

4343 02 JUN -3 PM '02

May 31, 2002

**VIA FEDERAL EXPRESS**

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

**CITIZEN PETITION**  
**EXPEDITED DECISION REQUESTED**

Mylan Pharmaceuticals Inc. (hereinafter "Mylan") respectfully submits this petition pursuant to 21 U.S.C. §355(j), 21 C.F.R. §§10.30, 314.94, 314.50(a)(1) and 314.420(a)(2) and (b). Mylan requests that the Commissioner of Food and Drugs ("Commissioner") determine that Mylan's Abbreviated New Drug Application ("ANDA") No. 76-122 was the first-filed application for a 45 mg strength of mirtazapine hydrochloride (reference drug, Remeron® - Organon) under 21 U.S.C. §355(j)(5)(B), and that Mylan is therefore entitled to 180 days of exclusivity under that statute. Because an exclusivity-triggering federal court decision in related patent infringement litigation may be imminent, Mylan respectfully requests that consideration of this Petition be expedited.

02P-0256

CP 1

**A. INTRODUCTION**

The basis of this petition is FDA's acceptance for filing of an incomplete ANDA submitted by Teva Pharmaceuticals ("Teva") for mirtazapine hydrochloride 45 mg ("Teva application"). The Teva application was not substantially complete as required by 21 C.F.R. §314.101(d) because it referenced a non-existent Drug Master File ("DMF"). The DMF referenced in the Teva application was not filed with the Agency until March 2, 2001, a date which is later than the date on which FDA improperly accepted the Teva application for filing. Therefore the agency should have "Refused to Accept" the Teva application on the grounds that it was not sufficiently complete. Had FDA done so, Mylan's 45 mg mirtazapine application, accepted on February 28, 2001, would have been the first filed containing a Paragraph IV certification.

Expedited consideration is requested because of the likelihood that within the next several weeks the U.S. District Court for the District of New Jersey will rule on motions for summary judgment in the actions brought by the patent/NDA holder and assignee Akzo Nobel, NV and Organon, Inc. ("Organon") against Mylan and Teva pursuant to 35 U.S.C. §271(e)(2). Should the District Court rule in favor of Mylan and Teva, the Agency will be required to give final approval and the 180 days of market exclusivity for each dosage strength of the mirtazapine product to the company that filed the first substantially complete ANDA for such dosage strength. 21 C.F.R. 314.107(c).

**B. STATEMENT OF GROUNDS**

**1. Legal Background**

An applicant for an ANDA is required to file a certification with respect to each patent listed in the Orange Book that claims the approved drug or a method of using the approved drug. 21 U.S.C. §505(j)(2)(vii). Among the certifications an applicant may make is that the listed patent is invalid or will not be infringed by the manufacture, use or sale of the product for which approval is sought. 21 U.S.C. §505(j)(2)(vii)(IV) ("paragraph IV certification"). The statute and applicable regulation provide that an applicant making a paragraph IV certification is entitled to 180 days of market exclusivity if it is the first applicant to file an ANDA containing a paragraph IV certification. 21 U.S.C. §355(j)(5)(B)(iii); 21 C.F.R. §314.107(c).

The required contents of an ANDA are set forth in 21 C.F.R. §314.94 which incorporates by reference certain requirements of 21 C.F.R. §314.50(a). An ANDA must contain, inter alia, "the identification numbers of all drug master files." 21 C.F.R. §314.50(a)(1). An ANDA which does not contain the required DMF information should not be accepted by FDA for filing and review purposes and may not be considered filed by FDA unless it contains the information required by the regulations. 21 C.F.R. §314.101.

**2. Factual Background**

Mylan's ANDA for a 45 mg tablet of mirtazapine hydrochloride was filed on February 27, 2001. FDA accepted the application for filing on February 28, 2001 and assigned it number 76-122. As required by 21 C.F.R. §314.50(a)(1), Mylan's ANDA referenced DMF No. 15300 submitted by Sumika Fine Chemicals Co. Ltd. on February 22, 2001. (See Exh. A to Declaration of Dawn Beto ("Beto Decl.")). On information and belief, the Teva application

contained a reference to a non-existent DMF.<sup>1</sup> In its April 8, 1994, letter to ANDA/ANDA applicants, the Agency discussed the problem of incomplete applications. The letter states in relevant part, "The most frequent reason for an application to be refused for filing is the failure of the applicant to provide an acceptable drug master file (DMF) authorization for the bulk drug." Since no DMF was on file at the time the Teva application purportedly referenced the DMF, the reference itself is fatally flawed. Therefore FDA should have issued a "Refusal to Accept" with respect to the Teva application. Teva did not file DMF No. 15323 until March 2, 2001. (See Exh. A to Beto Decl.) Therefore, the earliest date that Teva's ANDA No. 76-119 could be considered complete for FDA filing purposes is March 2, 2001, at least three (3) days after Mylan's application was accepted for filing.

On May 7, 2001, within 45 days of receiving Mylan's notice of its paragraph IV certification, Organon filed an action for patent infringement against Mylan pursuant to 35 U.S.C. §271(e)(2)(A), alleging that Mylan's submission of ANDA 76-122 was an act of infringement of Organon's U.S. Patent No. 5,977,099 (the "'099 patent"). The '099 patent claims inter alia a combination of mirtazapine and an SSRI for the treatment of depression. As a result of the filing of that lawsuit, final approval of Mylan's ANDA has been stayed for 30 months or until the court holds the patent invalid, unenforceable or not infringed. Mylan received tentative approval on January 14, 2002. (See Exh. B to Beto Decl.)

Organon sued Teva on June 8, 2001 pursuant to 35 U.S.C. §271(e)(2)(A) alleging that the submission of ANDA 76-119 constituted an act of infringement. ANDA 76-119 also received tentative approval on January 14, 2002. (See Exh. B. to Beto Decl.)

---

<sup>1</sup> Mylan's only information about the filing date of Teva's ANDA was obtained in connection with the patent infringement lawsuits referenced herein and was designated confidential pursuant to a court protective order. However the Teva ANDA was assigned No. 76-119. Therefore it apparently was received by FDA very shortly before Mylan's ANDA No. 76-122.

The Mylan and Teva cases were consolidated for pre-trial purposes in the District of New Jersey before the Honorable Faith S. Hochberg.<sup>2</sup> On March 1, 2001, Mylan and Teva filed motions for summary judgment of non-infringement. The Court heard oral argument on May 3, 2002. A decision is expected to issue shortly.

Expedited consideration is requested, because if the District Court grants the motions for summary judgment, the 30 month stay will be lifted and final approval with 180 days of market exclusivity will be granted to the filer of the first ANDA for each dosage strength. Should FDA reject this petition and award Teva 180 days of exclusivity with regard to the 45 mg strength of mirtazapine hydrochloride, Mylan will sustain immediate and irreparable harm.

**FDA SHOULD DETERMINE MYLAN WAS THE FIRST TO FILE A  
SUBSTANTIALLY COMPLETE ANDA FOR A 45 MG MIRTAZAPINE TABLET**

The requirements for a complete ANDA are set forth in 21 C.F.R. §314.94. Section 314.94(a)(1) incorporates by reference the requirements of 21 C.F.R. §314.50(a)(1). Among those requirements is a requirement for the identification of all DMFs referenced in the application. 21 C.F.R. §314.50(a)(1). FDA's regulations state that it "may not consider an abbreviated new drug application to be received if ... (3) the application does not on its face contain information required under ... §314.50." An ANDA cannot therefore be considered "complete" if it does not reference a DMF. Teva's ANDA could not have referenced a valid DMF and its FDA assigned number, because that DMF was not filed until March 2, 2001 – a period of at least several days after FDA accepted the Teva application for filing.

FDA has recognized the importance of the submission of a "substantially complete" ANDA to the proper functioning of the Hatch-Waxman legislative scheme. In a response to a comment that proposed regulation 21 C.F.R. §314.95(b) created a detrimental delay to ANDA

---

<sup>2</sup> Organon has filed similar actions against approximately nine other generic manufacturers. Each of those actions has been or is in the process of being consolidated by the Judicial Panel on Multidistrict Litigation.

applicants because it required an applicant to wait until FDA determines the application is complete before providing notice to the patent owner and NDA holder, FDA responded:

FDA disagrees with the comment. As stated above, the legislative history expressly states that notice of certification of invalidity or noninfringement of a patent must be given simultaneously with the submission of an ANDA and that the ANDA cannot be a "sham" ANDA or one that is substantially incomplete (see H. Rept. 857, 98th Cong., 2d Sess. 24 (1984)). As written, section 314.95(b) is consistent with the legislative history because it requires the ANDA applicant to provide notice once FDA has determined that the ANDA is substantially complete to permit a substantive review. To permit an ANDA to provide notice before FDA has determined whether the ANDA is sufficiently complete would be contrary to the legislative history because it would only encourage ANDA applicants to file incomplete or "sham" ANDAs to supplement them later to secure a place in the review queue as an attempt to secure the first ANDA approval. *FDA, Abbreviated New Drug Application Final Regulations; Patent and Exclusivity Provisions 59 Fed. Reg. 50338, 50350 (October 3, 1994).*

The logic of FDA's response applies to the present situation. As FDA's rules reflect, an appropriately referenced DMF is an essential part of an ANDA. In 1996 FDA again identified incomplete information with respect to DMFs as a key reason for refusing to file ANDAs. Under the section "Handling Application Process Issues; Refusal to File (A) DMF Issues," FDA stated "incomplete information about a DMF" is a key reason the office refuses to file abbreviated applications."<sup>3</sup> The DMF describes the processes, components and facilities used to produce the active drug substance. Until the DMF has been submitted, the Agency cannot assess whether the manufacture of the drug substance will comply with the agency's rigorous requirements. To consider an ANDA without a valid DMF reference to be sufficiently complete to allow substantive review would be arbitrary and capricious in light of the requirements of 21 C.F.R. §314.50(a)(1). It would allow ANDA holders to obtain a "first-to-file" status with an incomplete application. Such a result would be contrary to both the legislative history and FDA's own previously stated position.

---

<sup>3</sup> FDA, ANDA and AADA Applicants Letter (December 24, 1996).

**Conclusion**

For the foregoing reasons, Mylan respectfully requests that its petition be granted.

**C. ENVIRONMENTAL IMPACT STATEMENT**

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

**D. ECONOMIC IMPACT STATEMENT**

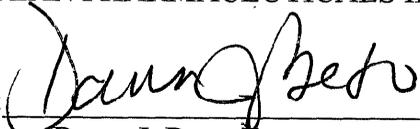
The Commissioner has not requested economic impact information at this time.

**E. CERTIFICATION**

The undersigned certifies, that, to the best of his knowledge and belief, this petition (including its attachments) 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,

MYLAN PHARMACEUTICALS INC.

By: 

Dawn J. Beto, Esq.  
Associate General Counsel  
Mylan Pharmaceuticals Inc.  
781 Chestnut Ridge Road  
Morgantown, WV 26505  
(304) 599-2595

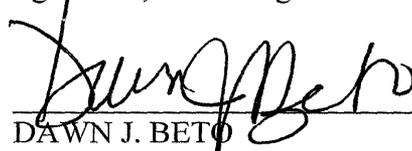
## DECLARATION OF DAWN J. BETO

I, Dawn J. Beto, hereby declare as follows:

1. I am Associate General Counsel for Mylan Laboratories Inc. ("Mylan"). I have been employed in Mylan Legal Department since 1989. I submit this declaration to put before the Commissioner of the United States Food and Drug Administration certain documents in connection with Mylan's Citizen's Petition dated May 29, 2002.
2. Unless noted otherwise, the information set forth below is based on my personal knowledge.
3. Attached hereto as Exhibit A is a true and correct copy of a portion of the Food and Drug Administration's ("FDA's") WebPage entitled "Drug Master Files" (under the ASCII link to "All Active,") accessible at <http://www.fda.gov/cder/dmf/> listing the date that Sumika Fine Chemicals Company LTD submitted its Drug Master File ("DMF") for mirtazapine (DMF # 15300) to FDA, and the date that Teva Group submitted its DMF (DMF #15323) for mirtazapine.
4. Attached hereto as Exhibit B is a true and correct copy of a portion of FDA's WebPage entitled "CDER New and Generic Drug Approvals: 1998-2002" accessible at <http://www.fda.gov/cder/approval/index.htm> listing the date of tentative approvals for mirtazapine.

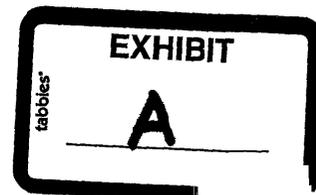
5. Pursuant to 28 U.S.C. §1746, I declare under penalty of perjury the  
foregoing is true and correct to the best of my knowledge and belief.

Signed on this 31<sup>st</sup> day of May, 2002, in Morgantown, West Virginia.

A handwritten signature in cursive script, appearing to read "Dawn J. Beto", written over a horizontal line.

DAWN J. BETO  
Associate General Counsel

1Q2002 ALLACTIVEEXCEL				
DMF #	Type	SUBMIT DATE	HOLDER	SUBJECT
15298	II	16-Mar-01	FARMABIOS SRL	BUDESONIDE AS MFG IN GROPELLO CAIROLI(PAVIA), ITALY.
15299	II	23-Feb-01	DOCTOR REDDYS LABORATORIES LTD	OLANZAPINE (FORM 1) AS MFG IN ANDHRA PRADESH, INDIA.
15300	II	22-Feb-01	SUMIKA FINE CHEMICALS CO LTD	MIRTAZAPINE AS MFG IN GIFU PREFECTURE, JAPAN.
15302	III	08-Feb-01	MA HANNA COLOR	MA HANNA COLOR PRODUCT NUMBER 506756JPMB AS MANUFACTURED IN SOMERSET, NJ
15303	II	16-Feb-01	KOWA CO LTD	NK-104 TABLETS AS MFG IN FUJI SHIZUOKA, JAPAN
15305	II	26-Feb-01	CAMBREX CORP	DEXTROAMPHETAMINE SACCHARATE AS MFG IN CHARLES CITY,IA.
15306	II	26-Feb-01	CAMBREX CORP	AMPHETAMINE ASPARTATE AS MFG IN CHARLES CITY, IA.
15307	II	26-Feb-01	CAMBREX CORP	DEXTROAMPHETAMINE SULFATE AS MFG IN CHARLES CITY, IA.
15308	II	26-Feb-01	CAMBREX CORP	AMPHETAMINE SULFATE AS MFG IN CHARLES CITY,IA.
15309	IV	20-Feb-01	TECHNICAL FLAVORS AND FRAGRANCES INC.	NATURAL ANISE EXTRACT(789-647B) AND ARTIFICIAL STRAWBERRY FLAVOR(789-780) AS MFG IN AMITYVILLE,NY.
15310	II	21-Feb-01	INTERNATIONAL SPECIALTY PRODUCTS	ALLANTOIN AS MFG IN CHATHAM, NJ.
15311	III	22-Feb-01	3M PHARMACEUTICALS INC	COTRAN 9752, NON-WOVEN WHITE RAYON MEDICAL TAPE, WITH ADHESIVE COATING ON ONE SIDE AS MFG IN BROOKINGS,SD.
15312	III	28-Feb-01	PHARM GLASS ASO SDN BHO	GLASS AMPOULES AND VIALS AS MFG IN MALAYSIA.
15313	III	26-Feb-01	EAGLE COLOR CORPORATION	SHEETFED OFFSET PRINTING INK AS MFG IN PENNSAUKEN, NJ.
15314	II	28-Feb-01	BIOIBERICA SA	SODIUM HYALURONATE AS MFG IN BARCELONA, SPAIN.
15315	IV	27-Feb-01	ARAKAWA CHEMICAL INDUSTRIES LTD.	ARKON P-100 (EXCIPIENT) AS MFG IN OKAYAMA, JAPAN.
15316	III	26-Feb-01	PERLOS OYJ CEP PLASTICS	DISPOSABLE SYRINGE FOR JELLY AS MFG IN LEHMO, FINLAND.
15317	II	28-Feb-01	SAUREFABRIK SCHWEIZERHALL	CDTP (DRUG INTERRMEDIATE) AS MFG IN PRATTELN, SWITZERLAND.
15318	II	28-Feb-01	RP SCHERER NORTH AMERICA	ROCALTROL (0.25MCG & 0.5MCG) SOFTGEL CAPSULE AS MFG IN ST. PETERSBURG, FL.
15319	II	23-Feb-01	YUNG SHIN PHARMACEUTICAL INDUSTRIES CO LTD	PACLITAXEL AS MFG IN TAIWAN, REPUBLIC OF CHINA.
15320	IV	02-Mar-01	METAROM CANADA INC	BLUE RASPBERRY NAT/ARTIFICIAL FLAVOR MC 4778 AS MFG IN GRANBY, CANADA.
15321	II	28-Feb-01	BIOINDUSTRIA LABORATORIO ITALIANO MEDICINALI SPA	PRAZOSIN HYDROCHLORIDE BULK SUBSTANCE AS MFG IN FRESONARA(AR), ITALY.
15322	II	28-Feb-01	LONZA LTD	KETOSULFON AS MFG IN VISP, SWITZERLAND
15323	II	02-Mar-01	TEVA GROUP	MIRTAZAPINE AS MFG IN BE'ER SHEVA, ISRAEL.
15324	II	28-Feb-01	ZAMBON GROUP SPA	KETOSULFONE AS MFG IN LONIGO, ITALY.
15325	II	28-Feb-01	DELMAR CHEMICALS INC	PYRAZINAMIDE AS MFG IN QUEBEC, CANADA.
15326	II	28-Feb-01	AMINO CHEMICALS LTD	FOSINOPRIL SODIUM AS MFG IN MARSA, MALTA.



<b>Minoxidil Topical Solution USP (for Men) 5% Solution, Tentatively Approved January 18, 2000, OTC</b>	Copley Pharmaceutical, Inc	ANDA 75-619	1/18/00	<u>2/4/00</u>		
<b>Miradon (anisindione) Tablets,</b>	Schering Corporation	NDA 10-909/S-013	2/6/02	<u>4/16/02</u>		
<b>MiraLax (polyethylene glycol 3350, NF) Powder, Rx</b>	Braintree Laboratories, Inc.	NDA 20-698	2/18/99	<u>2/24/99</u>	<u>2/24/99&amp;3/2/99</u>	<u>8/17/99</u>
<b>MiraLax Indication:</b> For occasional constipation.						
<b>Mirapex (pramipexolem dihydrochloride) Tablets, 0.125 mg, 0.25 mg, 1 mg, 1.25 mg, &amp; 1.5 mg.</b>	Pharmacia & Upjohn, Inc.	NDA 20-667	7/1/97			<u>5/13/99</u>
<b>Mircette/Desogestrel/ethinyl estradiol and ethinyl estradiol tablets</b>	Organon, Inc	NDA 20-713	4/22/98	<u>1/6/99</u>	<u>1/6/99</u>	<u>1/6/99</u>
<b>Mirena (levonorgestrel-releasing intrauterine system) Intrauterine delivery system, 20 mcgs/day of levonorgestrel/5-year, Rx</b>	Berlex Laboratories Inc.	NDA 21-225	12/6/00			
<b>Mirena Indications:</b> Intrauterine Contraception.						
<b>Mirtazapine Tablets, 15 mg, 30 mg and 45 mg, Rx Tentatively Approved</b>	Alphapharm Pty Limited	ANDA 76-176	2/25/02			
<b>Mirtazapine Tablets, 15 mg, 30 mg and 45 mg, Rx Tentatively Approved</b>	Mylan Pharmaceuticals Inc.	ANDA 76-122	1/15/02			
<b>Mirtazapine Tablets, 15 mg, 30 mg and 45 mg, Rx Tentatively Approved</b>	Teva Pharmaceuticals	ANDA 76-119	1/15/02			
<b>Mitomycin Injection, 5 mg/vial and 20 mg/vial</b>	SuperGen	ANDA 64-144	4/30/98	<u>5/6/98</u>		
<b>Mitomycin for Injection USP, 5 mg/vial and 20 mg/vial.</b>	ESI Lederle	ANDA 64-180	12/23/99	<u>12/27/99</u>		
<b>Mivacron (Mivacurium Chloride) Injection/Premixed Infusion</b>	Glaxo-Wellcome Inc.	NDA 20-098/S009	5/19/98			<u>7/3/00</u>
<b>Mobic (meloxicam) Tablets, 7.5 mg., Rx</b>	Boehringer Ingleheim Pharmaceuticals	NDA 20-938	4/13/00	<u>4/17/00</u>	<u>4/17/00</u>	<u>7/18/01</u>
<b>Mobic Indication:</b> Relief of the signs and symptoms of Osteoarthritis.						
<b>Mometasone Furoate Ointment USP, 0.1%, Rx</b>	Clay-Park Labs, Inc.	ANDA 76-067	3/18/02			
<b>Mometasone Furoate Ointment USP, 0.1%, Rx Tentatively Approved</b>	Clay-Park Labs, Inc.	ANDA 76-067	2/1/02			
<b>Monistat 1 Combination Pak, OTC</b>	Personal Products	NDA 21-308	6/29/01	<u>11/6/01</u>	<u>11/6/01</u>	<u>11/7/01</u>