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March 31, 2000

Dockets Management Branch  
Food and Drug Administration  
Room 1-23  
12420 Parklawn Drive  
Rockville, Maryland 20857

**Re: Docket No. 99P-5317/PSA 1 – Opposition Of Teva Pharmaceuticals USA, Inc.  
To Petition For Stay Of Approval Of Any ANDA For A Generic Version Of Enalapril  
Other Than The One Submitted By TorPharm, A Division Of Apotex, Inc.**

Dear Sir or Madam:

Teva Pharmaceuticals USA Inc. hereby respectfully submits this opposition to the December 7, 1999 Petition for Stay Of Agency Action ("TorPharm Petition" or "Petition") in which TorPharm, a Division of Apotex, Inc. seeks to delay effective approval of all Abbreviated New Drug Applications ("ANDAs") for enalapril until TorPharm has enjoyed a 180-day period of market exclusivity for its enalapril product. TorPharm's Petition seeks this unprecedented delay "regardless of the patent certification contained in [those] ANDA[s]," and even if such a delay extends beyond the expiration date of the enalapril patent. TorPharm's Petition is based upon two radical and unsupportable interpretations of the statutory provisions governing the so-called "180-day exclusivity period":

- 1) that "exclusivity can delay the approval of both Paragraph IV and Paragraph III ANDAs," and
- 2) that eligibility for the 180-day period "survives patent expiration."

See TorPharm Petition at 5.

TorPharm is wrong for two simple reasons. First, under the plain language of the statute the 180-day "exclusivity" period can only be applied to delay the effective approval date of subsequent Paragraph IV ANDAs. See 21 U.S.C. § 355(j)(5)(B)(iv). Second, the plain statutory language also states that ANDAs which contain certifications

99P-5317

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To: Dockets Management Branch – Food and Drug Administration

Date: March 31, 2000

Re: **Docket No. 99P-5317/PSA 1 – Opposition of Teva Pharmaceuticals USA, Inc.**

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under Paragraph I, II, and III are eligible for effective approval without regard to any such 180 day period, and that such eligibility begins no later than the date of patent expiration. See 21 U.S.C. § 355(j)(5)(B)(i)-(ii). And, because a subsequent Paragraph IV ANDA may be amended to include a Paragraph II or III Certification, any such amendment would allow the ANDA sponsor to receive effective approval as of the patent expiration date. Accordingly, TorPharm's Petition is without merit and should be denied.

## **I. THE STATUTE DOES NOT PERMIT TORPHARM'S STRAINED INTERPRETATIONS**

### **A. The 180-Day Period Set Forth In 21 U.S.C. § 355(j)(5)(B)(iv) Is Not An Unconditional Statutory Right To Exclusive Marketing, But Rather A Limited Potential Opportunity For A 180-Day Head Start Against Specified Generic Competitors**

TorPharm purports to rely upon the "plain language" of 21 U.S.C. § 355(j)(5)(B) in support of its position that the first company to file a Paragraph IV ANDA has an unconditional "statutory right to 180 days of generic exclusivity." Petition at 5. This position, in and of itself, shows the speciousness of TorPharm's Petition, because the term "exclusivity" appears nowhere in the statute. Rather, this term has been adopted as an informal (and imprecise) reference to the mechanism in 21 U.S.C. § 355(j)(5)(B)(iv) whereby the effective approval date of subsequent Paragraph IV ANDAs must be delayed for 180 days after an applicable court decision or the date of first commercial marketing by the first Paragraph IV ANDA applicant.

As the statute states in specifying the effective date of a subsequent Paragraph IV ANDA:

(iv) **If the application contains a certification described in subclause (IV)** of paragraph (2)(A)(vii) [i.e. a Paragraph IV Certification] and is for a drug for which a previous application has been submitted under this subsection containing **such a certification**, the application shall be made effective not earlier than one hundred and eighty days after –

(I) the date the Secretary receives notice from the applicant of the first commercial marketing of the drug under the previous application, or

(II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,

whichever is earlier.

21 U.S.C. § 355(j)(5)(B)(iv) (emphasis added). Thus, the statute on its face cannot operate to delay effective approval of ANDAs that do not contain a Paragraph IV

To: Dockets Management Branch – Food and Drug Administration  
Date: March 31, 2000  
Re: **Docket No. 99P-5317/PSA 1 – Opposition of Teva Pharmaceuticals USA, Inc.**

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Certification. Indeed, the only way TorPharm's theory could be supported by the "plain language" of the statute would be if the statute were re-written as follows:

*~~"(iv) If the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection containing such a certification, a certification described in subclause (IV) of paragraph (2)(A)(vii), the application shall be made effective not earlier than one hundred and eighty days after – . . .~~*

Of course Congress did not write the statute this way, and thus TorPharm's "plain language" argument must be rejected.

Moreover, even with respect to subsequent Paragraph IV ANDAs, the statute does not provide the unrestricted "exclusivity" period TorPharm seeks. In fact, an eligible Paragraph IV applicant's 180-day period may start before that applicant has even obtained final approval of its ANDA or entered the market. See Teva v. FDA, 182 F.3d 1003, 1005, n. 3 (D.C. Cir. 1999); Mova v. Shalala, 140 F.3d 1060 (D.C. Cir. 1998); Granotec, Inc. v. Shalala, No. 97-1873, 1998 WL 153410, at \*7 (4th Cir. April 3, 1998). Thus, there is no "right" to exclusivity.

B. TorPharm Misconstrues The Structure And Function Of 21 U.S.C. § 355(j)(5)(B) In Determining Effective Dates Of ANDAs

The function of 21 U.S.C. § 355(j)(5)(B) is to establish the effective date of approval for ANDAs based upon the type of patent certification contained therein. By their express terms, each subclause (i) through (iv) applies only to ANDAs that contain a specific patent certification. Thus, ANDAs that include certifications under Paragraph I (certifying that no patent has been listed) and Paragraph II (certifying that the patent has expired) are governed by 21 U.S.C. § 355(j)(5)(B)(i) and are eligible for immediately effective approval without regard to any patent or any 180 day delay period. ANDAs that include a Paragraph III Certification (certifying the date upon which the patent will expire), are eligible for effective approval on the date of patent expiration. 21 U.S.C. § 355(j)(5)(B)(ii). Finally, Paragraph IV ANDAs are governed by 21 U.S.C. § 355(j)(5)(B)(iii)-(iv), depending upon whether the application is the "first" Paragraph IV ANDA (21 U.S.C. § 355(j)(5)(B)(iii)) or a subsequent Paragraph IV ANDA (21 U.S.C. § 355(j)(5)(B)(iv)).

TorPharm attempts to shoehorn Paragraph III ANDAs into the limited scope of 21 U.S.C. § 355(j)(5)(B)(iv) by reference to the introductory clause of 21 U.S.C. § 355(j)(5)(B), which states "The approval of an application submitted under paragraph (2) [*i.e.*, an ANDA] shall be made effective on the last applicable date determined under" 21 U.S.C. § 355(j)(5)(B)(i) – (iv). See Petition at 5 (emphasis as used by TorPharm). Under TorPharm's implicit reasoning, in circumstances where a first Paragraph IV applicant's 180-day "exclusivity" period would extend

To: Dockets Management Branch – Food and Drug Administration

Date: March 31, 2000

Re: **Docket No. 99P-5317/PSA 1 – Opposition of Teva Pharmaceuticals USA, Inc.**

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beyond the patent expiration date, the “last applicable date” for purposes of the first clause of 21 U.S.C. § 355(j)(5)(B) would be the date that applicant’s 180-day period expires, and thus Paragraph III ANDAs could not be made effective before such time.

A fundamental flaw in TorPharm’s “last applicable date” argument is that it reads the word “applicable” out of the statute entirely. Under the plain language of the statute, the 180-day delay period of 21 U.S.C. § 355(j)(5)(B)(iv) is only “applicable” to delay effective approval of a subsequently filed ANDA if two conditions are true of that subsequent ANDA:

- (1) “the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) [i.e. a Paragraph IV Certification] and”
- (2) the application “is for a drug for which a previous application has been submitted under this subsection continuing such a [Paragraph IV certification].”

21 U.S.C. § 355(j)(5)(B)(iv) (emphasis added).

Because Paragraph III ANDAs, by definition, do not contain a Paragraph IV Certification, the 180-day delay period of 21 U.S.C. § 355(j)(5)(B)(iv) simply is not “applicable” to such ANDAs. The only “applicable” provision for determining the effective approval date of a Paragraph III ANDA is 21 U.S.C. § 355(j)(5)(B)(ii), which permits effective approval on the patent expiration date. Likewise, only § 355(j)(5)(B)(i) is applicable to Paragraph I and Paragraph II ANDAs.

C. The 180-Day “Exclusivity” Period Does Not Extend Beyond The Patent Expiration Date

Another fundamental flaw in TorPharm’s reasoning is that its “last applicable date” argument is wholly dependent upon its fallacious assertion that the 180-day “exclusivity” period under 21 U.S.C. § 355(j)(5)(B)(iv) can extend beyond the patent expiration date. Although such an outcome would be directly contrary to the unequivocal Congressional intent under Hatch-Waxman to expedite the availability of generic drugs, TorPharm argues that Congress’s purported silence on the issue (in not requiring FDA to grant effective approval to pending ANDAs on the date the patent expires) in fact reflects a “clear” “directive” that ANDAs may not be approved on the patent expiration date if the first Paragraph IV applicant has not received a 180-day “exclusivity” period. In TorPharm’s words:

The statute does not provide for approval of paragraph IV ANDAs upon patent expiration. Similarly, the statute states that approval of paragraph III ANDAs “may be made effective on the date” of patent expiration. The statute specifically does not require approval of paragraph III ANDAs to be

To: Dockets Management Branch – Food and Drug Administration

Date: March 31, 2000

Re: **Docket No. 99P-5317/PSA 1 – Opposition of Teva Pharmaceuticals USA, Inc.**

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effective upon patent expiration. Accordingly, Congress has, therefore, spoken directly – and favorably – on the issue of whether exclusivity survives patent expiration.

Petition at 6-7 (emphasis in original)

TorPharm's logic in this respect appears to be based upon a mangled application of the canon of statutory construction *expressio unius est exclusio alterius*, by which an express requirement of one particular outcome excludes, by implication, the possibility of an inconsistent outcome. TorPharm's logic is of course specious, because the fact that Congress did not affirmatively require Paragraph III ANDAs to be made effective on the patent expiration date cannot mean that Congress specifically intended to prohibit effective approval on such date if FDA's review of the application has been completed.

TorPharm's argument is particularly nonsensical because Congress granted express authority for FDA to do precisely what TorPharm says Congress implicitly prohibited – namely to make Paragraph III ANDAs effective on the patent expiration date. As 21 U.S.C. § 355(j)(5)(B)(ii) expressly provides, “the approval [of a Paragraph III ANDA] may be made effective on the [patent expiration] date certified under subclause (III) [i.e., 21 U.S.C. § 355(j)(2)(A)(vii)(III)].” (emphasis added). Because Congress did not prohibit, and indeed affirmatively permits, effective approval of Paragraph III ANDAs on the expiration date of the patent to which the Paragraph III Certification is addressed, without any reference to the “exclusivity” period under 21 U.S.C. § 355(j)(5)(B)(iv), TorPharm's argument that this “exclusivity” period blocks approval of Paragraph III ANDAs beyond the patent expiration date is simply incorrect.<sup>1</sup> Indeed, TorPharm's argument is simply, and preposterously, that the term “may” actually means “may not.”

## **II. TORPHARM'S INTERPRETATIONS, EVEN IF ADOPTED, DO NOT SUPPORT ANY STAY OF AGENCY ACTION**

TorPharm's unsupportable request to apply the 180-day delay period to non-Paragraph IV ANDAs would not even help TorPharm in this situation because it would only block effective approval of non-Paragraph IV ANDAs filed after TorPharm's Paragraph IV Certification was filed to its ANDA. This is because the second statutory condition necessary for imposition of the 180-Day Delay Period is that the ANDA be “for a drug for which a previous [Paragraph IV] application has been submitted.” 21 U.S.C. § 355(j)(5)(B)(iv) (emphasis added). Thus, even

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<sup>1</sup> It is a somewhat different question whether effective approval of a subsequent Paragraph IV ANDA may still be blocked beyond patent expiration under 21 U.S.C. § 355(j)(5)(B)(iv), but because any subsequent Paragraph IV applicant would be entitled to amend to a Paragraph II Certification once the patent expires, and thus be eligible for immediately effective approval, as a practical matter exclusivity also does not extend beyond patent expiration for Paragraph IV ANDAs either.

To: Dockets Management Branch – Food and Drug Administration

Date: March 31, 2000

Re: **Docket No. 99P-5317/PSA 1 – Opposition of Teva Pharmaceuticals USA, Inc.**

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under TorPharm's own (faulty) reasoning, the agency would not have to delay the effective approval of any Paragraph III ANDAs for enalapril that were filed before March 12, 1999, the date TorPharm amended its application to include a Paragraph IV Certification. To the best of Teva's knowledge no other applicant has submitted a Paragraph IV ANDA for enalapril, and few if any of the current enalapril applicants filed their Paragraph III ANDAs after TorPharm's Paragraph IV Certification. Thus, ironically, even if FDA were to adopt TorPharm's logic entirely, there would be no agency action that could be stayed as a result of that interpretation. Accordingly TorPharm's Petition is effectively moot and cannot be granted under any circumstances.<sup>2</sup>

### **III. THERE IS NO SOUND PUBLIC POLICY BASIS FOR TORPHARM'S PETITION**

TorPharm devotes only two cursory and wholly unconvincing paragraphs to a discussion of whether sound public policy supports its proposed re-interpretation of the statutory provisions at issue here. *See* Petition at 10. TorPharm's discussion amounts to nothing more than the statements that the public has an interest in FDA "adhering to the plain words of the statute," and its "faithful application of the laws." While those goals are indeed important, as shown herein, TorPharm's positions cannot be adopted under the plain language of the statute and to do so would violate FDA's duty to faithfully apply the laws.

### **IV. TORPHARM'S PETITION SHOULD BE SUMMARILY DISMISSED**

The complete lack of any factual or legal support for TorPharm's Petition is emblematic of the serious problem that the agency has sought to address in its recent proposed rule *Citizen Petitions; Actions That Can be Requested by Petition; Denials, Withdrawals, and Referrals for Other Administrative Action*, 64 Fed. Reg. 66822 (Nov. 30, 1999). In that proposal FDA seeks to deter petitions such as TorPharm's, in language that is strikingly appropriate here:

Some petitions contain little or no evidence or support or rely on obsolete, irrelevant, or erroneous information. Thus, the proposal would deter the submission of frivolous or unsupported petitions and petitions which simply disagree with an agency decision regardless of the scientific evidence or legal authority supporting that decision, the importance of the public health policies supporting that decision, or the petitioner's lack of sound scientific evidence or legal authority to support its request.

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<sup>2</sup> As a technical procedural matter, TorPharm's Petition is a stay petition under 21 C.F.R. § 10.35 and not a petition seeking the affirmative promulgation of a new FDA regulation. Even if TorPharm had filed such a Petition, however, granting such a Petition would be unlawful for the reasons set forth herein.

To: Dockets Management Branch – Food and Drug Administration

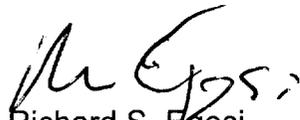
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Re: **Docket No. 99P-5317/PSA 1 – Opposition of Teva Pharmaceuticals USA, Inc.**

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64 Fed. Reg. at 66823-24. Unfortunately TorPharm was not deterred from filing its baseless Petition, and in response the agency would be well justified in denying the Petition in a brief one sentence response, under proposed 21 C.F.R. § 10.30(e)(2)(ii), or in treating the Petition as correspondence for which a response is not required under proposed 21 C.F.R. § 10.30(e)(4)(i)(F). In any event, TorPharm's Petition must be denied.

Respectfully submitted,

  
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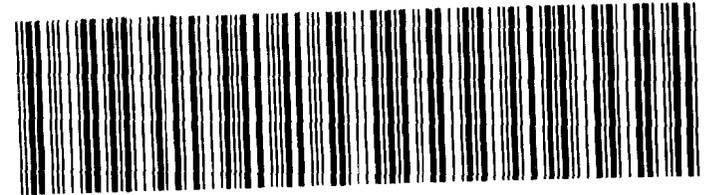
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