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Citizen Petition

The undersigned submits this petition under 21 C.F.R. §10.25(a) and §10.30, to request the Commissioner of Food and Drugs to reclassify cyclosporine ("CSA") as a non-antibiotic drug and to remove it from the proposed list of drugs[1] that are ineligible for marketing exclusivity and patent listing pursuant to Section 125(d) of the Food and Drug Administration Modernization Act of 1997 ("FDAMA").[2] In the alternative, the undersigned requests the Commissioner to find that Restasis® is not an antibiotic drug product which falls under the ineligibility provisions of Section 125(d) and to grant Restasis® three year marketing exclusivity and patent listing rights pursuant to Section 505 of the Food Drug & Cosmetic Act ("FDCA").[3]

A. Action Requested

Petitioner Allergan Inc. is the holder of an approved new drug application ("NDA") for Restasis® Ophthalmic Emulsion, 0.05%, an ophthalmic formulation which includes the active ingredient CSA and is indicated for the treatment of "dry eye disease" in humans.[4] Historically, CSA and all drug products containing CSA were regulated as antibiotics under the FDCA despite the fact that CSA

[1] *See* Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs, 65 Fed. Reg. 3223-02, Notice 99N-3088, proposed January 4, 2000 (to be codified at 21 C.F.R. pt. 314) ("Proposed Rule").
[2] Pub. L. No. 105-115, 111 Stat. 2296 (1997)
[3] Unless otherwise indicated, all references to the FDCA will be to sections of the Act rather than to sections of the U.S.Code.

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exhibits no proven antibiotic properties and has never been approved or labeled for any antibiotic use.

Before 1997, new antibiotic drugs were regulated under Section 507 of the FDCA. In 1997, Congress repealed Section 507, moved antibiotic drug regulation under Section 505 and declared certain pre-FDAMA antibiotic drugs ineligible for various Hatch-Waxman benefits[5] including marketing exclusivity and Orange Book patent listing. In 1998, FDA developed a Guidance Document for Reviewers to explain the regulatory treatment of antibiotics following the repeal of Section 507.[6] In January 2000, FDA proposed new regulations to implement the repeal amendments ("Proposed Rule").[7] These regulations contain a list of antibiotic drugs ("exclusion list"), including CSA, that are ineligible for Hatch Waxman benefits. Under the FDA's Guidance and Proposed Rule, no NDA containing an active moiety of any drug on the proposed exclusion list is eligible for Hatch-Waxman benefits.

Allergan began development of Restasis® in September 1994, when it took over an Investigational New Drug ("IND") application then held by Sandoz. On February 24, 1999, Allergan filed its NDA 21-023 for Restasis®. Allergan received approvable letters from FDA on August 3, 1999, March 25, 2000 and October 19, 2002; on December 23, 2002, Restasis® was approved pursuant to Section 505. On March 3, 2003, FDA notified Allergan, by letter, of its Guidance Document and Proposed Rule dealing with the repeal of Section 507. In that

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[4] The approved drug product is an ophthalmic emulsion of cyclosporine 0.05%, glycerin, castor oil, polysorbate 80, carbomer 1342 and sodium hydroxide to adjust the pH.

[5] Unless otherwise indicated, the term "Hatch-Waxman benefits" as used throughout this document means the marketing exclusivity, patent listing and patent certification benefits made available to pioneer drug manufacturers under Section 505.

[6] FDA's Guidance Document states that it "does not create or confer any rights on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the applicable statute, regulations or both." *See* GUIDANCE FOR INDUSTRY AND REVIEWERS: REPEAL OF SECTION 507 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, U.S. DEP'T. OF HEALTH AND HUMAN SERV., FOOD AND DRUG ADMIN. 1 fn 1 (1998).

[7] These regulations have never been adopted. *See* fn 1.

letter, FDA stated it was reassigning the Restasis® NDA 21-023 to an antibiotic application under NDA 50-790. Although Restasis® was not approved or labeled for any antibiotic indication, FDA refused to grant three year exclusivity or to accept patent information for Orange Book listing because Restasis® contains CSA, a drug on the FDA's exclusion list. As a result, Allergan currently has no protection under Hatch-Waxman against generic versions of Restasis® which could be approved at any time.

Allergan asserts that FDA's refusal to grant Hatch-Waxman protection to Restasis® is contrary to the FDCA and FDAMA and requests, therefore, that the following actions be taken immediately:

1. Removal of CSA from the proposed antibiotic exclusion list; and

2. Listing of Restasis® in the Orange Book for three years of marketing exclusivity as originally planned by FDA along with any patents which claim Restasis® or methods of using Restasis®.[8]

B. Statement of Grounds

CSA is not an antibiotic and, in fact, functions quite differently than an antibiotic. As explained further below, CSA should be removed from the FDA's antibiotic exclusion list for three reasons: (1) CSA was never approved by FDA as an antibiotic or labeled for any antibiotic indications; (2) CSA was initially, and mistakenly, classified as an antibiotic drug due solely to the literal reading of an overbroad definition; and (3) the 1997 FDAMA repeal amendments, which preclude marketing exclusivity for certain antibiotic drugs, were never intended to apply to drugs that were approved by FDA under 505 and for non-antibiotic indications. For these reasons, the inclusion of CSA on the FDA's proposed antibiotic exclusion list is both arbitrary and capricious.

[8] Patents which claim Restasis® or methods of using the drug are U.S. Pat. Nos. 4,649,047, 4,839,342 and 5,474,979.

Public policy also favors the removal of CSA from the exclusion list. By maintaining the improper classification of CSA as an antibiotic, new uses for this drug will not be pursued. Manufacturers will invest neither the time nor the resources to discover new indications for CSA if they cannot be assured of recovering their investments under the marketing exclusivity protections of the FDCA. When Allergan first began clinical studies on new indications for CSA, it understood that such indications would be eligible for Hatch-Waxman benefits under Section 505. Nothing in the legislative history of FDAMA remotely suggested to Allergan that such benefits were intended to be repealed. Moreover, Allergan relied, to its current detriment, on representations by FDA over a 10 year period that Restasis® was not an antibiotic drug and that exclusivity would be awarded. CSA and Restasis®, therefore, must be accorded the same Hatch-Waxman benefits available to other drugs regulated under Section 505.

Finally, despite CSA being on FDA's proposed exclusion list, Restasis® cannot be considered an "antibiotic drug" within the meaning of Section 125 of FDAMA. Restasis® was not the subject of an application for marketing received by the FDA under Section 507 prior to FDAMA. Accordingly, Restasis® is eligible to receive the Hatch-Waxman benefits accorded new antibiotic drug products regulated under Section 505.

1. Regulatory Background

Traditionally, the FDA approved non-antibiotic drugs pursuant to Section 505 and antibiotic drugs pursuant to Section 507. Prior to the 1984 Hatch-Waxman amendments, generic copies of non-antibiotic drugs were required to undergo the same level of clinical testing on safety and efficacy as required for pioneer drugs. For this reason, few non-antibiotic generics were approved before 1984. In the case of antibiotics, however, FDA routinely approved generic versions under Section 507 pursuant to monographs that were established

following initial drug approval. Thus, generic copies of antibiotics were not required to undergo lengthy and expensive clinical trials in order to obtain FDA approval. It was sufficient to show that they were identical to the chemical compound described in the pioneer drug monograph.

Hatch-Waxman changed the way non-antibiotic drugs were approved. Beginning in 1984, generic manufacturers were permitted to rely on the clinical data and other information submitted by the pioneer drug manufacturer and, as long as "bioequivalency" could be shown, the generic drug would be deemed safe and effective. In essence, Hatch-Waxman minimized many of the traditional distinctions between the two types of drug approval procedures. One other procedural distinction that previously existed was the requirement for batch certification of antibiotic drugs; however, this difference was also eliminated by regulations adopted in 1982, which exempted all antibiotics from batch certification.[9]

The 1982 regulations and 1984 amendments to the FDCA resulted in antibiotic and non-antibiotic drugs being treated in a very similar fashion.[10] Nonetheless, some important differences continued to exist in terms of the benefits available to drug manufacturers. One such benefit was five-year exclusivity under Section 505. Section 507(e) contained a "transfer" provision that required any antibiotic drug exempted from batch certification to be regulated under Section 505 following initial approval under Section 507.[11] This meant that an antibiotic drug would not be eligible for any of the Section 505 Hatch-Waxman benefits until after it was initially approved and exempted from batch certification. The effect of the transfer provision was to deny pioneer antibiotic drugs the five-year exclusivity rights that Section 505 grants to all pioneer non-antibiotic drugs. Nonetheless, three-year exclusivity was available under Section

[9] *See* 21 C.F.R. §433.1(1982).
[10] *See Glaxo v. Heckler* 623 F.Supp. 69 (E.D.NC 1985) ("*Glaxo I*").
[11] *See Glaxo v. Bowen*, 640 F.Supp. 933 (E.D. NC 1986)("*Glaxo II*").

505 for subsequent drug approvals (e.g. for new indications) as long as the antibiotic NDA contained clinical data supporting safety and efficacy.[12]

Following the Hatch-Waxman amendments in 1984, an antibiotic that was initially approved under Section 507 and exempted from batch certification was regulated identically to, and under the same statutory provisions as, a non-antibiotic drug. Indeed, many antibiotics such as CSA were regulated in this manner until the 1997. In that year, Congress enacted FDAMA, which, among other things, repealed Section 507 and placed all remaining antibiotic drug regulation[13] under Section 505. Congress' reason for doing this was to make five-year exclusivity available for pioneer antibiotic drugs to stimulate new research and investment.[14] The repeal amendment, set forth in Section 125(d) of FDAMA, also contained specific exclusionary language to ensure that antibiotic drugs that already had been the subject of industry research (i.e. approved antibiotics and Section 507 applications "received" by FDA prior to FDAMA) would not benefit from this new grant of exclusivity. Subsequently, FDA proposed regulations to implement the repeal of Section 507 and compiled a list of antibiotic drugs (including CSA) which would be subject to the Section 125(d)(2) exclusionary rules. FDA also proposed that any NDA submitted after 1997 that contains an antibiotic on the exclusion list would not be eligible for Hatch-Waxman benefits.

2. The Definition of "Antibiotic Drugs" was not Meant to Include CSA

CSA has never been approved by the FDA or labeled for any antibiotic indications and should not be considered an antibiotic drug under the law. Because no manufacturer has ever sought an antibiotic indication for CSA or submitted data to FDA showing CSA to be safe and effective as an antibiotic

[12] *Id. See* FDCA §§ 505(c)(3)(D) and 505(j)(3)(D).
[13] Pioneer antibiotic approvals and antibiotics not exempt from batch certification were then still regulated under Section 507.

agent, it should never have been regulated under Section 507. This historical oversight by FDA is an insufficient basis for denying Hatch-Waxman benefits for new drug products that provide new uses of CSA.

CSA was first approved by FDA in 1983 and regulated under Section 507 pursuant to the following antibiotic drug definition[15]:

> "antibiotic drug" means 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).

What is striking about this definition is its overbreadth. Applied literally, it encompasses products that are neither approved nor marketed for antibiotic indications. Indeed, it includes any drug product that contains even the smallest amount of <u>any</u> chemical substance produced by <u>any</u> microorganism as long as the substance has the capacity to inhibit or destroy any other microorganisms in a dilute solution. It does not matter how therapeutically ineffective such drug substance might be as an antibiotic nor how miniscule the drug's capacity for inhibiting other microorganisms. Moreover, the definition provides no guidance on what is meant by the term "inhibit" or what constitutes a "dilute solution." As a result, 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 when it adopted Section 507. [16]

Common sense dictates that any drug approved and regulated by FDA as an antibiotic must include the following essential elements: the drug must exhibit

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[14] House Rep. No. 105-310, 105th Cong., 1st Sess. 77(1997).
[15] Section 507 contains essentially the same definition now found in Section 201(jj)
[16] Congressional intent for defining antibiotics under Section 507 was to encourage the development of antibiotic drugs by standardizing the approval process for this important class of chemical entities. At the time, Congress was unaware that the ultimate definition would prove to be overbroad and would include new technologies including drugs produced using recombinant DNA technologies.

at least some therapeutic properties of an antibiotic; it must contain at least one approved antibiotic indication; and it must be labeled and marketed as an antibiotic. Absent such essential elements, FDA would be forced to apply the definition to a host of drugs that are produced by micro-organisms but which are not thought to be, nor are regulated as, antibiotics.[17] For example, under a literal reading of the statute any drug produced by recombinant DNA technology would have to be tested for its capacity to inhibit micro-organism growth in a dilute solution and, if found to satisfy this requirement, would have to be approved as an antibiotic regardless of the indications being sought.[18] Many drugs approved as biologics would also have to be evaluated in this same fashion. Yet many such drugs are routinely approved by FDA under the non-antibiotic drug provisions of Section 505 and under the biologic provisions of the Public Health Service Act.[19] What this indicates is FDA uses additional screening criteria when determining whether a particular drug should be classified as an antibiotic and made to undergo the antibiotic approval process.

One obvious criterion is whether the drug manufacturer is seeking to have its drug labeled for antibiotic indications. In the examples cited (e.g. recombinant DNA and biologics), the drugs were obviously not seeking antibiotic labeling and thus, were approved under non-antibiotic provisions in the law. Applying the same criterion to CSA, once it was clear that CSA was not being approved for any antibiotic indications it should never have been classified as an antibiotic and regulated under Section 507.

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[17] For an interesting list of possible drugs that may qualify see the pre-FDAMA drugs in the list of Approved Biotechnology Drugs 1999 *available at* http://www.bio.org/aboutbio/guide2.html (last visited May 28, 2003).

[18] By definition, a drug produced by recombinant DNA technology is produced by a microorganism, and thus should have been tested for inhibitory effect. Examples of such drugs are non-antibiotic approved drugs such as insulin, human growth hormone, other hormones, alglucerase, cladribine etc, and a host of biologics approved chemical entities including interferons, interleukins, erythropoeitin, streptokinase, etc.

[19] Public Health Service Act, Pub. L. No. 107-377, 58 Stat. 682 (codified as amended at 42 U.S.C. §§ 201-300hh-11 (2002)).

FDA cannot be allowed to arbitrarily pick and choose how it wants to classify drugs in isolation from the rest of the FDCA. To ignore the FDCA's overarching regulatory scheme of safety and effectiveness, in deference to an overbroad definition that is inconsistently applied, is to regulate in an arbitrary and capricious manner in violation of Constitutional requirements.[20] FDA must apply its drug classification regulations consistent with how drugs are approved and labeled. In such event, neither CSA nor Restasis® should be classified as an antibiotic drug under the FDCA.

3. CSA was Initially Regulated Under Section 507 by Mistake.

In 1957, a program was set up at Sandoz Ltd. whereby employees on business trips and vacations would gather soil samples as part of the search for new antibiotics from fungal metabolites.[21] In 1970, the fungus *Tolypocladium inflatum*[22] was isolated from two soil samples. Sandoz then set up a rigorous screening program that identified unknown metabolites from samples of fungi and tested them through a series of 50 pharmacological tests. Based on such testing, CSA was shown to have very weak inhibition of growth for a very select group of fungi and was virtually abandoned by Sandoz because of its lack of antibiotic activity. Eventually, however, CSA was revived when it was also

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[20] A statute should not be read in isolation. *FDA v. Brown & Williamson*, 120 S.Ct.1291 (2000). Rather, the words of the statute must be read in their context with a view to their place in the overall statutory scheme. *Id* at 1301 (quoting *Davis v. Michigan Dept of Treasury*, 489 U.S. 803 (1989)). The statutory definition of antibiotic drug, if read in isolation from the rest of the FDCA or applied out of context with the rest of the statutory language, can result in a regulatory taking. *See Kolender v. Lawson*, 461 U.S. 352, 357 (1983) (holding that to be Constitutional a statute must not lend itself to arbitrary enforcement).

[21] The historical information in this section is all taken from an excellent discussion of the history of the development of cyclosporin that is available online as Harriet Upton, *Origin of Drugs in Current Use: The Cyclosporin Story, available at* http://www.oldkingdom.org/UG_projects/Harriet_Upton/Harriet_Upton.htm (last visited 03/27/2003). *See also* Karl Heusler and Alfred Pletscher, *The Controversial Early History of Cyclosporine,* 131 SWISS MED. WKLY 299-302 (2001); J.F. Borel and Z.L. Kis, *The Discovery and Development of Cyclosporine (Sandimmune®),* 23 TRANSPLANT PROC. 1867-74 (1991); and H.F. Stähelin, *The History of Cyclosporine A (Sandimmune®) Revisited· Another Point of View,* 52 EXPERIENTIA 5-13 (1996).

[22] Cyclosporine is now taken from other fungal sources, but the molecule is the same.

found to have strong immunosuppressive activity. After much debate and further study, CSA was approved in November 1983 for the prevention of transplant rejection.[23]

CSA has always functioned therapeutically as an immunomodulator. It suppresses the growth of T-cells by blocking a specific chemical pathway.[24] More specifically, it has been shown to block the signal in lymphocytes to produce IL-1, IL-2, IL-3, IL-4 and γ-interferon, which results in the suppression of T-cell proliferation. Hence, CSA is not an antibiotic. Antibiotics act to kill or inhibit the growth of bacteria or other organisms in a human host. When dealing with infections, the last thing one would want to do is suppress the immune system. Understood in this manner, CSA operates essentially as an anti-antibiotic. Given its immunosuppressive properties, a doctor would never prescribe CSA to combat infection. Moreover, it is unclear that such a treatment would be worthwhile even for a fungal infection involving one of the few fungi that CSA was shown to inhibit *in vitro*. In view of other available effective antifungal therapies, it would make little clinical sense to suppress the very system that is in need of bolstering; accordingly, CSA cannot be considered an antibiotic within any accepted scientific meaning of such term.

CSA was originally submitted to FDA and accepted as an antibiotic because it met the overbroad definition in Section 507 based on the early studies performed showing the weak inhibition of certain fungi. As noted, however, CSA was never submitted to FDA for any antibiotic indications of use. And because there was little difference in the approval processes for antibiotic and non-antibiotic drugs when CSA was first approved, no advantage was to be gained

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[23] Since that time, CSA has also been approved for use against severe psoriasis and rheumatoid arthritis.
[24] Cyclosporine specifically blocks activation of the phosphorylase enzyme calcineurin, which affects the immune response cascade. *See* Alexander M. Marsland and Christopher E.M. Griffiths, *The Macrolide Immunosuppressants in Dermatology: Mechanisms of Action,* 12 EURO. J DERM. 6 (November-December 2002).

from one classification or another.[25] As a result, CSA was inadvertently classified and accepted as an antibiotic in 1983.

Since CSA's initial approval, three additional indications have been approved for CSA in different forms. These indications are severe psoriasis and rheumatoid arthritis, both approved in 1997, and for dry eye (Restasis®) approved in 2002. None of these indications are antibiotic in nature and each benefit from the immunomodulatory effects of CSA. Immunomodulators work exactly the opposite of antibiotics in that they have immunosuppressive effects and not antimicrobial effects found in antibiotics. Given the regulatory history of CSA including all of the approved indications for use, it is clear that CSA should be classified as a non-antibiotic drug. In this regard, the final arbiter of any drug's classification must be the approved indications for use or such classification scheme becomes meaningless and arbitrary. For FDA to continue denying CSA its proper classification as a non-antibiotic drug will be to compound a 20-year-old mistake; accordingly, FDA must remove CSA from the proposed exclusion list.

4. Allergan has Detrimentally Relied on FDA's Representations that CSA and Restasis® are not Antibiotic Drugs.

For over 10 years Allergan had been in discussions with FDA on the development of its CSA-containing drug, Restasis®, and not once, prior to NDA approval, did FDA ever indicate to Allergan that Restasis® should be regulated as an antibiotic. It was only after Allergan had expended more than $5 million on research, development and clinical trials that FDA suddenly and unexpectedly declared, after approval, that Restasis® was an antibiotic drug ineligible for Hatch-Waxman benefits. Allergan submits that it is patently unfair for FDA to reclassify Restasis® at such a late date, so as to deny it the important Hatch-

[25] *See Glaxo I*, fn 10 *supra*.

Waxman benefits to which Allergan assumed it was entitled and which are accorded to other drugs similarly approved under Section 505. 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.

Allergan first began discussing CSA drug development with the FDA on June 17, 1992, after being authorized by Sandoz, the holder of the original CSA NDA. Allergan held a pre-IND meeting with FDA on July 11, 1994, during which FDA requested Allergan to investigate any changes in conjunctival flora -- before and after treatment -- to determine whether CSA's immunosuppressive properties might cause infections. There were no discussions whatsoever as to CSA having any antimicrobial effects. On September 29, 1994, Sandoz transferred its IND rights to Allergan.

On February 24, 1999, Allergan filed its NDA (No. 21-023) for Restasis® requesting five years of exclusivity and received approvable letters from FDA on August 3, 1999, March 25, 2000 and October 19, 2000. On December 23, 2002, Restasis® was approved. Seven days later, FDA's Project Manager (HFD-550) contacted Allergan to say that Allergan had made a mistake on its exclusivity request and would be eligible for three years of exclusivity rather than the five years originally requested. Allergan, at this time, fully expected that FDA was carrying out its administrative function typical of approved 505 applications and would file all submitted patents in the Orange Book and list the three years of exclusivity. On January 21, 2003, Allergan was again contacted by the Project Manager and this time was told that it would be receiving no exclusivity based on FDA's "proposed" regulations that classified CSA, and all drugs containing CSA, as antibiotics. On March 3, 2003, FDA reclassified Restasis® as an antibiotic and issued a new NDA number 50-790.

Based on this record, there can be little doubt that Allergan was mislead by FDA from the beginning as to the proper classification of Restasis®. The drug had been developed and submitted under the non-antibiotic provisions of Section 505[26] and both Allergan and FDA discussed the Hatch-Waxman benefits that would be available upon approval. Allergan relied in good faith and to its detriment on the various statements, instructions and other representations made by FDA that Restasis® was not being treated as an antibiotic drug. Had there been any cause to doubt, during the10 years of FDA oversight, that such classification might be incorrect Allergan would have immediately addressed and resolved the matter in order to protect its substantial investment in this new drug.

As matters now stand, generic versions of Restasis® can be inexpensively developed and routinely approved by FDA, at any time, putting Allergan's entire $5 million plus invested in Restasis® at risk. This is grossly unfair to Allergan and its stockholders who are forced to bear the cost of FDA's oversight. Under the circumstances, the proper course of action is for FDA to take corrective action by removing CSA from its proposed exclusion list and declaring Restasis® to be eligible for the Hatch-Waxman benefits under Section 505.[27] FDA has the

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[26] Allergan's NDA, for example did not contain any microbiology data that is required for an antibiotic drug approval. *See* 21 C.F.R.§314.50(d)(4).

[27] Government agencies, like private corporations, have an obligation to conduct their affairs in a reasonably efficient manner. *See Potomac Elec. Power Co. v. ICC*, 702 F.2d 1026, 1034 (D.C.Cir.1983) (warning that "excessive delay saps the public confidence in an agency's ability to discharge its responsibilities"). An entity that chooses to indulge inefficiencies cannot expect to be granted special dispensations. If "[t]he mills of the bureaucrats grind slow," *United States v. Meyer*, 808 F.2d 912, 913 (1st Cir.1987), then the agency, having called the tune, must pay the piper. *See, e.g., United States v. Baus*, 834 F.2d 1114, 1123 (1st Cir.1987) (holding that the government "should not be allowed by words and inaction to lull a party into a false sense of security and then by an abrupt volte-face strip the party of its defenses"); *Cutler v. Hayes*, 818 F.2d 879, 896 (D.C.Cir.1987) (explaining that, when an administrative agency loiters, "the consequences of dilatoriness may be great"). *Texaco Puerto Rico Inc. v Dep't. of Consumer Affairs*, 60 F.3d 867, 879 (1995).

requisite authority under FDCA and FDAMA to take such action and, moreover, the equities in this matter compel that such corrective actions be taken.[28]

5. Restasis® is not an "Antibiotic Drug" within the meaning of Section 125 (d)(2) of FDAMA.

When Congress passed FDAMA in 1997, it repealed Section 507 specifically to make pioneer antibiotic drugs eligible for the Hatch-Waxman benefits.[29] Congress believed that five-year exclusivity was needed to increase industry "research toward the development of new antibiotics." Congress made clear that it wanted to stimulate new research, rather than to reward old research,[30] and thus, it was careful to limit the grant of new rights "to those products that are New Chemical Entities and to products for which a New Drug Application has not been submitted to FDA.[31]

Section 125(d) of FDAMA carried out this regulatory scheme. Subsection (d)(1) set forth the general rule that any antibiotic drug previously approved by FDA under Section 507 would, henceforth, be regarded as having been approved under Section 505 [32]; and subsection (d)(2) provided an "Exception" to the Hatch-Waxman benefits for any antibiotic drugs which were the subject of applications

[28] The FDAMA repeal amendment was directed to antibiotic drugs that were properly regulated under Section 507. A drug that was improperly or mistakenly regulated under Section 507 was never intended by Congress to be denied the Hatch-Waxman benefits under Section 505.

[29] In *Glaxo I*, a drug manufacturer argued that the transfer provision, in fact, conferred Section 505 marketing exclusivity on the new antibiotic drug as of the FDA application filing date thereby qualifying such drug for five years of marketing exclusivity. The district court disagreed with this reading of the statute, and held that "[o]nly following approval is an antibiotic drug then exempted and treated as a nonantibiotic by virtue of [the] transfer provision.

[30] Applications received by the FDA prior to FDAMA were, by definition, the subject of antibiotic research and development activities that had already been completed. Five-year exclusivity was not needed, therefore, to incentivize the pursuit of these applications.

[31] *See supra* fn 13 and accompanying text.

[32] By treating pre-FDAMA approvals as having been made under Section 505, Congress eliminated the possibility of the any approved drug, or active ingredient of any approved drug, becoming eligible for five-year exclusivity.

that had been filed under Section 507 and received by FDA prior to FDAMA.[33] Together these provisions brought all new antibiotic drug applications within the scope of Section 505 but without creating new rights in existing drug products.

In the January 2000 Proposed Rule implementing the Section 507 repeal, FDA interpreted Section 125(d)(2) in an unusual manner. It interpreted the amendment as actually denying Hatch-Waxman benefits for any antibiotic drug product – old or new – if the product's active moiety was previously the subject of an application received under Section 507. Under such interpretation, any antibiotic product regulated under Section 505 prior to FDAMA would no longer be eligible for Hatch-Waxman benefits pursuant to the Section 507(e) transfer provision.[34] Moreover, any Hatch-Waxman benefits, which were in existence at the time of FDAMA passage, would now be nullified. Such a reading of the repeal amendments, which comes perilously close to a legislative taking, finds no support anywhere in the public record. Indeed, the rare bit of legislative history that deals with Section 507 repeal comes from the House Report, which states that new grant of exclusivity was intended to *increase* drug research on new "products" – not just active moieties. Had Congress intended Section 125(d)(2) to limit Hatch-Waxman benefits to new active moieties rather than new antibiotic products, it presumably would have spoken clearly as it had in the 1984 amendments.[35]

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[33] Section 125(d)(2) provides that various Hatch-Waxman rights 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 FDA] under Section 507 ...before the date of [FDAMA]." (emphasis added).

[34] CSA was initially approved in 1983 and exempted from batch certification in the 1984 pursuant to an FDA monograph. Hence, any CSA-based drug product submitted to FDA with clinical trials, prior to the passage of FDAMA, would have been eligible for three-year marketing exclusivity and patent listing rights in the Orange Book under Section 505 and the holdings in *Glaxo I and II.*

[35] It must be presumed that Congress knew the difference between drugs and active moieties when it drafted Section 125. The original exclusivity provisions in the 1984 Hatch-Waxman Act referred to a drug's "active ingredients", a term that FDA found later to be synonymous with active moiety. Congress chose not to use the same term in its FDAMA amendments and FDA is required to give significance to such fact.

Instead, Congress specifically elected to use the term "antibiotic drug,"[36] which is defined broadly in the FDCA as "any drug containing any quantity of any chemical substance ...or any derivative thereof."[37] To determine what Congress meant by such term in the context of Section 125(d)(2), FDA chose not to look to the plain language in the statute but to the FDA's history of applying Hatch-Waxman exclusivity. It found that it had consistently looked at a drug's active moiety[38] in determining whether exclusivity protections should apply and concluded from this that the same test should be used for limiting the Hatch-Waxman benefits under the FDAMA repeal amendments.[39] But such analysis is flawed as it ignores the fact that in 1984, when marketing exclusivity was first introduced, Congress specifically directed the FDA to look to a drug product's active ingredient -- a term which FDA considers synonymous with active moiety -- when determining such rights. By comparison, the 1997 amendments do not contain a single reference to an antibiotic drug's active ingredient, a term with which Congress was long familiar. If anything then, FDA should have construed the term "antibiotic drug" to mean antibiotic drug product rather than antibiotic active moiety. Such interpretation would give effect to Congress' intent of encouraging research and development of new antibiotic products and would preserve the Hatch-Waxman benefits that were available, prior to FDAMA, to new antibiotic drug products like Restasis®.

Insofar as Restasis® is a drug product that was not the subject of any Section 507 marketing application "received" by FDA prior to FDAMA and was never developed as an antibiotic drug nor shown to have any antibiotic properties during its many years of development, it does not come within the exclusionary

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[36] *See supra* fn. 15 and accompanying text.
[37] 21 U.S.C. § 321(jj) (200) (emphasis added).
[38] An active moiety is defined narrowly by FDA as "the molecule or ion responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.108 (a) (2002).
[39] *See* Proposed Rule at 3625.

language of Section 125(d)(2). Restasis®, therefore, is eligible for Hatch-Waxman benefits based on its Section 505 approval.

Conclusion

CSA should be removed from the FDA's exclusion list for the reasons stated. In any event, Restasis® is neither approved nor labeled for any antibiotic indications and, therefore, cannot be considered an antibiotic drug under the law. Restasis® must be given the full Hatch-Waxman benefits provided under Section 505. To deny such benefits represents a gross misreading of the 1997 FDAMA repeal amendments and will stifle industry research on new drug products in contravention of Congressional intent, public policy and the FDCA.

C. Environmental Impact

This petition is categorically excluded from the environmental impact statement requirement under 21 C.F.R. §25.31.

D. Economic Impact

The Commissioner has not requested any economic impact information at this time.

E. Certification

The undersigned certifies, that to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

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