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April 20, 2007

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

Re: Patent Listing and Market Exclusivity for Combination Drugs When One Component is a pre-1997 Antibiotic Ingredient

Dear Sir or Madam:

Please file the enclosed copies of cover letters in the file that will be created for the above referenced petition, which we are filing today. Thank you.

Respectfully submitted,

Donald O. Beers

Enclosure

2007P-0158

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April 20, 2007

Andrew C. von Eschenbach, M.D.,
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20957

Re: Petition requesting change in FDA policy that discourages innovation

Dear Commissioner von Eschenbach:

Enclosed is a petition that we are filing today on behalf of Medicis. We are sending this copy directly to you because we believe the issue the petition raises is an important one of public policy, to which we invite your personal attention.

On behalf of Medicis, we are asking FDA to change a policy that affirmatively--and for no rational reason--discourages innovation with respect to combination products that include antibiotics, even though some such products may be useful in combating the significant health problem of antibiotic resistance.

We recognize that policy issues raised by citizen petitions are generally raised to your level, if at all, only when staff have drafted a response, usually a denial. Because of the importance of this issue, however, we hope that you will address it now. We are also sending copies to Dr. Woodcock and to Sheldon Bradshaw.

Sincerely,

Donald O. Beers

cc. Sheldon Bradshaw, Esq.
Dockets Management Branch

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April 20, 2007

Janet Woodcock, M.D.
Deputy Commissioner for Operations
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20957

Re: Petition requesting change in FDA policy that discourages innovation

Dear Dr. Woodcock:

Enclosed is a petition that we are filing today on behalf of Medicis. We are sending this copy directly to you because we believe the issue the petition raises is an important one of public policy, to which we invite your personal attention.

On behalf of Medicis, we are asking FDA to change a policy that affirmatively--and for no rational reason--discourages innovation with respect to combination products that include antibiotics, even though some such products may be useful in combating the significant health problem of antibiotic resistance.

We recognize that policy issues raised by citizen petitions are generally raised to your level, if at all, only when staff have drafted a response, usually a denial. Because of the importance of this issue, however, we hope that you will address it now. We are also sending copies to Commissioner von Eschenbach and to Sheldon Bradshaw.

Sincerely,

Donald O. Beers

cc. Sheldon Bradshaw, Esq.
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April 20, 2007

Sheldon T. Bradshaw, Esq.
Chief Counsel
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20957

Re: Petition requesting change in FDA policy that discourages innovation

Dear Sheldon:

Enclosed is a petition that we are filing today on behalf of Medicis. We are sending copies of this petition directly to Commissioner von Eschenbach and to Dr. Woodcock because we believe the issue the petition raises is an important one of public policy, to which we invite their (and your) personal attention.

On behalf of Medicis, we are asking FDA to change a policy that affirmatively--and for no rational reason--discourages innovation with respect to combination products that include antibiotics, even though some such products may be useful in combating the significant health problem of antibiotic resistance. As you will see, we argue that FDA's current policy is inconsistent with the applicable law. Whether or not you agree with us on that point, we think that you will agree that principles of administrative law would permit FDA, with appropriate explanation, to change its policy, should it choose to do so. We hope you will agree that careful consideration of such a change is appropriate.

I enclose copies of our cover letters to the Commissioner and to Dr. Woodcock.

Sincerely,

Donald O. Beers

cc. Dockets Management Branch

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April 20, 2007

Division of Dockets Management
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5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Patent Listing and Market Exclusivity for Combination Drugs When One Component is a pre-1997 Antibiotic Ingredient

Dear Sir or Madam:

CITIZEN PETITION

We file this petition on behalf of Medicis. Medicis markets innovative drug products, some of which combine antibiotic and non-antibiotic ingredients. An important example of such products is Ziana™, which was approved by the Food and Drug Administration ("FDA") on November 7, 2006 for the topical treatment of acne vulgaris in patients 12 years and older.

FDA has refused to grant market exclusivity to Ziana™ and has refused to list the patents covering Ziana™ in the Orange Book. This reflects a policy that seems irrational on its face: A non–antibiotic single ingredient product is given market exclusivity and patent listing. When that ingredient is combined with an antibiotic ingredient that was included in a product for which an application for approval was submitted prior to the November 21, 1997 effective date of the Food and Drug Administration Modernization Act ("FDAMA") (a "pre–1997 antibiotic ingredient"), it suddenly is ineligible for exclusivity or patent listing. FDA's position, which has been applied to other combinations involving pre–1997 antibiotic ingredients, discourages innovation in an important category of drug products. It has not previously been the subject of a careful policy review by FDA decision-makers or legal challenge.

Medicis believes that the FDA policy in this respect is at odds with the intent and the dictates of the applicable law, as will be discussed in more detail below. Medicis first requests, however, that FDA focus on this question as a matter of public policy. FDA would have the power--if it chose to do so--to change its policy and to rationalize the incentives for drug development by beginning to recognize exclusivity and to list patents for products combining non–antibiotic active ingredients and pre–1997 antibiotic

ingredients. We believe it is important that FDA make a carefully considered policy decision whether it wishes to continue to discourage innovation in this area. We ask that FDA, consistent with the general statutory plan, change its policy and in so doing provide the necessary incentives for development of combination products that would benefit patients and that may, in at least some circumstances, be essential to combat the significant public health threat of antibiotic resistance.

A. Action Requested

1. Medicis asks that FDA reconsider, as a matter of policy, its current position that any combination drug that has, as one of its active ingredients, a pre–1997 antibiotic ingredient is denied the incentives of market exclusivity and patent listing and that FDA reverse that position.

2. Medicis asks that FDA list the patents submitted for the Medicis product Ziana™ and acknowledge the 3–year period of market exclusivity earned by that product.

B. Statement of Grounds

1. FDA should reconsider its position that any combination drug that includes, as one of its active ingredients, a pre–1997 antibiotic ingredient should be denied incentives for development.

FDA has taken the position, which it has implemented with respect to Medicis' drug Ziana™, that it will deny market exclusivity and patent listing for any drug that contains a pre-1997 active ingredient. Medicis respectfully suggests that FDA should reconsider this policy. As discussed in section 2 below, we believe that the statute in fact requires FDA to change its position. If FDA does not accept that interpretation, however, it is certainly the case that the statute does not unambiguously require the current FDA interpretation. Thus, FDA has it within its legitimate administrative power to change its policy. Such a change in policy by an administrative agency is entirely appropriate, if the change is acknowledged and the basis for change is explained. *Nat'l Cable & Telecommunications Ass'n v. Brand X Internet Services*, 545 U.S. 967, 981-82 (2005); *Rust v. Sullivan*, 500 U.S. 173, 186-87 (1991). In fact, the courts have made it clear that

an administrative agency, such as FDA, "must consider varying interpretations and the wisdom of its policy on a continuing basis." *Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 863-64 (1984).

Here, FDA has often stated its desire to encourage the development of new pharmaceutical products to treat important diseases and conditions. *See, e.g.*, Andrew C. von Eschenbach, M.D., Acting Commissioner, FDA, Address at Food and Drug Law Institute Annual Conference (Apr. 6, 2006). It is undeniable that market exclusivity and patent listing are important incentives to the development of particular types of pharmaceuticals.[1] Indeed, that was the basis behind their inclusion within the statute as passed in 1984. *See, e.g., Barr Laboratories, Inc. v. Thompson,* 238 F. Supp. 2d 236, 239 (D.D.C. 2002) ("Congress recognized that periods of market exclusivity would provide valuable incentives for drug manufacturers to engage in the research and development of new drugs."); *Glaxo Wellcome, Inc. v. Andrx Pharmaceuticals, Inc.*, 190 F. Supp. 2d 1354, 1357 (S.D. Fla. 2002) (patent listing and the resultant opportunity for 30-month stay in approval of generic product are statutory provisions "providing incentives for promoting the development of new drug products"). It was also the basis for the Congressional decision, in the 1997 FDAMA amendments, to provide these benefits to antibiotics that are the subject of applications first submitted after the FDAMA effective date. *See, e.g.*, 143 Cong. Rec. S12241, S12243 (Nov. 9, 1997) (Senator Kennedy) ("incentives . . . for development of new antibiotics to deal with emerging, drug–resistant strains of disease").

In almost all cases, those with the resources to invest in pharmaceutical development have alternative potential projects for which such investments can be made. One factor that is inevitably considered, and is usually determinative, in a decision as to whether or not to fund a potential pharmaceutical development project is whether market

[1] *See, e.g.*, FDA Consumer Magazine, "Battle of the Bugs: Fighting Antibiotic Resistance" at 3 (July-Aug. 2002): "Through such incentives as exclusivity rights, the FDA hopes to stimulate new antimicrobial drug development. Exclusivity protects a manufacturer's drug from generic drug competition for a specific length of time."

exclusivity and enforceable patent protection will be available.[2] *See* Declaration of Mitchell Wortzman, M.D., ¶8.

Thus, the question presented by this petition is, very simply: **Does FDA wish to encourage or discourage the development of potentially lifesaving drugs for which one of the ingredients is a pre–1997 antibiotic?** If the FDA does wish to encourage such development, there is no statutory bar to its doing so. As noted, FDA can change its policy on interpretation of this statutory provision if it wishes to do so. Thus, a decision to deny this petition is an affirmative decision by FDA to discourage this type of innovation.

Nor can the issue fairly be analyzed as one in which the appropriate policy decision is to deny exclusivity and patent listing in order to expedite approval of less expensive generic drugs. At the most basic level, if innovators do not create new drugs because the FDA's policy discourages innovation, there will be no opportunity for the generic drug industry to create generic versions of those new drugs. Thus, an agency decision in favor of innovation aids both the innovator industry and the generic drug industry that ultimately benefits from the development of new products for it to copy. More importantly, of course, development of these new products benefits patients, whose welfare is always FDA's primary concern.[3]

As discussed in the Declaration of Dr. Wortzman, the combination of tretinoin with the antibiotic ingredient clindamycin in Ziana™ provides an example of the benefits of combining a non–antibiotic drug with a pre–1997 antibiotic ingredient. The tretinoin, by increasing absorption of the antibiotic into the cells of bacteria, allows effective treatment with a relatively lower dose of the antibiotic. *Id.* at ¶3. This has the effect of

[2] It is no answer that such products can still obtain patent protection. Patents are not always available and, in the absence of patent listing, patents do not provide assurance that a generic product may not enter the market--and thus effectively destroy the market for the innovator--before the applicability and validity of the patent can be litigated.

[3] If combination products are not developed, patients will receive less than optimum treatment, and may in some cases be subject to the risks and vagaries of pharmacist compounding of untested combinations of existing drugs.

providing more efficacious treatment for patients with acne vulgaris. It also provides that effective treatment with less exposure to an antibiotic, and thus reduces the risks associated with the antibiotic resistance that may result from unnecessary exposure to any antibiotic ingredient.

Similar benefits may be expected with other combinations of non–antibiotic ingredients with pre–1997 antibiotic ingredients. Many such products, however, will simply never be developed in the absence of appropriate statutory incentives.[4]

Of potentially even greater importance, an FDA decision to remove incentives for development of combinations of ingredients with pre–1997 antibiotic ingredients will undercut research and development of combinations that have the potential to defeat antibiotic resistance. Researchers have found exciting evidence of the potential to defeat antibiotic resistance to old antibiotics, including penicillin, by combining an old antibiotic with an ingredient that attacks the bacteria's defense mechanism against the antibiotic. *See id.*, Exhibit C: "Genes and Antibiotic Resistance." There is, in fact, one successful antibiotic–non–antibiotic combination that shows that this strategy may be successful. The drug Augmentin™ combines the pre–1997 antibiotic ingredient amoxicillin with clavulanate potassium, which serves to inactivate an antibiotic–neutralizing enzyme that is secreted by resistant bacteria. While that drug was successful and was developed without the incentives associated with market exclusivity and patent listing, to date the innovator drug industry has not developed successor products, even as the risk of antibiotic resistance has steadily increased.

Similarly, research has shown that deadly drug–resistant bacteria infections can be treated by a combination of a new antibiotic ingredient with a pre–1997 antibiotic

[4] The developers of Ziana™, and indeed FDA's Review Division, expected these incentives to be available at the time the NDA for this product was submitted. In fact, the Ziana™ NDA was originally provided a number indicating that it would not suffer from the disabilities associated with FDA's current interpretation of the statute. Then, by letter of November 26, 2004, Jonathan K. Wilkin, M.D., Director of the Division of Dermatologic and Dental Drug Products, informed Dow Pharmaceutical Sciences, which handled the regulatory submission for this drug, that the NDA was being renumbered because the product included a pre–1997 antibiotic ingredient.

ingredient. *See id.*, Exhibit D: "UF Research Suggest Antibiotic Combination Could Beat Bacterial 'Super Bugs'." No company has to date come forward with any such combination product. Indeed, to do so would be very bad business, because of FDA's current policy. While market exclusivity and patent listing are available for the post–1997 ingredient, a combination of the new antibiotic ingredient with a pre–1997 ingredient would suddenly forfeit all protection.

As discussed below, when Congress passed the 1997 FDAMA amendments that FDA is interpreting, it was very focused on the development of products that could treat antibiotic resistance. Indeed, FDA itself has stated its concern to foster development of products that could assist in combating antibiotic resistance. *See, e.g.*, FDA, "FDA Task Force on Antimicrobial Resistance: Key Recommendations and Report" (Dec. 2000).[5] The central role of incentives in encouraging development of products that can assist in defeating antibiotic resistance counsels strongly in favor of an FDA consideration of a change in policy on this issue.

As it stands, FDA's current policy frankly makes no sense. With respect to Ziana™ (which, as noted, is a combination of tretinoin and clindamycin), a tretinoin product standing alone would be granted an opportunity for market exclusivity and would merit patent listing.[6] As soon as that ingredient is combined with a pre–1997 antibiotic, on the other hand, those incentives disappear. There is, we respectfully suggest, no rational public health argument in favor of such a policy. Nor, as is clear from the discussion in the next section, is FDA's current policy required by the statute (indeed, we assert that it conflicts with the statute).

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[5] In that report, the FDA Task Force identified the following objective: "FDA should form a high level, inter-center committee to seek outside input and consider issues related to incentives/exclusivity for optimal human and animal drug, vaccine, device (both anti-infective and diagnostic) and biologics development and appropriate use to meet antimicrobial resistance public health needs." *Id.* at 8 (emphasis added).

[6] *See*, for example, the drug Avita™, a single ingredient tretinoin product for which patents are listed in the Orange Book.

2. FDA's current policy is at odds with the statutory requirement.

The statutory provision at issue is Section 125(d)(2) of FDAMA. That provision states that the patent listing and market exclusivity protections available under Section 505 of the FFDCA

> 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 [FDA] under Section 507 of such Act (21 U.S.C. § 357) before the date of enactment of this Act.

FDA has interpreted this provision in such a way that any combination drug that contains as one of its ingredients an antibiotic ingredient that was included in a drug that was the subject of an application that was received by FDA by the November 1997 FDAMA effectiveness date is disqualified. This reading requires unwarranted verbal gymnastics with respect to the meaning of "drug," which FDA apparently interprets three different ways in the same sentence of the statute--as meaning drug product, drug ingredient, and, somehow, both at once. Thus, FDA reads the statute to say that the incentives "shall not apply to any application for marketing in which the [drug product] that is the subject of the application contains an antibiotic [drug ingredient] and the antibiotic [drug ingredient was one component of a drug product and that drug product] was the subject of any application for marketing."

With all due respect, this is not a sensible way to read a statute. Instead, Congress clearly intended the reference to "contains" to follow the normal understanding of the term: when one asks "what does a combination of tretinoin and clindamycin contain," the answer is "tretinoin and clindamycin," not "clindamycin." Any physician prescribing this drug generically would prescribe tretinoin and clindamycin. Thus, the drug product is in common parlance the active ingredient or ingredients it contains. If the word "contains" is read as intended to mean "is," the statute then parses: the statutory incentives are not available when the drug product that is the subject of the application is an antibiotic drug product and that antibiotic drug product was the subject of an application for marketing under Section 507 on the FDAMA effective date.

This is consistent with the sparse legislative history of this provision, in which the House Committee explained that market exclusivity for new antibiotic drugs was intended for "products for which a New Drug Application has not been submitted prior to the date of enactment." H.R. Rep. No. 105-310, at 77 (1997) (emphasis added). Thus, here, a combination of a non–antibiotic ingredient with a pre-1997 antibiotic ingredient should qualify if that product (as opposed to simply the antibiotic ingredient in that product) was one "for which a New Drug Application has not been submitted prior to the date of enactment."

As noted, this interpretation, by allowing combinations of new active ingredients with pre–1997 antibiotic ingredients, serves the purpose of providing incentives for the development of combination drugs that may be used to address the problem of antibiotic resistance. This was a concern of sponsors of the 1997 FDAMA provision in both the Senate and the House. *See, e.g.*, 143 Cong. Rec. S12241, S12243 (Nov. 9, 1997) (Senator Kennedy): "incentives . . . for development of new antibiotics to deal with emerging, drug–resistant strains of disease"; 143 Cong. Rec. H8455, H8479 (Oct. 7, 1997) (Rep. Deutsch): "exclusivity . . . limited in scope very narrowly to the challenge that we face in terms of resistant strains."

C. Environmental Impact

The relief requested by this petition would result in incentives for the development of new drug products containing combinations of active ingredients of which one component is a pre–1997 antibiotic ingredient. The effect of this policy change would be to delay the approval of some generic applications (thus not changing the status quo). Because the grant of the petition would not have an effect on the environment, no environmental assessment is required. 21 C.F.R. § 25.31(a).

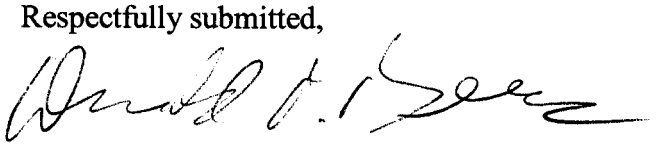
D. Economic Impact

Information on the economic impact of the action requested by this petition will be submitted if requested by the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, 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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