These scientific determinations are within the ambit of the Agency's scientific expertise. The Agency's reliance on relevant *in vitro* studies and *in vivo* animal studies to classify cyclosporine as an antibiotic drug substance is reasonable even assuming *arguendo* there are no *in vivo* human data to support the classification. In determining whether the drug substance "has

the capacity to inhibit or destroy micro-organisms in dilute solution," reliance on *in vitro* and *in vivo* animal data is reasonable for the reasons explained below.⁴⁴

When sponsors conduct adequate and well-controlled clinical studies in humans (*i.e.*, *in vivo* human data), they are generally testing to see whether a drug is safe and effective for a specific indication. Efficacy data from adequate and well-controlled *in vivo* human studies can provide evidence of a drug's clinical efficacy in the treatment of, among other things, an infectious disease.

There are circumstances, however, under which *in vivo* human studies may not demonstrate efficacy in the treatment of a particular type of infection despite the fact that the drug substance has the capacity to inhibit or destroy micro-organisms in dilute solution. For example, the demonstration of clinical efficacy from adequate and well-controlled clinical studies involves a number of factors in living systems that include, among other things, the antimicrobial activity of the drug, whether the drug achieves sufficient concentrations at the site of infection that is being studied, the immune response of the host, the metabolic state of the infecting micro-organism, and the microbial microenvironment. An antimicrobial drug that merely does not achieve adequate concentrations at the site of infection (*e.g.*, an antimicrobial drug that achieves poor concentrations in the bloodstream, or the central nervous system) may have significant microbiologic activity (*i.e.*, the capacity to inhibit or destroy micro-organisms), but may fail to demonstrate clinical efficacy because of inadequate concentrations at the site of infection in the human body. Therefore, reliance upon *in vivo* human data may fail to identify drugs that have the capacity to inhibit or destroy micro-organisms in dilute solution simply because the antimicrobial drug failed to achieve adequate concentrations at the site of infection under study — although the antimicrobial drug substance if evaluated for the treatment of infections at other sites in the body might be found to have clinical efficacy.

The statutory definition of antibiotic drug (under former section 507 of the Act and current section 201(jj) of the Act) does not require the demonstration of clinical efficacy in patients with infections, nor does it require data from *in vivo* animal models of infection demonstrating effectiveness. The definition asks whether the drug substance has the capacity to inhibit or destroy micro-organisms in dilute solution.

Data from animal models of infection (*in vivo* animal studies) can provide information on an antimicrobial drug's capacity to inhibit or destroy micro-organisms in a living animal. Like *in vivo* studies in humans, the response in an animal model of infection involves factors other than just the antimicrobial activity of the drug under study, including the ability of the drug to attain therapeutic tissue levels at the site of infection under study, the immune response, the size of the inoculum (large inoculum may lead to an infection that even an effective antimicrobial drug cannot effectively treat), the timing of initiation of antimicrobial therapy, and subsequent dosing. Hence, as is the case for *in vivo* studies

⁴⁴ There is, of course, a distinction between clinical efficacy (which is determined by adequate and well-controlled studies), and antimicrobial activity (which can be determined by the drug substance's capacity to inhibit or destroy micro-organisms).

in humans, although a finding of antimicrobial effect in an animal model can provide evidence of an antimicrobial drug's capacity to inhibit or destroy micro-organisms, a negative finding for antimicrobial effect in an animal model does not necessarily exclude the possibility that the drug is an active antimicrobial agent.

The use of *in vitro* testing methods to determine whether a particular micro-organism is inhibited or destroyed by a particular concentration of an antimicrobial drug is one of the cornerstones of clinical microbiology. *In vitro* testing methodologies are typically designed to determine concentrations of an antimicrobial drug that inhibit microbial growth (e.g., the minimal inhibitory concentration for bacterial micro-organisms) or the concentration that destroys micro-organisms (e.g., the minimal bactericidal concentration for bacterial micro-organisms). *In vitro* testing methodologies are not dependent upon many of the complex factors that influence outcomes in infections in animals or humans such as achieving a specific drug concentration at the site of the infection or the host immune response. *In vitro* methods measure the effect of an antimicrobial drug in a less complex system than an *in vivo* animal model or in naturally occurring human infection. *In vitro* methods are dependent upon the techniques used, including factors such as the inoculum size and characteristics of the microbial growth media used. In addition, inhibitory concentrations cannot be determined for all micro-organisms. *In vitro* testing methodologies are important in identifying the antimicrobial activity of drug substances against particular micro-organisms and are relied upon for the selection of antimicrobial therapy every day in hospitals across the United States. *In vitro* testing methods provide information on the capacity of a drug substance to inhibit or destroy the micro-organism being tested.

Results from *in vivo* human studies, *in vivo* animal studies, or *in vitro* studies can provide evidence of the capacity of a drug substance to inhibit or destroy micro-organisms. There are strengths and limitations to each of these approaches for the purposes of measuring the capacity of a drug substance to inhibit or destroy micro-organisms. These limitations are inherent to the biology of the micro-organisms and the settings (*in vivo* human studies, *in vivo* animal studies, or *in vitro* studies) within which the drug is being evaluated.

In summary, evidence of clinical efficacy from *in vivo* human studies can provide evidence of a drug substance's capacity to inhibit or destroy micro-organisms, but a negative result does not necessarily exclude significant antimicrobial activity. The same is true for animal models of infection. Measurement of antimicrobial effect in humans and in animal models is affected by a number of factors. *In vitro* studies can provide information from a system that measures the capacity of the drug substance to inhibit or destroy micro-organisms. Reliance upon data from *in vivo* human studies, animal models of infection, or *in vitro* data can be used to evaluate whether a compound possesses the capacity to inhibit or destroy micro-organisms in dilute solution.

The definition of antibiotic drug does not require the demonstration of clinical efficacy from *in vivo* human studies. Nor does the definition require the demonstration of antimicrobial effect in *in vivo* animal models of infection. The definition of antibiotic

drug asks only for demonstration of the drug substance's capacity to inhibit or destroy micro-organisms. The capacity to inhibit or destroy micro-organisms in dilute solution can be demonstrated using data from *in vivo* human studies, *in vivo* animal studies, or *in vitro* studies. Hence, it is reasonable and appropriate that the Agency has relied upon data derived from *in vivo* animal models of infection and *in vitro* data demonstrating the capacity of cyclosporine to inhibit or destroy micro-organisms in dilute solution.

C. FDA has a long history of classifying cyclosporine as an antibiotic drug substance and has classified all drugs containing cyclosporine as antibiotic drugs.

You acknowledge that "historically, CSA [cyclosporine] and all drug products containing CSA [cyclosporine] were regulated as antibiotics under the FDCA [the Act]." (petition at 1). The Agency has consistently classified cyclosporine drug products as antibiotic drugs in accordance with former section 507 of the Act and current section 201(jj) of the Act.⁴⁵

After FDA approved the first two cyclosporine drug products as antibiotic drugs, the Agency in 1984 added cyclosporine to the "[d]efinitions of antibiotic substances" in the final rule titled *Antibiotic Drugs; Cyclosporine*. See 49 Fed. Reg. 22631 (May 31, 1984) (21 CFR 430.4(a)(51)) (corresponding regulations on "cyclosporine oral solution" and "cyclosporine for infusion" were also promulgated; note these regulations were subsequently revoked along with the other antibiotic regulations with the repeal of section 507 of the Act).⁴⁶ The Federal Register notice invited anyone adversely affected by the rule to file objections to it and request a hearing. No comments or objections were submitted to Docket No. 84N-0105. Thus, industry, including Allergan, was on notice as early as 1984 that the Agency regarded cyclosporine as an antibiotic drug substance.

The Agency's consistent treatment of cyclosporine as an antibiotic drug is further reflected in its approvals for drugs containing cyclosporine: to date *FDA has approved 13 other drug products containing cyclosporine — all of which have been classified as antibiotic drugs*. (see electronic *Orange Book*).

In addition, FDA has approved other drugs as antibiotic drugs even though they are approved for nonantimicrobial uses. These drugs include the immunomodulator drugs containing tacrolimus and mycophenolate.

⁴⁵ We note that longstanding policies consistently applied are afforded deference. *See INS v. Cardoza Fonseca*, 480 U.S. 488 n.30 (1987).

⁴⁶ These regulations not only help to show the agency's consistent classification of cyclosporine as an antibiotic drug, but they are also entitled to deference. Under *Chevron*, legislative rules, promulgated under specific grants of authority, "are given controlling weight unless they are arbitrary, capricious or manifestly contrary to congressional intent." *Id.* at 844. In this case, former section 507 required the agency to publish regulations (antibiotic monographs) that set forth the standards of identity, strength, quality, and purity for each marketed antibiotic drug. (*See Repeal of Section 507 Guidance* at 1). Accordingly, the cyclosporine regulations (*i.e.*, antibiotic monographs) were promulgated under a specific grant of authority from Congress and should be given much weight.

Consistent with FDA's classification of cyclosporine as an antibiotic drug substance, the Agency listed cyclosporine as an antibiotic drug in a January 24, 2000 proposed rule titled *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs*, 65 Fed. Reg. 3623 (January 24, 2000) (*Antibiotic Exclusivity and Patent Proposed Rule*). This proposed rule is discussed elsewhere in this response.

In summary, cyclosporine has been, and continues to be, properly classified as an antibiotic drug substance. All drug products containing cyclosporine have been properly classified as antibiotic drugs. The Agency has been consistent with respect to this classification.

IV. CLASSIFICATION OF RESTASIS AS AN ANTIBIOTIC DRUG IS SUPPORTED BY THE PLAIN LANGUAGE OF SECTION 201(jj) OF THE ACT, LEGISLATIVE INTENT, AND FDA'S CLASSIFICATION OF OTHER DRUGS.

FDA's classification of Restasis as an antibiotic drug is compelled by the plain language of the statutory definition of antibiotic drug under section 201(jj) of the Act, the legislative intent, and FDA's classification of other drugs.

A. Under the plain language of section 201(jj), Restasis is an antibiotic drug.

Restasis meets the criteria in the second part of the statutory definition of antibiotic drug.⁴⁷ That is, Restasis is a "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." (emphasis added). Because (i) Restasis is a drug intended for human use, (ii) Restasis contains a quantity of cyclosporine, (iii) cyclosporine is produced by a micro-organism, and (iv) cyclosporine has the capacity to inhibit or destroy micro-organisms in dilute solution, Restasis is an antibiotic drug.

Restasis is a drug intended for human use. In your petition, you state that Restasis is "indicated for the treatment of 'dry eye disease' in humans" (petition at 1).⁴⁸

Restasis contains a quantity of the chemical substance (i.e., drug substance) cyclosporine. In your petition, you state that Restasis contains the active ingredient cyclosporine (petition at 1). Restasis contains 0.05 percent of the drug substance cyclosporine (i.e., the only drug substance in Restasis). As noted elsewhere in this

⁴⁷ Restasis does not fall under the first part of the statutory definition of antibiotic drug. Restasis is a drug for human use; however, Restasis is not composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin.

⁴⁸ Specifically, Restasis is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs. (See Restasis package insert).

response, to be classified as an antibiotic drug, under the statutory definition, the human drug must contain *any quantity* of a particular type of drug substance; and it need not contain a particular quantity of the drug substance. Restasis contains *a quantity* of cyclosporine.

The drug substance cyclosporine is produced by a micro-organism. FDA interprets the term *micro-organism* to include bacteria, fungi, viruses, and other microscopic organisms. In your petition, you assert that cyclosporine is produced by *Tolypocladium inflatum* (and other fungi) (petition at 9). You do not claim that the drug substance cyclosporine in Restasis is not produced by a micro-organism.

Cyclosporine has the capacity to inhibit or destroy micro-organisms in dilute solution. As discussed above, cyclosporine has antifungal activity against the human pathogens *Cryptococcus neoformans* and *Coccidioides immitis* in dilute solution.⁴⁹ At levels expected to be found in human tissue (e.g., plasma) following administration of a recommended dose of a drug containing cyclosporine, cyclosporine has been shown to have antifungal activity against *Cryptococcus neoformans* and *Coccidioides immitis* in both *in vitro* and *in vivo* animal tests.

Furthermore, it does not matter that Restasis is not indicated for antimicrobial use. The plain language of the statute does not require a drug to be indicated for a particular use to be classified as an antibiotic drug. Restasis therefore meets the statutory definition of an antibiotic drug.

B. Restasis' classification as an antibiotic drug is supported by legislative intent.

Restasis' classification as an antibiotic drug is supported by legislative intent. That is, Congress in enacting section 125(e), which added section 201(jj) of the Act, was well-aware of the Agency's interpretation and application of the statutory definition under former section 507 of the Act. In 1997, the Agency already had a long history of classifying drugs as antibiotic drugs based on the type of drug substance. As such, well before 1997, FDA had already approved oncologic drugs and immunomodulator drugs for nonantimicrobial uses, and had classified them as antibiotic drugs under section 507 of the Act. Monographs for some of these antibiotic drug substances were published in the *Code of Federal Regulations*. Conversely, FDA had approved a number of antimicrobial drug products that were not considered to be antibiotic drugs under section 507 of the Act because they did not meet the statutory definition of antibiotic drug. Yet, Congress chose not to change the definition of antibiotic drug in 1997 to include an intended use element when it enacted section 201(jj) of the Act.

Accordingly, the foregoing supports Restasis' classification as an antibiotic drug. That is, Restasis contains a quantity of cyclosporine — a chemical substance which is produced

⁴⁹ Your petition acknowledges cyclosporine has antifungal activity. In your petition, you state, “[b]ased on such testing, CSA [cyclosporine] was shown to have very weak inhibition of growth for a very select group of fungi . . .” (petition at 9).

by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution. It does not matter that Restasis is not approved or labeled for antimicrobial uses.

C. FDA's classification of Restasis as an antibiotic drug is consistent with FDA's classification of other drugs.

FDA's classification of Restasis as an antibiotic drug is consistent with its treatment of other similarly situated products.⁵⁰ FDA has consistently applied the statutory definition of antibiotic drug.

Accordingly, FDA has approved 13 other drug products containing cyclosporine as antibiotic drugs (*see* electronic *Orange Book*). FDA has also approved other immunomodulator drugs as antibiotic drugs even though they are all approved for nonantimicrobial uses (*e.g.*, tacrolimus, mycophenolate).

In addition, bleomycin sulfate, doxorubicin hydrochloride, daunorubicin hydrochloride, daunorubicin citrate, and plicamycin, which are antibiotic drugs originally approved under section 507, are indicated for cancer therapy — not antimicrobial uses.

Conversely, a number of antimicrobial drugs are not considered to be antibiotic drugs because they do not meet the test of the statutory definition of antibiotic drug ("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"). Examples of these drugs include the quinolone antibacterial products (*e.g.*, ciprofloxacin, levofloxacin, and trovafloxacin mesylate) and most antiviral products that have been regulated under section 505 of the Act.

Accordingly, FDA's classification of Restasis as an antibiotic drug is consistent with the statutory definition of antibiotic drug, and FDA's classification of other drugs.

V. BECAUSE CYCLOSPORINE IS AN ANTIBIOTIC DRUG SUBSTANCE THAT WAS THE SUBJECT OF AN APPLICATION RECEIVED BY FDA BEFORE NOVEMBER 21, 1997, CYCLOSPORINE WAS PROPERLY INCLUDED ON THE PROPOSED LIST OF ANTIBIOTIC DRUGS SUBJECT TO SECTION 125(d)(2).

You request that FDA remove cyclosporine from the proposed list of drugs that are ineligible for marketing exclusivity and patent listing pursuant to section 125(d) of the

⁵⁰ We note that FDA's classification of Restasis is consistent with that of Periostat (doxycycline hydiate 20-mg tablets) in regard to FDA's interpretation of section 201(jj) of the Act. Periostat was classified as an antibiotic drug because Periostat contains doxycycline, which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution. Further, Periostat itself contains a quantity of doxycycline that has the capacity to inhibit or destroy micro-organisms at the dose approved for Periostat. A copy of the Periostat administrative record is publicly available in the docket.

Modernization Act (petition at 1). Because cyclosporine is an antibiotic drug substance that was the subject of an application received by FDA before November 21, 1997, cyclosporine was properly included on the proposed list of antibiotic drugs subject to section 125(d)(2).

The Agency published the *Antibiotic Exclusivity and Patent Proposed Rule* on January 24, 2000. This proposed rule includes cyclosporine on the proposed list of active moieties of antibiotic drugs that were the subjects of marketing applications received by FDA before November 21, 1997. The comment period closed on April 24, 2000.

Although Allergan had submitted an NDA for a drug product containing cyclosporine that was pending approval at that time, Allergan did not submit any comments to Docket No. 99N-3088. In fact, FDA received no comments to Docket No. 99N-3088 concerning the inclusion of cyclosporine on the proposed list of active moieties of antibiotic drugs.

In your petition, you now advance the position that section 125(d)(2) of the Modernization Act should be interpreted using the term "antibiotic drug," under section 201(jj) of the Act — as opposed to the proposed term "active moiety,"⁵¹ as described in the *Antibiotic Exclusivity and Patent Proposed Rule*. You state that FDA interpreted section 125(d)(2) in an "unusual manner" in the *Antibiotic Exclusivity and Patent Proposed Rule* (petition at 15).⁵²

FDA need not resolve the question of whether to use of the concept of active moiety in interpreting section 125(d)(2), in order to determine that cyclosporine is properly subject to section 125(d)(2). As described in detail elsewhere in this response, FDA interprets the term "antibiotic drug" in sections 507 and 201(jj) as requiring an analysis of the drug substance (or active ingredient) contained in the drug product. There appears to be no dispute that the drug substance in Restasis – cyclosporine – is the same drug substance that was present in the cyclosporine drug products previously regulated by FDA under section 507 as antibiotic drugs. Therefore, FDA does not need to reach the question of whether it is appropriate to use the concept of active moiety to interpret the phrase "any derivative thereof" in section 125(d)(2).

Because cyclosporine is an antibiotic drug substance that was the subject of an application received by FDA before November 21, 1997, cyclosporine was properly included on the proposed list of antibiotic drugs subject to the transition provision exception in 125(d)(2).

VI. BECAUSE RESTASIS IS AN ANTIBIOTIC DRUG THAT FALLS UNDER SECTION 125(d)(2) OF THE MODERNIZATION ACT, IT IS NOT ELIGIBLE FOR HATCH-WAXMAN BENEFITS.

⁵¹ Under 21 CFR 314.108(a), "[a]ctive moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." Different active ingredients, or drug substances, can have the same active moiety.

⁵² We note that the agency received comments to the proposed rule specifically on the agency's proposed interpretation of section 125(d)(2) as it relates to active moieties.

After approving Restasis, FDA determined that Restasis contains the antibiotic drug substance cyclosporine, and the antibiotic drug substance cyclosporine is the subject of marketing applications that were received before the enactment of the Modernization Act. Consequently, FDA determined that Restasis is subject to section 125(d)(2) of the Modernization Act, which made Restasis ineligible for Hatch-Waxman benefits. Your petition requests that FDA: 1) find that Restasis is not an antibiotic drug product that falls under the transition provisions of section 125(d) of the Modernization Act; and 2) grant Restasis three-year marketing exclusivity and patent listing rights under section 505 of the Act (petition at 1). These requests are denied. Below we first set forth the relevant statutory background, and then we explain the bases for denying your request.

A. Relevant Statutory Background

1. Summary of Approval Process

Under the Act, sponsors seeking to market innovator drugs must first obtain FDA approval by filing an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug. *See* section 505(a), (b) of the Act. The NDA applicant is also required to submit to FDA patent information on any patent that it claims will protect its exclusive marketing of the drug. Specifically, the sponsor is to submit information on any patent that "claims the drug . . . or a method of using such drug" and for which a claim of patent infringement could reasonably be asserted against an unauthorized party engaged in the manufacture, use, or sale of the drug. *See* section 505(b)(1), (c)(2) of the Act. FDA is required to publish patent information for approved drugs, and does so, in the *Orange Book*. *See* section 505(b)(1), (c)(2), (j)(7) of the Act; 21 CFR 314.53(e).

The Act permits the submission of ANDAs for approval of generic versions of approved drug products. *See* section 505(j) of the Act. The ANDA process shortens the time and effort needed for approval by, among other things, allowing the applicant to demonstrate that its drug product is bioequivalent to the innovator drug, rather than reproduce the safety and effectiveness data for the innovator drug. *See Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990). The timing of approval of an ANDA depends in part on statutory patent listing, patent certification, and exclusivity protections added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Pub. L. No. 98-417, 98 Stat. 1585 (1984).

2. Summary of NDA Exclusivity

The Act provides different marketing exclusivity periods for drugs approved in NDAs, based on the level of innovation represented by the drug product. While these five- and three-year exclusivity periods are in effect, FDA may not accept or approve certain applications that rely on the protected product for approval. *See* sections 505(c)(3)(D)(ii)-(iv), (j)(5)(D)(ii)-(iv) of the Act.

Five-year exclusivity is granted to a drug that contains no active ingredient (including any ester or salt of the active ingredient) previously approved under section 505(b) of the Act. See section 505(c)(3)(D)(ii), (j)(5)(D)(ii) of the Act; 21 CFR 314.108. During this five-year period that begins with approval, FDA may not receive for review any ANDA referring to the listed drug with this protection. However, if the NDA holder for the listed drug with five-year exclusivity has submitted a patent for the drug pursuant to section 505(b)(1) or (c)(2) of the Act, an ANDA applicant wishing to challenge that patent may submit an application referencing the listed drug at the end of four years. See sections 505(c)(3)(D)(ii), (j)(5)(D)(ii) of the Act; 21 CFR 314.108.

Three-year exclusivity is granted to a drug for which approval of an NDA or NDA supplement requires FDA to review new clinical studies conducted or sponsored by the applicant that are essential to the approval. This exclusivity bars FDA from approving for three years an ANDA referencing the listed drug (or a change to the listed drug) for which the new studies were submitted. See sections 505(c)(3)(D)(iii), (iv), (j)(5)(D)(iii), (iv) of the Act; 21 CFR 314.108.

3. Summary of Patent Protection

The proposed drug described in an ANDA may not be finally approved until the patents and marketing exclusivity have expired or until the NDA holder and patent owners for patents on the listed drug⁵³ have had an opportunity to defend their patent rights in court. With respect to each patent submitted by the sponsor for the listed drug and listed in the *Orange Book*, the ANDA applicant must submit to FDA one of four specified certifications. See section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

- (I) that the required patent information relating to such patent has not been filed;
- (II) that such patent has expired;
- (III) that the patent will expire on a particular date; or
- (IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought.

If the ANDA applicant does not challenge the listed patents, the application will not be approved until all the listed patents claiming the listed drug have expired. If an applicant wishes to challenge the validity of the patent or to claim that the patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant must also provide a notice to the NDA holder and

⁵³ Under 21 CFR 314.3(b), "[l]isted drug means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's 'Approved Drug Products with Therapeutic Equivalence Evaluations' (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product."

the patent owner stating that the application has been submitted and explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed. *See* sections 505(b)(2)(B), (j)(2)(B) of the Act. The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement. 35 U.S.C. § 271(e)(2)(A). If the patent holder or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, FDA will stay approval of the ANDA for 30 months from the date that the patent owner and NDA holder received notice, unless a final court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period. *See* sections 505(c)(3)(C), (j)(5)(B)(iii) of the Act.

Thus, under the procedures established in the Hatch-Waxman Amendments, an ANDA will not be approved until all applicable listed drug product exclusivity has expired and the listed patents have expired, have been successfully challenged by an applicant, or any applicable 30-month stay has expired. *See* 21 CFR 314.107.

4. Summary of Antibiotic Scheme Under the Modernization Act

In November 1997, Congress enacted section 125(d) of the Modernization Act, which among other things, repealed section 507 of the Act.⁵⁴ Section 125(d)(1) of the Modernization Act declared that an application approved under section 507 of the Act before enactment of the Modernization Act will be considered to be an application submitted, filed, and approved under section 505 of the Act (transition provision).

Congress created an exception to the transition provision in section 125(d)(2) of Title I of the Modernization Act (transition provision exception). This transition provision exception exempted certain applications for antibiotic drugs from those provisions of 505 that provide, for example, for new drug exclusivity, patent listing, patent certification, and 30 month stays on approval of abbreviated new drug applications ANDAs. Section 125(d)(2) exempts an application from these Hatch-Waxman benefits when "the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application" received by FDA under section 507 of the Act before November 21, 1997.

B. The plain language of section 125(d)(2) supports the Agency's interpretation, and the Agency has been consistent in the application of its interpretation.

After approving Restasis (containing cyclosporine), FDA determined that Restasis was subject to the transition provision exception in section 125(d)(2) of the Modernization Act. That is, Restasis contains cyclosporine and cyclosporine was the subject of marketing applications received before the enactment of the Modernization Act.

⁵⁴ In May 1998, the agency published the *Repeal of Section 507 Guidance*, which set forth some policies with respect to section 125 of the Modernization Act.

The plain language of section 125(d)(2) of the Modernization Act supports the Agency's interpretation.⁵⁵ Section 125(d)(2) of the Modernization Act reads as follows:

The following subsections of section 505 (21 U.S.C. 355) shall not apply to any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of this Act: [list of patent listing and marketing exclusivity provisions].

In other words, section 125(d)(2) exempts an application from Hatch-Waxman benefits when "the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application" received by FDA under section 507 of the Act before November 21, 1997.

The first part of the section 125(d)(2) refers to: "any application for marketing in which the drug that is the subject of the application." In this case, the drug that is the subject of the marketing application is Restasis.

The second part of this provision reads: "contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing" received by FDA under section 507 of the Act before the date of the enactment of the Modernization Act.

To make sense of the word *contains*, the most reasonable reading of the plain language of the statute is to focus on the antibiotic drug substance contained in the antibiotic drug. An antibiotic drug by definition is not only the drug product, but also the antibiotic drug substance. Section 125(d)(2) reads "any application for marketing in which the drug that is the subject of the application *contains* an antibiotic drug . . ." That is, a drug product does not contain a drug product; rather, a drug product *contains* a "drug substance." This reading also mirrors the construction in section 201(jj) of the Act, which defines an antibiotic drug as a "drug intended for human use *containing* any quantity of a chemical substance" with certain properties. In enacting the definition of antibiotic drug, Congress' focus, as evident by the plain language of the statute, is on the antibiotic drug substance.

In this case, Restasis contains cyclosporine (*i.e.*, the antibiotic drug substance in the antibiotic drug Restasis); cyclosporine (*i.e.*, the drug substance in, for example, Sandimmune) was the subject of any application for marketing received by FDA under section 507 before the date of the enactment of the Modernization Act (*e.g.*, as evidenced by the Sandimmune approval in 1983). Therefore, section 125(d)(2) exempts Restasis from receiving Hatch-Waxman benefits. The plain language of the statute dictates this interpretation.

⁵⁵ FDA has consistently applied the interpretation set forth in the text. You do not provide any examples of purported inconsistent application of this provision.

The Agency's reading of section 125(d)(2) is also consistent with its interpretation of the publication provision in section 125(d)(3). Section 125(d)(3) reads as follows:

For purposes of this section, the Secretary is authorized to make available to the public the *established name* of each antibiotic drug that was the subject of any application for marketing received by the Secretary for Health and Human Services under section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357) before the date of enactment of this Act. (emphasis added)

The established name of the drug is not the trade name or proprietary name of the drug. *See generally* 21 CFR 299.4. The established name, for the purposes of section 125(d)(2), is the established name of the drug substance. As discussed above, the antibiotic drug substance is also the primary focus of the antibiotic drug definition. Accordingly, the established name of the drug substance cyclosporine (among others) was made available to the public as part of the *Antibiotic Exclusivity and Patent Proposed Rule*. This list contains the established names of antibiotic drug substances, not antibiotic drug products.

The Agency's focus on the drug substance contained in the antibiotic drug leads to a reasonable outcome with respect to the publication provision. That is, Congress authorized the Agency to make publicly available the established name of each drug substance that was the subject of any marketing application received by FDA under section 507 before the date of enactment of the Modernization Act. This provision would allow the Agency to publish a list of antibiotic drug substances to put sponsors that develop drug products in the future on notice as to whether they would be eligible for Hatch-Waxman benefits.

C. Your interpretation is patently inconsistent with the plain language of section 125(d)(2).

You assert in your petition that FDA should interpret the term "antibiotic drug" to mean "antibiotic drug," as defined in section 201(jj) of the Act (petition at 16). That is, you assert the term "antibiotic drug" should refer to the drug product.⁵⁶ *Id.* You state that FDA chose not to look to the plain language of the statute. *Id.*

First, FDA's interpretation of section 125(d)(2) is consistent with the plain language of the statute. That is, the Agency, as mentioned above, uses the definition of antibiotic drug in section 201(jj) of the Act, together with the plain language of section 125(d)(2), in concluding that the relevant focus is the antibiotic drug substance contained in the drug product.

To read section 125(d)(2) as referring to the *drug product*, as you suggest, would be contrary to the plain language of section 125(d)(2). As stated above, section 125(d)(2)

⁵⁶ Under section 21 CFR 314.3, "[d]rug 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."

applies when "the drug that is the subject of the application *contains* an antibiotic drug and the antibiotic drug was the subject of any application" received by FDA under section 507 of the Act before the enactment of the Modernization Act. Under your reading, the statute (as applied to Restasis) would effectively mean that Hatch-Waxman benefits would not apply when — Restasis *contains* cyclosporine ophthalmic emulsion and cyclosporine ophthalmic emulsion was the subject of any application received by FDA under section 507 of the Act before the enactment of the Modernization Act.

"Restasis *contains* cyclosporine ophthalmic emulsion" does not make sense on its face. That is, drug products do not contain drug products; rather, drug products contain drug substances. The Supreme Court has stated that it is a court's duty "to give effect, if possible, to every clause and word of a statute." *See Duncan v. Walker*, 533 U.S. 167, 174 (2001) (internal citations omitted); *see also Dean Foods Co., v. Wisconsin Dept. Of Agriculture, Trade and Consumer Protection*, 478 F. Supp. 224 (W.D. Wis. 1979) (stating "rules of statutory construction require me to avoid, if possible, the conclusion that the phrases are redundant").

Moreover, if Congress intended to make each new drug *product* eligible for Hatch-Waxman benefits, Congress could have stated as much in a more clear and simple way.⁵⁷ Congress could have stated that section 125(d)(2) applies when the drug that is the subject of the application *is* an antibiotic drug and the antibiotic drug was the subject of any application received by FDA under section 507 of the Act before the enactment of the Modernization Act.

D. Legislative history supports the Agency's interpretation, which strikes the proper balance between innovation and the availability of generic drugs.

The Agency's interpretation of section 125(d)(2) is supported by the legislative history. Congress' statements clearly support the Agency's interpretation that Hatch-Waxman benefits do not attach to an antibiotic drug where the drug substance contained in the antibiotic drug was a drug substance contained in an antibiotic drug that was the subject of an application for marketing received by FDA under section 507 before November 21, 1997. That is, Congress was focused on providing incentives for *new antibiotic drug substances*. Congress' intent was to strike the proper balance between providing incentives for truly innovative antibiotic drugs and ensuring the availability of generic antibiotic drugs — a goal consistent with the regulatory history. (*See* regulatory history section in Part I.)

This intent is evidenced by Congressman Deutsch's statements made in the House of Representatives. Before entering the Conference Report stage, Congressman Deutsch stated, "[t]his Congress has made very significant strides in promoting the use of generic

⁵⁷ It is not clear from your petition whether you are asserting that antibiotic drug refers to "cyclosporine ophthalmic emulsion" or the exact drug product, in this case, "Restasis." To the extent you are asserting the latter, Congress could have simply stated that any antibiotic drug applications received before the enactment of the Modernization Act would not be eligible for Hatch-Waxman benefits. However, Congress did not do so.

drugs in the United States of America as a cost containment and a health issue for all Americans. In an attempt to both balance the need for innovation in terms of resistant strain antibiotics, while at the same time balancing the need for generics and the purpose for generics that this Congress has stated very strongly on many occasions over the last years. I think it is *important that any additional exclusivity* that we grant in terms of antibiotics, which would be the first time that there would be exclusivity for antibiotic drugs, that it *be limited in scope very narrowly to the challenge we face in terms of resistant strains.*" See Cong. Rec. H8479 (October 7, 1997).

The Senate made similar statements on the Conference Report on S. 830 (which contains the exact language with respect to section 125(d)(2) that was subsequently signed into law). In considering the Conference Report on S. 830, Senator Kennedy stated that the legislation "provides incentives for research on pediatric applications of approved drugs and *for development of new antibiotics to deal with emerging, drug-resistant strains of disease.*" See Cong. Rec. S12243 (November 9, 1997) (emphasis added); *see also Id.* at 12251. Moreover, in commenting on the importance of the legislation, Senator Mikulski stated that the legislation "creates an FDA that rewards *significant science* while protecting the public health." *Id.* at 12245 (emphasis added).

These statements clearly support the Agency's position that Hatch-Waxman benefits do *not* attach to an antibiotic drug when the drug substance contained in the antibiotic drug was a drug substance contained in an antibiotic drug that was the subject of an application for marketing received by FDA under section 507 before November 21, 1997. Congress' intent, as demonstrated by these statement, was to provide incentives for significant science that would result in the development of *new antibiotic drug substances* to protect against new drug-resistant strains of diseases.

Congress' intent, as set forth above, is at odds with your interpretation. If the Agency were to interpret the statute as you suggest, a change in dosage form, for example, could result in eligibility for Hatch-Waxman benefits. A change in dosage form of an antibiotic drug subject to section 125(d)(2), however, would not be a development of a new antibiotic to deal with emerging, drug-resistant strains of disease. As stated above, the scope of exclusivity should be interpreted narrowly to strike the proper balance between innovation and the availability of generic drugs.

The Agency's interpretation strikes this balance and gives effect to both the intent of the Hatch-Waxman Amendments and the Modernization Act. During the 1997 hearings on the Modernization Act, Congress noted, "[i]n enacting the Hatch-Waxman Amendments, Congress recognized the fundamental difference between antibiotic drugs and non-antibiotic drugs."⁵⁸ (refer to Part I of this response for a discussion of regulatory history). Congress specifically stated, "[a] complete repeal of Section 507 – and the resulting application of all existing requirements for generic non-antibiotic drugs under section 505 to generic antibiotics — would upset the delicate balance of the Hatch-Waxman Act created in 1984 and would represent an unintended windfall for brand name antibiotic

⁵⁸ See Hearings of the Committee on Labor and Human Resources United States Senate, 105th Cong. 1 Sess. 228 March 19 and April 11, 1997.

manufacturers, at the expense of generic antibiotic manufacturers, consumers, and taxpayers.⁵⁹ Thus, Congress, in enacting the Modernization Act, clearly intended to preserve the balance of the Hatch-Waxman Amendments.

Likewise, the Agency's interpretation maintains the balance created by the Hatch-Waxman Amendments in 1984, and does not afford sponsors of certain non-generic antibiotic drugs an "unintended windfall," at the expense of generic antibiotic drug sponsors and the public. Moreover, it maintains the incentive of all the Hatch-Waxman benefits for innovative antibiotic drugs.⁶⁰

F. Your other assertions as to why Restasis should not be subject to section 125(d)(2) are not persuasive.

You assert in a footnote that any drug product containing cyclosporine that was submitted to FDA with clinical trials before the passage of the Modernization Act would have been eligible for Hatch-Waxman benefits under the holdings in *Glaxo I* and *Glaxo II*.⁶¹ (petition at 15, footnote 34). Not only is the statement incorrect, it is also irrelevant because your application was submitted after the enactment of the Modernization Act. Your application is subject to section 125(d)(2).

You assert in your petition that the Agency's interpretation "comes perilously close to a legislative taking." (petition at p. 15). This argument is unavailing. Antibiotic drugs were not eligible for exclusivity before the enactment of the Modernization Act, and antibiotic drugs that fall under section 125(d)(2) are not eligible for exclusivity now. Congress' refusal to extend the benefits of exclusivity and patent listing rights to a class of drug products cannot be viewed as being akin to a taking.

You also make other assertions in support of your position in your petition for stay of action. Those assertions will be addressed below in the section addressing your petition for stay of action.

VII. ALLERGAN'S CLAIM THAT IT DETRIMENTALLY RELIED ON FDA'S "REPRESENTATIONS" AND THEREFORE SHOULD BE ENTITLED TO EXCLUSIVITY AND PATENT LISTING UNDER SECTION 505 OF THE ACT IS REJECTED.

In your petition, you assert that you detrimentally relied on FDA's "representations" that "CSA [cyclosporine] and Restasis are not [a]ntibiotic [d]rugs" (petition at 11). Your claim, however, is not persuasive.

⁵⁹ *Id.*

⁶⁰ Moreover, the Supreme Court noted that an agency's interpretation is entitled to deference where it represents a reasonable accommodation of manifestly competing interests, particularly where, as here, the regulatory scheme is technical and complex. *See Chevron*, 467 U.S. 837, 864 (1984).

⁶¹ *See Glaxo v. Heckler*, 623 F. Supp. 69 (E.D.N.C. 1985); *Glaxo v. Heckler*, 640 F. Supp. 933 (E.D.N.C. 1986).

A. It appears that the issues of whether Restasis was an antibiotic drug and whether cyclosporine was an antibiotic drug substance were not discussed before you submitted your NDA.

You argue that Allergan "[d]etrimentally [r]elied on FDA's [r]epresentations that CSA [cyclosporine] and Restasis® are not [a]ntibiotic [d]rugs" (petition at 11-14). You state that Allergan had been in discussions with FDA on the development of Restasis for over 10 years, and FDA never indicated, until after approval, that Restasis should be regulated as an antibiotic drug ineligible for Hatch-Waxman benefits (petition at 11).

Before Allergan submitted the NDA for Restasis in 1999, the status of Restasis as an antibiotic drug was apparently not discussed. You do not allege, and review of our available records does not indicate, that you raised the classification issue of Restasis as an antibiotic drug with the Division. The fact that Allergan apparently never asked the Division whether Restasis was an antibiotic drug under the Act, and the fact that the Division never raised the issue, cannot be construed as an answer to the question. The Division's primary focus, quite properly, was on the safety and effectiveness of Restasis.

Moreover, the classification of Restasis as an antibiotic drug should not have come as a surprise to Allergan. Allergan cannot claim that it did not know that all products containing cyclosporine have been regulated as antibiotic drugs.

First, Sandoz's original NDAs for oral liquid and injectable cyclosporine drug products (NDAs 50-574 and 50-573) were antibiotic drugs. Three of Sandoz's products were approved in 1990 and 1992,⁶² roughly the period in which Sandoz authorized Allergan to move forward on an ophthalmic cyclosporine drug product (petition at 12).

Second, the Agency published monographs in the Federal Register classifying cyclosporine as an "antibiotic substance." See 49 Fed. Reg. 22631(May 31, 1984). The Supreme Court has noted "[j]ust as everyone is charged with knowledge of the United States Statutes at Large, Congress has provided that the appearance of rules and regulations in the Federal Register gives legal notice of their contents." See *Federal Crop Ins. Corp. v. Merrill*, 332 U.S. 380, 384-85 (1947). Accordingly, Allergan was on notice that cyclosporine had been classified by the Agency as an antibiotic drug substance.

Third, at the time of Restasis' approval, FDA had already approved 13 other cyclosporine drug products as antibiotic drugs ineligible for Hatch-Waxman benefits.

Not surprisingly then, even your petition acknowledges, "[h]istorically, CSA [cyclosporine] and all drug products containing CSA [cyclosporine] were regulated as antibiotics under the FDCA [the Act] . . ." (petition at 1). Accordingly, the Agency does not find Allergan's plea of ignorance persuasive. If Allergan had a question as to whether

⁶² Sandimmune 25-mg cyclosporine capsules and Sandimmune 50-mg cyclosporine capsules (approved March 2, 1990); Sandimmune 100-mg cyclosporine capsules (approved November 23, 1992).

Restasis was an antibiotic drug, despite the preponderance of evidence to the contrary, Allergan should have sought an opinion from the Agency.

B. You have not shown that reclassification of Restasis as a nonantibiotic drug eligible for Hatch-Waxman benefits is justified.

You state that "under the circumstances, the proper course of action is for FDA to take corrective action by removing CSA [cyclosporine] from its proposed exclusion list and declaring Restasis® to be eligible for the Hatch-Waxman benefits under Section 505" (petition at 13). As discussed below, the circumstances do not warrant reclassification of Restasis as a nonantibiotic drug eligible for Hatch-Waxman benefits.

When Allergan contacted FDA to request an NDA number for its application, the CDER Central Document Room administratively assigned a 20 series NDA number to Restasis (NDA 21-023). Allergan submitted the Restasis NDA on February 24, 1999. The Division did not reclassify the application. On December 23, 2002, the Restasis NDA was approved. The approval letter made no reference whatsoever to eligibility for exclusivity although it referred to the NDA number as NDA 21-023. According to the petition, seven days after approval, the Division's Project Manager for Allergan's Restasis NDA notified Allergan that Allergan made a mistake on its exclusivity request and could be eligible for three-year exclusivity, not the five-year exclusivity as originally requested (petition at 12).

Shortly thereafter, CDER determined that Restasis was subject to the transition provision exception and would not be eligible for exclusivity, and that the Restasis NDA had incorrectly been assigned a 20 series NDA number, instead of a 50 series NDA number. The Division's Project Manager for Allergan's Restasis NDA contacted Allergan about three weeks later, and told Allergan that Restasis was not eligible for exclusivity. This information was memorialized in a follow-up letter to Allergan dated March 3, 2003. At no time did FDA ever list any patents or exclusivities for Restasis in the *Orange Book*.

Your "detrimental reliance" argument is based on "representations" made by FDA employees. First, the Agency is not aware of any statements before the NDA submission to the effect that Restasis would be eligible for Hatch-Waxman benefits. Your petition vaguely claims that the Agency made representations, but no details are provided (petition at 13). Even assuming *arguendo* that such statements were made, informal statements would not provide a basis upon which FDA can ignore statutory requirements as discussed below.

Second, after approval (or thereabouts), it appears that the Division's Project Manager told Allergan that Restasis could be eligible for three-year exclusivity. That communication was corrected about three weeks later. Allergan's claimed reliance on employee statements is not a basis for granting exclusivity. The Supreme Court has stated that "[t]he doctrine of equitable estoppel is not a bar to the correction by" an agency "of a mistake of law." See *Automobile Club of Michigan v. Commissioner*, 353 U.S. 180, 183-184 (1957); *Udall v. Oelschlaeger*, 389 F.2d 974, 977 (D.C. Cir. 1967),

cert. denied, 392 U.S. 909 (1968) ("the Government is never disabled from protecting the public interest by reason of the past mistakes of its agents"); *L'Enfant Plaza Properties, Inc. v. District of Columbia Redevelopment Land Agency*, 564 F.2d 515, 522 (D.C. Cir. 1977).

Third, in any event, any "representations" would have been informal communications that represented the best judgment of the employees at that time. These statements do not necessarily represent the formal position of FDA, and do not bind or otherwise obligate or commit the Agency to the views expressed. *See* 21 CFR 10.85(k). Further, "[a]ction on meetings and correspondence does not constitute final administrative action subject to judicial review under § 10.45. *See* 21 CFR 10.65(a). *See also Fisons Corp. v. Shalala*, 860 F. Supp. 859, 867-68 (D. D.C. 1994)(stating "meetings, conferences, and statements are not final agency actions and may therefore not be challenged under the APA").

C. The fact that you requested five-year exclusivity in your NDA is irrelevant because exclusivity determinations are made at the time of approval, not submission.

In your petition, you assert that Allergan filed its NDA for Restasis and requested five years of exclusivity (petition at 12). You state in your petition that had Allergan "known ahead of time that Restasis would be without any protections against generic entry, it likely would not have risked the substantial investment required to develop the product" (petition at 12).

Allergan, with FDA approval of more than 25 prescription drug products, is no stranger to the drug approval process. Allergan should be well aware that exclusivity determinations are made at the time of approval, not at the time applications are submitted. The preamble to the proposed rule titled, *Abbreviated New Drug Application Regulations; Proposed Rule*, states the following with respect to three-year exclusivity: "[w]hat studies will be essential to the approval of an application cannot be determined, in each case, by a review of protocols without knowing what drugs have been approved and what is in the published literature at the time the application is approved." *See* 54 Fed. Reg. 28872, 28901 (July 10, 1989). Accordingly, these exclusivity determinations are made at the time of approval or shortly thereafter, not at the time of submission.

Even assuming *arguendo*, that Restasis had not been subject to section 125(d)(2), Allergan mistakenly requested five-year exclusivity. Allergan now claims that it is eligible for three-year exclusivity. Although Allergan tries to impart some significance to the NDA submission request for five-year exclusivity, even Allergan implicitly acknowledges that the original request bears no significance because it has essentially abandoned that request.

D. The amount of money Allergan expended for the development of Restasis is irrelevant; and your claim of unreasonable delay is not persuasive.

You provide a declaration from Stephen Johnson that breaks down expenses associated with the development of Restasis. (see supplement to petition dated August 1, 2003). This declaration is irrelevant. As noted above, exclusivity determinations are made at the time of approval or shortly thereafter, not at the time of submission.

In addition, in your petition, you cite to a number of cases involving, among other things, "excessive delay" and "inefficiency" (petition at 13, fn. 27). You have not specified what Agency action allegedly constituted such excessive delay or inefficiency. You have not identified any representations by the Division regarding Restasis' status as a nonantibiotic drug before the submission of the NDA (other than the error regarding assignment of a 20 series NDA number). Moreover, if your assertion is intended to refer to the Project Manager's statement, the Project Manager corrected her statement within a few weeks. For all of these reasons, we reject your contention that FDA should grant Hatch-Waxman benefits to Restasis because of Allergan's alleged "detrimental reliance."

VIII. PETITION FOR STAY OF ACTION

In your petition for stay, you ask that FDA stay approval of any applications for Restasis submitted under section 505(j) of the Act and section 505(b)(2) of the Act, pending disposition of your petition.⁶³ Should FDA deny the petition in whole or part, you ask that Allergan be allowed 20 days to seek a judicial stay.

FDA will grant a stay only when *all* the provisions set forth in 21 CFR 10.35(e)(1)-(4) have been satisfied.⁶⁴ FDA has carefully considered all the arguments raised and information provided in your petition. FDA denies your petition for stay.

FDA need not address your claim that you would otherwise suffer irreparable injury because the Agency concludes that you have not demonstrated sound public policy grounds supporting the stay, nor that the potential delay resulting from the stay is outweighed by public health or other public interests. Although we need not address whether your case is not frivolous and is being pursued in good faith, we note that you make some statements in your petition for stay with respect to this element that warrant attention. We will address those statements at the end of this section.

A. Sound public policy grounds do not support the stay.

Sound public policy grounds do not support a stay. You state that the need for a stay is "particularly compelling" because of the streamlined regulations set forth in 21 CFR

⁶³ Your petition for stay also asks that we list patents for Restasis in the *Orange Book*. This request was denied in the sections above.

⁶⁴ Under 21 CFR 10.35(e)(1)-(4), FDA will grant a stay of a proceeding if *all* of the following apply:

- (1) The petitioner will otherwise suffer irreparable injury.
- (2) The petitioner's case is not frivolous and is being pursued in good faith.
- (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
- (4) The delay resulting from the stay is not [outweighed] by public health or other public interests.

320.22(b) (petition for stay at 2). Although FDA regulations provide for waiver of evidence of *in vivo* bioavailability or bioequivalence for ophthalmic *solutions* if certain criteria are met, those regulations do not apply to ophthalmic *emulsions*, like Restasis. See 21 CFR 320.22(b)(1)(i).

Furthermore, Restasis is an antibiotic drug subject to the transition provision exception, as discussed in this petition response. Restasis is not entitled to exclusivity under the law.

B. The delay resulting from the stay would be outweighed by the public health or other public interests.

The delay resulting from the stay would be outweighed by the public health or other public interest. First, no delay is warranted because the Agency has properly classified cyclosporine and Restasis as antibiotic drugs. Restasis is properly subject to the transition provision exception. This provision exempts Restasis from the patent information submission requirements in section 505 of the Act. The Agency only lists in the *Orange Book* those patents it is required to list. (see page AD-2 of the *Orange Book*, 23rd edition (2003)). As such, no patents for Restasis will be listed in the *Orange Book*. It would be misleading and not in the public interest for the Agency to list the Restasis patents. Second, the public health and public interest is served by the possibility of having a safe and effective generic cyclosporine ophthalmic emulsion drug product.

C. Two other statements in your petition for stay warrant response.

Although there are a number of assertions in your petition with which we disagree, two warrant particular attention here.

First, in your petition for stay, you state that "one court recently held that FDA cannot classify a drug product as an antibiotic if, in fact, it exhibits no antibiotic properties" (petition at 3). You cite *CollaGenex Pharmaceuticals, Inc. v. Thompson*, No. Civ. A 03-1405 (RMC) (D.D.C. 2003) for this proposition. *Id.* You represent this statement as the court's decision, although the court has not reached a decision on the merits. Rather, the court granted a preliminary injunction pending submission of the Agency's administrative record.

Second, you also refer to a letter submitted to FDA from the drafters of the transition provision exception (petition for stay at 6). However, this letter is dated May 21, 1998. Once again your reliance on this letter is misplaced. Courts have stated that "post-passage remarks of legislators, however explicit, cannot serve to change the legislative intent of Congress expressed before the Act's passage." *See Regional Rail Reorganization Act Cases*, 419 U.S. 102, 132 (1974); *see also N.C. Freed Company, Inc. v. Board of Governors of the Fed. Reserve Sys.*, 473 F.2d 1210, 1216, fn. 23 (2d Cir. 1973) (rejecting appellees reliance on letter from sponsor written one year after enactment of statute to support contrary view of legislative intent; "[t]he letter does not

constitute part of legislative history and is entitled to no weight. . . ."); *Pfizer, Inc. v. Food and Drug Administration*, 753 F. Supp. 171, 175 (D. Md. 1990).

In sum, because all criteria must be met for FDA to grant a petition for mandatory stay of action under 21 CFR 10.35(e), and you have clearly not met either of the last two criteria, you are not entitled to a mandatory stay.

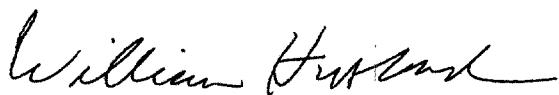
D. A discretionary stay is not appropriate.

You have not demonstrated that a discretionary stay would be in the public interest or in the interest of justice. In fact, a stay would be contrary to the public interest of having generic competition, and could work an injustice against sponsors who have submitted, or may wish to submit, ANDAs or 505(b)(2) applications that refer to Restasis.⁶⁵ Accordingly, a discretionary stay is not appropriate.

IX. CONCLUSION

Restasis and cyclosporine clearly meet the statutory definition of antibiotic drug. Restasis is subject to the transition provision exception in section 125(d)(2) of the Modernization Act. For the preceding reasons, Restasis is not entitled to any period of exclusivity, nor do any of the patent listing provisions enumerated in section 125(d)(2) apply to Restasis, and your petition is denied.

Sincerely yours,


William K. Hubbard
Associate Commissioner
for Policy and Planning

⁶⁵ This statement does not mean ANDAs have or have not been submitted. The agency will not publicly disclose the existence of an ANDA, unless it has been previously publicly disclosed or acknowledged. See 21 CFR 314.430.