

LAW OFFICES
ROTHWELL, FIGG, ERNST & MANBECK

A PROFESSIONAL CORPORATION

1425 K STREET, N.W.
SUITE 800
WASHINGTON, D.C. 20005
TELEPHONE (202) 783-6040
FACSIMILE (202) 783-6031
www.rothwellfigg.com

OF COUNSEL
DON M. KERR*
JEFFREY L. IHNEN
GLENN E. KARTA
MARK I. BOWDITCH
MINAKSI BHATT
MICHAEL G. SULLIVAN
SHARON L. DAVIS

G. FRANKLIN ROTHWELL
E. ANTHONY FIGG
BARBARA G. ERNST
HARRY F. MANBECK, JR.
GEORGE R. REPPER
STEVEN LIEBERMAN
VINCENT M. DELUCA
JOSEPH A. HYNDS
ROBERT J. JONDLE, Ph.D.†
ELIZABETH A. IEFF
MARTHA CASSIDY, Ph.D.
GREGG L. JANSEN*†
NANCY T. MORRIS*†
LISA FAHIEN ULDRICH*†
ROBERT H. CAMERON
RICHARD WYDEVEN
THOMAS E. MCKIERNAN*
JASON M. SHAPIRO*
MICHAEL J. MORAN, Ph.D.*
ANNE M. STERBA
LISA N. PHILLIPS*
LEIGH M. ZANOWSKI*
C. NICHOLE GIFFORD
REGINA A. BAILEY

April 9, 2002

MIDWEST OFFICE
OMAHA, NEBRASKA

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/b

Via Hand Delivery

* NOT ADMITTED IN D.C.
† IN NE OFFICE

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

Re: Citizen Petition to Establish Appropriate Approval
Standards for Generic Clonidine Transdermal Products
Docket No.: 01P-0470/CP 1

Dear Sir or Madam:

We represent Mylan Technologies, Inc. ("Mylan"), holder of a pending application for a generic clonidine transdermal product. Pursuant to 37 C.F.R. §10.30(d), Mylan submits these comments in opposition to the above-referenced Citizen Petition to Establish Appropriate Approval Standards for Generic Clonidine Transdermal Products (the "Citizen Petition"), filed by Arnold and Porter on behalf of Boehringer Ingelheim Pharmaceuticals, Inc. ("BI") on October 10, 2001. Mylan has an interest in the outcome of the Citizen Petition because the petitioner has requested, inter alia, that the FDA not approve any new or pending ANDA for a generic clonidine transdermal product that has a controlled release mechanism or inactive ingredients that differ from BI's own clonidine transdermal product (Catapres-TTS), unless a showing is made that the proposed generic product is safe and effective, and meets new bioequivalence standards proposed by BI.

Mylan respectfully submits that the BI Citizen Petition should be denied for at least the following reasons. First, the requirement that an ANDA holder make a showing of safety and efficacy, and the imposition of different, heightened standards for bioequivalence, are contrary to

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the statute and beyond the authority delegated to the FDA by Congress. Second, BI fails to establish the necessity for imposing the heightened safety, efficacy and bioequivalence standards. Third, the heightened bioequivalence standards and methodology proposed by BI have already been rejected by the FDA, and do not provide any more or better information regarding bioequivalence than do the current standards. Fourth, the actions proposed in the Citizen Petition are against the public interest. Lastly, Mylan disagrees with BI's contention that the ANDA filing by Hercon Laboratories IN 1988 invokes the 180-day market exclusivity provided by 21 U.S.C. § 355(j)(5)(B)(iv), because, inter alia, it is Mylan's understanding that Hercon has withdraw its ANDA for its clonidine transdermal product and they are therefore no longer eligible for a grant of exclusivity.

I. THE FDA DOES NOT HAVE THE AUTHORITY TO REQUIRE SUBMISSION OF SAFETY AND EFFICACY DATA IN THE CONTEXT OF AN ANDA AS REQUESTED BY THE CITIZEN PETITION

Submission and approval of Abbreviated New Drug Applications ("ANDAs") is governed by 21 U.S.C. § 355(j). The statute sets out with specificity the required contents of an ANDA:

- 1) information showing that the conditions of use for the proposed new drug have been previously approved for a listed drug (§355(j)(2)(A)(i));
- 2) information showing that the active ingredient(s) of the proposed new drug is/are the same as those of the listed drug (§355(j)(2)(A)(ii));
- 3) information showing that the route of administration, the dosage form, and the strength of the proposed new drug are the same as those of the listed drug (§355(j)(2)(A)(iii));
- 4) information to show that the proposed new drug is bioequivalent to the listed drug (§355(j)(2)(A)(iv));
- 5) information showing that the labeling from the proposed new drug is the same as that of the listed drug (§355(j)(2)(A)(v)); and
- 6) patent certification information (§355(j)(2)(A)(vi)-(viii)).

Section 355(j)(2)(A) specifically states that "[t]he Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)"

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(emphasis added). The FDA therefore does not have the statutory authority to require of an ANDA applicant any information in addition to that specified in §355(j)(2)(A)(i)-(viii).

The Citizen Petition requests that the FDA not grant final approval of any ANDA for any generic clonidine transdermal product that differs from the BI clonidine patch, absent a showing of the safety and efficacy of the proposed generic product. Citizen Petition at 2 and 5-11. The Citizen Petition does not argue that such a showing falls within one or more of the requirements of an ANDA enumerated in § 355(j)(2)(A), but rather that this showing be made in addition to those requirements. Because this requested action imposes a requirement for information in addition to that specified in §355(j)(2)(A)(i)-(viii), it is directly contrary to the statute and outside the authority delegated to FDA by Congress. The Citizen Petition therefore must be denied for this reason alone.

II. THE CITIZEN PETITION DOES NOT DEMONSTRATE ANY NECESSITY FOR THE ADDITIONAL REQUIREMENTS

A. BI's Assertion That It Would Be Treated Unfairly If the FDA Does Not Adopt The Additional Requirements Is Baseless

BI argues that generic companies should be held to the same standards as the producers of brand-name drugs, citing the FDA's position that testing requirements for generics must be no less rigorous than those imposed on the brand-name producers. Citizen Petition at 12-13. From this basis, BI argues that generics should be required to perform the same testing to establish bioequivalence that BI was "required" to perform in order to gain approval for a change in the manufacturing site of Catapres-TTS. Citizen Petition at 13. BI carefully chooses its words in order to convey the impression that the FDA required BI to perform the type of testing described in this Citizen Petition, stating that:

when petitioner changed the manufacturing site for the BI patch, FDA required it first to complete an *in vivo* bioequivalence test. (See Exhibit H to this Petition.) BI performed a test of the type described in this petition and FDA approved the change on the basis of the test. This requirement was imposed

Citizen Petition at 13. However, based on the evidence provided by BI, the FDA did not require "a test of the type described in this petition," only that an *in vivo* bioequivalence test be done. In fact, Exhibit H of the Petition simply states that:

[s]tandard policy within the Division of Biopharmaceutics excludes everything except immediate release, orally ingested products from

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qualifying a manufacturing site change simply on the basis of in vitro dissolution. Consequently, it will be necessary for you to perform in [sic, an] in vivo bioequivalence study in support of your application.

Exhibit H. Nowhere is it stated that BI was required to perform the specific protocol that it now proposes -- indeed, no particular way of doing the testing was required, only that an in vivo study be performed instead of in vitro dissolution testing. BI appears to have adopted its heightened bioequivalence standards of its own volition, something it is free to do. The reason for the careful wording in the Citizen Petition is clear -- the FDA required only an in vivo study, it was BI who adopted the heightened standard it now proposes be imposed on applicants seeking approval for a generic clonidine patch. There is simply no issue of "fairness and evenhandedness" here, because the FDA did not treat BI any differently than it treats any other NDA, or ANDA, holder.¹

B. BI Has Not Established That The Additional Requirements Are Needed To Protect The Public Health And Safety

Throughout the Citizen Petition, BI describes dire consequences for public health and

¹Under its "Actions Requested," BI suggests that the purported differences between Elan's clonidine patch and the Catapres-TTS patch makes the Elan product inappropriate for submission or approval as an ANDA. Citizen Petition at 1. This suggestion is without merit for at least three reasons. First, BI has provided no evidence or reasoning to show why these statements make the Elan product inappropriate subject matter for an ANDA. Second, BI's reliance on statements in Elan's Paragraph IV notice letter that its product does not infringe BI's U.S. Patent No. 4,559,222 under the doctrine of equivalents is without merit. This is a doctrine of patent law that governs the scope of a patent claim, and the legal rights that it conveys to its owner, and has no relation to therapeutic equivalency. The fact that the Elan clonidine patch does not fall within the scope of the particular claims of BI's patent, as a matter of law, simply does not relate to whether or not, from a clinical point of view, the Elan patch is therapeutically equivalent to Catapres-TTS. It is the showing of bioequivalence that is required for every ANDA application that in fact establishes that the products are therapeutically equivalent, not the legal standard applied to patent claim interpretation and claim scope. Third, under the definitions provided in 21 C.F.R. § 310.3(h)(5), and in the FDA Uniform Terms for Dosage Forms, the Elan patch and the BI patch would be considered to be the same "dosage form" (i.e., a "transdermal"), and thus a NDA would not be required for this product, no matter how "different" in construction or ingredients it was from Catapres-TTS, provided that it was otherwise approvable.

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safety that could arise if its heightened standards are not adopted by the FDA.² However, every statement made by BI in this regard is completely speculative in nature and without evidentiary support. For example, the Citizen Petition states that "the *absence* of an inactive component (such as a rate-controlling membrane for a transdermal product) may compromise the safety of a product." Citizen Petition at 5 (*italics original, underline added*). BI provides no evidence that shows, or even suggests, that any generic clonidine patch being considered for approval is in fact, or likely to be, unsafe. Instead, BI offers speculation and attorney argument.³

BI also states that the silicone adhesive used by Elan "is not as bio-compatible" as the polyisobutylene used in Catapres-TTS, and that "this substitution, along with the lack of rate control ... will thus likely have a substantial impact on the degree of irritation/sensitization, and particularly the rate of drug delivery." Citizen Petition at 8 (*emphasis added*). This is pure speculation. The Citizen Petition does not cite one article, study, or expert opinion that establishes, or even suggests, that this alleged risk exists. The Citizen Petition further states that "it may be presumed that the irritation/sensitization and the rate and extent of absorption may be drastically increased in the Elan product." Citizen Petition at 8. There is no basis for making this presumption. BI offers no scientific support for its speculation. Such speculation does not outweigh clinical data proving bioequivalence. The type of data to demonstrate such differences, such as bioequivalence testing, skin sensitization/irritation studies and adhesion tests, are already required to support ANDA approval of a transdermal product, and are appropriately evaluated by the agency during the bioequivalence review process. Estradiol Petition Response, Exhibit A of the Citizen Petition, page 4.

BI asserts that the absence of a rate-limiting membrane on a clonidine transdermal patch "might result" in the "potential" for sudden spikes in drug delivery. Citizen Petition at 9. Again, this is pure speculation and BI cites to no evidence to support its argument, other than the declarations of BI and Alza employees, which are no less speculative. In fact, BI's own publications show that the potential for "sudden spikes" in drug delivery with any sort of transdermal clonidine patch is low and does not present a health risk. In Lowenthal, et al., Clin. Pharmacokinetics, 14:287-310 (Exhibit Q to the Citizen Petition) ("Lowenthal"), a publication by BI scientists, it is stated that "[l]arge changes in skin temperature for short periods of time, as

²BI submitted these very same standards to the FDA over three years ago, and the FDA declined to adopt them then. It should decline to do so now.

³The declarations provided by BI in support of the Citizen's Petition are no better supported than the attorney argument in the Citizen's Petition itself. They are simply the speculations of employees of BI and Alza (the assignee of the listed patent), regarding possible, and unsubstantiated, effects that could result from a change in patch formulation over Catapres-TTS.

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might be expected from soaking in a hot tub, will have an influence on any dermal preparation." Lowenthal at 295 (emphasis added). But even under these extreme conditions, which might lead to a doubling of the rate of clonidine delivery for 15 to 30 minutes ("equivalent to switching from a Catapres TTS-1 to a Catapres-TTS-2"), "clinical effects would be expected to be negligible." Lowenthal at 295. Thus, according to BI's own publication, any transdermal product, including Catapres-TTS, may be affected by extreme changes in skin temperature. However, not only is the likelihood of a significant change in skin permeation very low, even a sudden doubling of the delivered dose would have negligible clinical effects.

Additionally, the Catapres-TTS Package Insert and publications by BI scientists indicate that the skin is the most significant rate-limiting factor for drug absorption into the bloodstream. The Package Insert (as well as the Citizen Petition) states that with the Catapres-TTS patch, the skin is kept saturated with clonidine, meaning that delivery to the skin is at the maximum rate for skin absorption at all times, and the rate at which the drug reaches the bloodstream is dictated by how fast it leaves the skin, not how fast it enters it. Package Insert, page 1, "Release Rate Concept", Citizen Petition at 4. Publications by BI scientists also indicate that the skin is the significant rate-limiting factor. For example, the Lowenthal publication states that "[t]he diffusional barrier properties of the skin dampen the sharp spike of drug seen *in vitro* ... resulting in a smooth, gradual plasma drug concentration rise to steady-state ... and continuous steady-state plasma drug concentrations upon system replacement." Lowenthal at 295. Accordingly, the skin provides a significant rate-limiting effect on drug delivery from the Catapres-TTS patch, perhaps more significant than does the rate-limiting membrane. In view of this evidence, BI's speculation that "without a rate-controlling barrier, a patient would be expected to experience significant variations in absorption of this potent drug" (Citizen Petition at 9) is unsupported and cannot justify requiring full safety and efficacy studies for any generic clonidine patch that lacks a rate-limiting membrane.⁴

Similarly, BI predicts a litany of consequences if silicone dioxide is not used in a clonidine patch. See Citizen Petition at 10. According to BI, the silicone dioxide is included in order to prevent "cold flow" of the adhesive in layers 2 and 4 of the Catapres-TTS patch. From this starting point, BI launches into a series of "what if" scenarios, each building upon the other, to reach the conclusion that the absence of silicone dioxide in a clonidine patch presents a significant public health risk. Specifically, the BI petition speculates that "if" the adhesive were

⁴The fact that the Catapres-TTS patch is designed to provide a burst of drug delivery immediately upon application (approximately five times greater in the first 8 hours, while the drug is being released from the adhesive) (Lowenthal at 294-295), and that this "burst" of drug release from the adhesive is not reflected in the blood levels upon system replacement (i.e., after the skin has been saturated with the drug), provides additional evidence that the skin has the most significant rate-limiting effect.

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to exhibit cold flow, there would be a "tendency" for adhesive to ooze into the foil pouch containing the patch, which "could lead" to the patient getting clonidine on his/her fingers during application, which in turn "could result" in a "potentially" dangerous condition "if" the patient were then to rub his/her eyes without first washing his/her hands, which "could present" dangerous conditions "if" the patient were then to drive, operate heavy machinery or exercise. This speculative, worst-case scenario is neither credible nor reasonable. Furthermore, BI can only speculate that the absence of silicone dioxide in a clonidine transdermal patch "may be subject to increased incidence of cold flow." Citizen Petition at 10

The final alleged health risk identified by BI is increased skin sensitization allegedly caused by a change in inactive ingredients. Allergic contact sensitization is a known adverse event with any transdermal product, and is listed in the Catapres-TTS Package Insert as occurring in only 5 out of 101 patients in a three-month trial. Catapres-TTS Package Insert, Exhibit F to the Citizen Petition. BI states that "[m]any materials commonly employed as inactive ingredients in patch products are known to potentiate significantly the occurrence of allergic sensitization." Citizen Petition at 11. BI does not, however, name a single such inactive ingredient, and significantly, does not assert that any inactive ingredient used in the Elan product is known to potentiate allergic sensitization. BI only states that Elan's use of different inactive ingredients "may have the effect" of potentiating sensitization at a level greater than that observed with Catapres-TTS. *Id.* BI does not even cite to one of its employee's declarations to support this attorney argument, yet suggests that the FDA should require full safety and efficacy studies for the "apparently" different Elan product, and every other generic patch that differs from Catapres-TTS. Even assuming that the actions proposed by BI were within the FDA's statutory authority, which they are not, such speculation and attorney argument can not justify the significant changes in the ANDA approval process that BI is proposing.

III. THE STANDARDS PROPOSED BY BI ARE NOT NEEDED TO SHOW CLINICAL BIOEQUIVALENCE

In the Citizen Petition, BI sets out what it contends to be the minimum standards by which bioequivalence between a generic clonidine patch and Catapres-TTS should be shown. However, the additional testing, and more stringent statistical analysis, suggested by BI do not provide any relevant information regarding bioequivalence that is not already provided by the current standards. They are simply an attempt to raise the bar for generic competitors, and are inconsistent with current FDA guidance. *See* Guidance for Industry, October, 2000, Exhibit I to the Citizen Petition.

Under 21 U.S.C. § 355(j)(8)(B), bioequivalence is established if the rate and extent of drug absorption from the compared products does not show a significant difference when administered in the same molar dose under the same experimental conditions. Many of the

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standards suggested by BI simply reflect current standards and clinical practice (i.e. using a two-way cross-over study; administering the dosage in accordance with label instructions; adequate wash-out periods; regular daily collection, and preservation, of blood samples; measurement of C_{max} and AUC), and are nothing new. However, BI proposes at least four requirements that are not contemplated by the statute, and that in fact do not relate to bioequivalence as defined therein. First, BI proposes that the FDA require that the steady-state blood concentrations at days 4, 5 and 6 after system application be measured and compared. Second, BI proposes establishing equivalence of the total drug delivered by measuring drug excreted in urine. Third, BI proposes that the point estimates for each variable ratio be shown to fall with the 0.90 to 1.10 confidence interval. Fourth, BI proposes that the FDA not approve any clonidine patch containing an amount of drug that varies more than 10% from the content of Catapres-TTS. None of these showings do anything to enhance the showing of bioequivalence of two products. They are simply a way to force generic companies to spend more money on their clinical trials, and delay the approval of generic clonidine patches.

A. The Proposed Comparison Of The Steady-State Plasma Clonidine Levels At Days 4, 5 and 6 Is Not Helpful In Determining Bioequivalence.

BI suggests that in order to determine equivalence in the rate of drug delivery, the steady-state plasma clonidine concentrations at days 4, 5 and 6 must be measured and compared. Citizen Petition at 16. BI does not, however, provide any reasoning or evidence to support this proposed requirement, or to show that steady state plasma levels on these days provide any information regarding the rate of delivery that is not obtainable under the current standards. The remark that "increases and decreases in plasma clonidine concentrations should be of comparable magnitude to the consecutive changes of fresh product from one source" (Citizen Petition at 17) does not relate to the proposed test, because a measurement of plasma levels over the mid-point of one dosing interval does not provide any information regarding plasma levels in consecutive changes of the same product.

B. The Measurement Of Total Drug Delivered By Measuring Drug Excreted In The Urine Is Not Helpful In Determining Bioequivalence

BI provides no evidence or reasoning showing that measuring the total amount of clonidine excreted unchanged in the urine provides any better measure of drug delivery than do the various measurements required under current standards. For example, current FDA standards require, as part of the bioequivalence study, that the total drug delivered by measured by AUC and assaying the residual drug content in patches after removal. BI has provided no support for the contention that this standard is in any way inadequate as an actual measurement of drug delivered. Further, the data obtained by measuring urine content provides, at best, only an estimate of the total drug delivered, as even BI concedes. Citizen Petition at 18. In contrast, the

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current bioequivalence standards are fully adequate to address whether or not the products being compared deliver equivalent amounts of the drug to the patient.

C. BI Has Not Established That The Proposed Statistical Analysis Is Necessary To Prove Bioequivalence

BI suggests that, in addition to the statistical analysis currently required by the FDA, that an ANDA applicant also calculate the point estimates for each variable ratio, and show that the 90% confidence interval falls within the narrowed interval 0.90 to 1.10. Citizen Petition at 19. BI simply states that "this is consistent with FDA's requirements generally. Id. However, this requirement does not exist, and BI has provided no reason for why it should be adopted, or explained how it is relevant to determining bioequivalence.

D. There Is No Requirement That The Drug Content Of A Transdermal Product Be Within 10% Of That Of The Reference Product, And BI Provides No Reason Why It Should Be

Finally, BI asserts that FDA can not approval any ANDA for a clonidine patch unless that patch contains an amount of drug equal to that contained in corresponding strength of Catapres-TTS, plus or minus 10%. Citizen Petition at 20. BI's support for this assertion is a 12-year-old statement made by an FDA official during a meeting of the Generic Drugs Advisory Committee, before ANDAs on transdermal products were even permitted. See Exhibit H of the Citizen Petition. However, this 12-year-old statement was never implemented as a regulation, guideline, or internal policy at FDA, and has never been made a condition for approval of any ANDA on a transdermal product. BI has provided no compelling reason why it should be adopted. Whatever might have been contemplated in 1990, Mylan submits that the FDA took the correct action in ultimately not implementing such a standard, as it places an entirely arbitrary and unnecessary limitation on formulations for generic transdermal products that does not protect the public health and safety.

Also, this artificial standard does nothing to address the underlying safety issue, that is, what amount of residual drug in a used patch presents a risk to public safety. This issue has already been considered by the FDA in the context of approving the Catapres-TTS product (which itself is recognized as a potential hazard) and determined to be adequately addressed by label instructions to keep both unused and used patches out of the reach of children, and to carefully dispose of used patches. Package Insert, page 2. BI has presented no evidence to show that these safety measures, already in place, are in any way inadequate, either generally or in the specific context of a generic clonidine patch.

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IV. GRANT OF THE CITIZEN PETITION IS AGAINST THE PUBLIC INTEREST

The Citizen Petition does not establish any compelling public interest that would be served by the FDA taking the requested actions. All of the public health risks raised by BI are purely speculative and entirely unsupported by evidence. Furthermore, BI's own publications show that these dangers do not in fact exist, or are no different than those presented by the approved Catapres-TTS patch. The FDA has in fact already evaluated every one of the risks listed by BI, in the context of approving the Catapres-TTS patch, and has determined that they are either insignificant, or can be managed by appropriate precautions that are listed in the Package Insert.

The only interest that would be served by taking the actions suggested in the Citizen Petition is that of BI, which would benefit immensely from a further delay in generic competition. Any delay in the entry of generic clonidine patches will result in significant harm to the public, which will have to continue paying BI the high price of the brand-name product. It is specifically this harm that the Hatch-Waxman Act was enacted to prevent.

V. HERCON IS NOT ENTITLED TO THE 180-DAY GENERIC EXCLUSIVITY

BI argues that the ANDA filing by Hercon Laboratories invokes the 180-day generic exclusivity provided by 21 U.S.C. § 355(j)(5)(B)(iv), and that the 180-day period has not yet begun to run because neither statutory trigger has occurred. Citizen Petition at 21-22. BI suggests that Hercon is entitled to the generic exclusivity because it was the first company to file a paragraph IV certification and defend a lawsuit. Citizen Petition at 23. It is Mylan's understanding that it is the FDA's position that Hercon has withdrawn its ANDA's for transdermal clonidine for at least the 0.2 mg and 0.3 mg patch, and for that reason Hercon is not entitled to any 180-day exclusivity period.

It has long been the policy of the Office of Generic Drugs that if an applicant that is first to file an ANDA with a paragraph IV certification later withdraws its ANDA, not only would that applicant no longer be eligible for the 180-day exclusivity period, no one would. It is stated in 21 C.F.R. 314.107(c)(3) that:

(3) For purposes of paragraph (c)(1) of this section, if FDA concludes that the applicant submitting the first application is not actively pursuing approval of its abbreviated application, FDA will make the approval of subsequent abbreviated applications immediately effective if they are otherwise eligible for an immediately effective approval.

If an applicant withdraws its ANDA, it clearly is no longer actively seeking approval, and all

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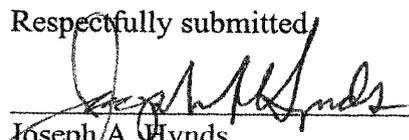
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subsequent applications will be made effective if they otherwise meet approval requirements. Furthermore, even if Hercon has not withdrawn its ANDA -- and we understand that they have -- the passage of 12 years without approval provides strong evidence that they are not actively seeking approval of that ANDA.

CONCLUSION

For all of the foregoing reasons, the Citizen Petition should be denied.

Respectfully submitted,



Joseph A. Hynds
Rothwell, Figg, Ernst & Manbeck, P.C.
1425 K Street NW, Suite 800
Washington, DC. 20005
tel. (202) 783-6040
fax (202) 783-6031