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March 13,2007

[Filed Electronically]

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

CITIZEN PETITION

Dear Sir/Madam:

The undersigned, on behalf of Purdue Pharma L.P. and its affiliates (hereinafter "Petitioner"), submits this Citizen Petition pursuant to 21 C.F.R. §§ 10.30, 314.50(i), 314.52 and 21 U.S.C. § 355(b)(2).

I. Action Requested

Petitioner requests that the Food and Drug Administration take the following actions with respect to the New Drug Application ("NDA") submitted by Cipher Pharmaceuticals Inc. seeking approval for CIP-TRAMADOL ER, a 24 hour extended release oral formulation of tramadol:

(1) If the Cipher NDA was submitted (or is resubmitted) under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), refuse to approve the Cipher NDA until such time as i) Cipher includes in its application an appropriate certification with respect to U.S. Patent No. 6,254,887 listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") for the listed drug Ultram® ER (tramadol hydrochloride) Tablets (NDA # 21-692)

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and ii) if Cipher certifies that said patent is invalid, unenforceable, or will not be infringed by the manufacture, marketing and distribution of the Cipher CIP-TRAMADOL ER product, Cipher complies with the notice provisions of 21 U.S.C. § 355(b)(3), and

(2) If the Cipher NDA was submitted (or is resubmitted) under Section 505(b)(1) of the FFDCA, refuse to approve the Cipher NDA until such time as Cipher complies with the requirement that the NDA include full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use, which investigations either were conducted by or for Cipher or are investigations to which Cipher has a right of reference.

II. Statement of Grounds

A. Ultram® ER - Biovail's 24 Hour Extended Release Oral Formulation of Tramadol

On September 8,2005, FDA approved NDA No. 21-692 for tramadol HCI 24 hour extended release tablets, 100,200, and 300 mg, currently held by Biovail Laboratories International SLR ("Biovail"). Biovail's NDA was submitted under Section 505(b)(2) of the FFDCA and cited immediate release tramadol (Ultram® (tramadol hydrochloride tablets)) as the reference listed drug.

In the Orange Book, FDA designated the 300 mg strength of the Biovail product as the reference listed drug for 24 hour extended release oral formulations of tramadol. In addition, the Orange Book also lists U.S. Patent No. 6,254,887 ("the '887 Patent"), which has been listed in NDA 21-692 for Biovail's 24 hour tramadol product. The '887 Patent is owned by Petitioner and claims controlled release preparations for oral administration containing tramadol, or a pharmaceutically acceptable salt of tramadol. The

'887 Patent expires on May 10, 2014. *See* Attachment A (Orange Book excerpts).'

B. Cipher's Application for CIP-TRAMADOL ER, a 24 Hour Extended Release Oral Formulation of Tramadol

According to public announcements, Cipher submitted an application seeking approval of CIP-TRAMADOL ER, a 24 hour extended release oral dosage form of tramadol on June 29,2006, and that application has been accepted for filing by FDA. Cipher's public pronouncements indicate that the company expects to market its CIP-TRAMADOL ER product well before expiration of the '887 Patent in 2014. Based on publicly available descriptions of the data submitted by Cipher in support of its application, it appears that Cipher has submitted a 505(b)(2) application.

In light of the above, Petitioner had expected to receive notice that Cipher had filed a patent certification under Section 505(b)(2)(A)(iv) of the FFDCA for the '887 Patent. However, neither Petitioner nor, to our understanding, Biovail has received such a notice, though more than twenty days have passed since Cipher's announcement that FDA had accepted the application for filing. Petitioner's counsel has twice written to Cipher concerning this matter, but has not received any response.

C. Cipher Must Comply With Certification Requirements If Its Application Was Filed Under Section 505(b)(2) Of The FFDCA

An application submitted under Section 505(b)(2) of the FFDCA that relies on FDA's finding that a previously approved drug is safe and effective must identify the listed drug upon which it relies. 21 C.F.R. §

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[1] **The Orange Book listing for NDA No. 21-692 also states that the product is protected by 3 year non-patent exclusivity through September 8,2008. See Attachment A. According to publicly available information regarding the FDA reviews of the NDA, that exclusivity was based on the conduct by or on behalf of Biovail of multiple clinical studies necessary to demonstrate the safety and effectiveness of tramadol in a 24-hour extended-release dosage form.**

314.54(a)(1)(iii). Such an application must contain a certification with respect to all patents that claim the relevant listed drug or drugs. 21 U.S.C. § 355(b)(2)(A); 21 C.F.R. § 314.54(a)(1)(vi); *see Guidance for Industry, Applications Covered by Section 505(b)(2),* CDER, Draft Guidance (Oct. 1999) (hereinafter "505(b)(2) Guidance").

If there is a listed drug that is the pharmaceutical equivalent of the product that is the subject of the 505(b)(2) application, the applicant is to submit certifications, and provide notices where applicable, with respect to all of the patents listed for the pharmaceutically equivalent listed drug. *See* 505(b)(2) Guidance, p. 8. When there is no listed drug that is a pharmaceutical equivalent to the drug product proposed in the 505(b)(2) application, FDA considers the relevant listed drug to be the one that is the most similar to the drug product that is the subject of the 505(b)(2) application. *See* FDA Response to Citizen Petition, Docket No. 2004P-0386 (Nov. 30, 2004), p. 9, available at: http://www.fda.gov/ohrms/dockets/-dockets/04p0386/04p-0386-pdn00001-vol1.pdf. In the words of the agency: "[W]hen a section 505(b)(2) application has been submitted and no pharmaceutically equivalent drug product has been previously approved, the 505(b)(2) applicant should choose the listed drug or drugs that are most similar to the drug for which approval is sought."[2]

In this case, the Orange Book identifies three reference listed drugs for oral dosage forms of tramadol: Biovail's NDA No. 21-692, for extended-release tramadol tablets (once a day administration); NDA No. 21-693, for orally disintegrating tramadol tablets; and NDA No. 20-281, for immediate release tramadol tablets. From publicly available information, it appears that the Cipher product is in an oral capsule dosage form. This would indicate that, under current FDA policies, the Cipher product is not strictly considered a "pharmaceutical equivalent" of any of the previously-

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[2] FDA further explained that requiring applicants to select the most similar product as the reference listed drug advances a number of interests, including (a) minimization of the amount of data required to support the change proposed in the 505(b)(2) application, thus avoiding unnecessary duplication of research and review by the agency, (b) ensuring the patent certification obligations for 505(b)(2) applications and ANDAs are parallel, and (c) preventing use of the 505(b)(2) process to circumvent protections that would have applied had an ANDA been permitted to be filed for the proposed product.

approved tramadol products (which are all in oral tablet dosage form). However, despite this difference, the product approved in Biovail's NDA No. 21-692 for extended release tramadol is clearly most similar to the Cipher extended-release (once a day administration) capsule product and, accordingly, is the relevant reference listed drug. Cipher is therefore required to certify to U.S. Patent 6,254,887, and, if it submits a Paragraph IV certification with respect to that patent, is also required to provide Petitioner and Biovail with a patent notice pursuant to 21 U.S.C. § 355(b)(3).[3]

D. Cipher Must Comply With The Requirements of Section 505(b)(1) If It Filed Its Application Under Section 505(b)(1) Of The FFDCA

As noted above, based on publicly available descriptions of the data submitted by Cipher in support of its application, it does not appear that Cipher has submitted an application that complies with the requirements of Section 505(b)(1). If indeed the application relies on literature, the agency's previous approval of any other tramadol product, or any other third-party data to satisfy any safety or efficacy data requirements, and Cipher has not submitted an appropriate right of reference to such data, FDA must refuse to approve the Cipher NDA until such time as Cipher either (1) complies with the requirement that the NDA include full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use that were either conducted by or for Cipher or for which Cipher has a right of reference, or (2) amends its application to reflect that it is a 505(b)(2) application, and complies with the patent certification and notice requirements discussed above.'

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[3] Cipher's NDA should, for these same reasons, be subject to the unexpired three-year exclusivity awarded to Biovail in connection with the September 8,2005 approval of NDA 21-692. Cipher may also be required to certify to any patents listed for the original immediate-release tramadol NDA No. 20-281. *See* FDA Response to Citizen Petition, Docket No. 2004P-0386 (Nov. 30, 2004), p. 10, n.14.

[4] *See* FDA Response to Citizen Petition and Petition for Stay of Action, Docket No. 99P-1589 (Feb. 3, 2000), available at: http://www.fda.gov/ohrms/dockets/dailys/00/mar00/-030200/pav1.pdf

III. Environmental Impact

Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

IV. Economic Impact

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

V. 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 Petitioner which are unfavorable to the petition.

Respectfully submitted,

Peter R. Mathers
Jennifer A. Davidson

cc: Elizabeth Dickinson, Esq.
Kim Dettlebach, Esq.
David Read, Esq.

Search results from the **"OB_Rx"** table for query on **"021692."**

Active Ingredient:	TRAMADOL HYDROCHLORIDE
Dosage Form;Route:	TABLET, EXTENDED RELEASE; ORAL
Proprietary Name:	TRAMADOL HYDROCHLORIDE
Applicant:	BIOVAIL LABS INTL
Strength:	100MG
Application Number:	021692
Product Number:	001
Approval Date:	Sep 8,2005
Reference Listed Drug	No
RXIOTCIDISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	TRAMADOL HYDROCHLORIDE
Dosage Form;Route:	TABLET, EXTENDED RELEASE; ORAL
Proprietary Name:	TRAMADOL HYDROCHLORIDE
Applicant:	BIOVAIL LABS INTL
Strength:	200MG
Application Number:	021692
Product Number:	002
Approval Date:	Sep 8,2005
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	TRAMADOL HYDROCHLORIDE
Dosage Form;Route:	TABLET, EXTENDED RELEASE; ORAL
Proprietary Name:	TRAMADOL HYDROCHLORIDE
Applicant:	BIOVAIL LABS INTL
Strength:	300MG
Application Number:	021692
Product Number:	003
Approval Date:	Sep 8,2005
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

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Patent and Exclusivity Search Results from query on Appl No **021692** Product **001** in the **OB_Rx** list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021692	001	6254887	MAY 10,2014		Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021692	**001**	NP	SEP **08,2008**

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.

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Patent and Exclusivity Search Results from query on Appl No **021692** Product **002** in the **OB_Rx** list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021692	002	6254887	MAY 10,2014		Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021692	**002**	NP	SEP **08,2008**

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Patent and Exclusivity Search Results from query on Appl No **021692** Product **003** in the **OB_Rx** list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021692	003	6254887	MAY 10,2014		Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021692	**003**	**NP**	SEP **08,2008**

Additional information:

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2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
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