Department of Health and Human Services | Public Health Service
Food and Drug Administration
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DEC 24 2014

Pradaxa
Docket No.: FDA-2011-E-0117
Patent No.: 6,087,380

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RE: Boehringer Ingelheim Pharma GmbH & Co. KG — Request for Revision of Regulatory Review Period, Pradaxa

Dear Sir:

This letter is in response to your June 27, 2012, request on the behalf of Boehringer Ingelheim Pharma GmbH & Co. KG (BI) for reconsideration and revision of the determination of the regulatory review period for Pradaxa (dabigatran etexilate mesylate), U.S. Patent No. 6,087,380. In the May 3, 2012, issue of the *Federal Register* (77 Federal Register 26289), the Food and Drug Administration (FDA or the Agency) published its determination of this product's regulatory review period for purposes of patent term extension, as required under 35 U.S.C. 156(d)(2)(A). That *Federal Register* (FR) notice stated that anyone with knowledge that any of the dates as published are incorrect was permitted to submit written or electronic comments to the Division of Dockets Management and ask for a redetermination by July 2, 2012.

Your request for reconsideration and redetermination was submitted in a timely fashion. After consideration of the petition, however, your request for revision of the regulatory review period is denied for the reasons outlined below.

I. Your Request

You request revision of the regulatory review period dates noted in the FR notice based on the following assertions:

- Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI), an affiliate of BI, submitted the new drug application (NDA) 22-512, Pradaxa, as several modules of a rolling review at the request of the Agency.
- BIPI submitted the first module for rolling review on September 17, 2009, and the final required elements of the NDA were submitted to FDA as of December 15, 2009. The Agency acknowledged receipt of the NDA on December 15, 2009.

- The governing statute, legislative history, and the Agency's own regulations provide that it is the date of the initial submission of an NDA that triggers the regulatory review period, not the date of subsequent corrections or amendments to that submission, and not the date of filing.
- Although FDA issued a refuse-to-file (RTF) letter to BIPI on February 12, 2010, the Agency continued to review the NDA, as documented in the Agency's own written correspondence with BIPI.
- In the RTF letter to BIPI, FDA noted:

> "In recognition of the importance of this priority application, we propose a rolling review. We will, of course, continue our review of parts of your application that are complete and reviewable such as the chemistry and pharmacology toxicology sections."

- Individual FDA reviewers acknowledged that they had continued their ongoing review activities despite the RTF decision. FDA refused to file the December 15, 2009, submission on February 12, 2010, for clinical reasons. However, due to the priority/rolling status of the application, the Chemistry, Manufacturing and Controls (CMC) review remained ongoing after the RTF.
- On April 19, 2010, BIPI resubmitted the Pradaxa NDA.
- Because review of the Pradaxa application continued uninterrupted and unabated from December 15, 2009, to the NDA's approval on October 19, 2010, BIPI requests that FDA revise the initial submission date from April 19, 2010, to December 15, 2009.

II. Regulatory Review Period for Patent Term Extension Purposes

For purposes of patent term extension, a regulatory review period is the sum of two periods of time: a testing phase and an approval phase. With respect to regulatory review periods for a patent term extension, 35 U.S.C. 156(g) states:

> For purposes of this section, the term "regulatory review period" has the following meanings:
>
> . . .
>
> (1)(B) The regulatory review period for a new drug, antibiotic drug, or human biological product is the sum of—
>
> > (i) the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 351 [of the Public Health Service Act (PHS Act)], or sections 505 or 507 [of the Federal Food, Drug, and Cosmetic Act (FFD&C Act)], and

> (ii) the period beginning on the date the application was initially submitted for the approved product under section 351, subsection (b) of section 505, or section 507 and ending on the date such application was approved under such section.

As clarified in section 21 CFR 60.22(a)(1), for human drug products, the testing phase of the regulatory review period begins on the date an exemption under section 505(i) of the FFD&C Act becomes effective for the approved human drug product and ends on the date a marketing application under section 351 of the PHS Act or section 505 of the FFD&C Act is initially submitted to FDA.

Section 60.22(a)(2) generally tracks the statutory language and states that:

> [t]he approval phase begins on the date a marketing application under section 351 of the [PHS] Act or section 505(b) of the [FFD&C] Act is initially submitted to FDA . . . and ends on the date the application is approved.

Section 60.22(f) states that:

> For purposes of determining the regulatory review, for any product, a marketing application... is *initially submitted* on the date it contains sufficient information to allow FDA to commence review of the application.

(Emphasis in original.)

Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted, as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a drug product will include all of the testing phase and approval phase, as specified in 35 U.S.C. 156(g)(1)(B).

III. FDA Response

You correctly state that the approval phase of the regulatory review period begins when an NDA is initially submitted to FDA; however, you believe that FDA is incorrectly reading the patent term extension statute and FDA's implementing regulations when it concludes that an application that is refused filing cannot trigger the approval phase. You argue that there is no language in the statute or regulations that requires the Agency to hold applicants to an administrative filing standard in order to trigger the start of the approval phase. You also contend that Congress rejected the idea of using an administrative "filing" standard as a basis for determining whether a sponsor has initially submitted its application.

We disagree with your conclusions. According to 21 CFR 60.3(b)(12)(i), for patent term extension purposes, a marketing application means an application for human drug products

submitted under section 505(b) of the FD&C Act or section 351 of the PHS Act. As noted in the legislative history of the Drug Price Competition and Patent Term Restoration Act of 1984:

> [F]or purposes of determining the regulatory review period and its component periods, an application for Agency review is considered to be "initially submitted" if the applicant has made a deliberate effort to submit an *application containing all information necessary* for Agency review to begin. The legislative committee recognizes that the Agency receiving the application might decide it needs additional information or other changes in the application. As long as the application was complete enough so that Agency *action* could be commenced, it would be considered to be "initially submitted."[1]

A marketing application may contain a number of different elements (e.g., CMC, pharmacology, toxicology, clinical, statistical analysis, microbiology, labeling, etc.). It is FDA's position that, for the purposes of patent term extension, a marketing application is considered to be "initially submitted" when the Agency has *all* the elements required by statute and regulation to make an approval decision. The legislative record, cited above, is consistent with this interpretation — it is more than reasonable to infer that where Congress refers to a submission that contains not just some of the information necessary, but "all information necessary," to allow Agency review to begin, it meant to describe a document that is sufficiently complete to permit FDA to begin a substantive review of all required components of the application.
As outlined in 21 CFR 314.101:

> Within 60 days after FDA receives an application, the Agency will determine whether the application may be filed. The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review.

For determining the regulatory review period, the application filing review provides a measure of whether an application contains *all* the information necessary for Agency review to begin. If an application can be filed, then it is considered sufficiently complete. If the application is sufficiently complete, then the end date of the testing phase of the regulatory review period and the beginning of the approval phase can be declared and the initially submitted date is the NDA receipt date. However, if the application cannot be filed (RTF), then it is not sufficiently complete and the approval phase has not yet begun. [2]

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[1] H. Report No. 98-857, part 1, June 21, 1984 (emphases added).

[2] This has been, so far as we are aware, FDA's consistent policy since enactment of the statute in 1984. Your request cited one example of such a decision with respect to the drug Pravachol, Letter from Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, to Terry Coleman, Esq. (January 27, 1994). A similar decision was made with respect to the drug Lovenox, Letter from Stuart L. Nightingale, M.D., Associate Commissioner for Health Affairs, to Peter O. Safir, Esq. (July 14, 1994).

In the regulatory review period determination, FDA stated that BIPI's NDA submission of December 15, 2009, was incomplete as evidenced by the February 12, 2010, RTF letter. In that RTF letter, FDA noted that BIPI claimed an overall data error rate of 0.1% or less for primary outcome data and 0.25% or less for all other data. However, in FDA's initial analysis of the data, FDA found multiple clinical data errors, including transcription errors, transposition errors, and auditing errors. In the RTF letter, FDA recognized that occasional inaccuracies in a large trial database may occur, but the frequency of errors in the BIPI data sets impeded FDA's ability to perform an adequate review and undermined FDA's confidence in the data presented. As a result, FDA refused to file the Pradaxa application until the clinical data sets could be audited and corrected for FDA review.

FDA, at that point, had clearly stated its position that the application was **not** "complete enough so that Agency action could be commenced," the standard stated in the House report quoted above, with respect to the entire application. Review of the clinical data section of the application could not begin at that point. While BI had an opportunity, under FDA regulations, to contest FDA's position, assert that its application was in fact sufficiently complete to be reviewed, and ask FDA to file the application over protest, see 21 CFR 314.101(a)(3), BI did not do so. FDA accordingly refunded 75% of the user fee for this application and awaited submission of additional and corrected data that would permit the application to be considered sufficiently complete such that FDA review of the entire application could commence. On April 19, 2010, BI submitted the necessary data to complete its application, together with a user fee required for the resubmission of a new drug application.[3]

Nothing in the legislative history suggests that the submission of an incomplete application can trigger the approval phase, even if other parts of the application, such as chemistry, pharmacology, or toxicology sections, submitted under a rolling review plan for a priority product could continue to be reviewed by those other FDA review disciplines. Indeed, a very similar issue, presented by a request for patent term extension related to an animal drug, led to litigation and ultimately affirmance of the FDA's position. In Wyeth Holdings Corp. v. Sebelius, 600 F. 3d 1291 (Fed. Cir. 2010), the Court considered FDA's position that a new animal drug application was not submitted until all parts of that application were submitted in an "administrative" new animal drug application, which was submitted to FDA only after FDA had completed its review of each of the technical sections of that application under a procedure available for such applications. The Court concluded that the statutory provision at issue here, 35 U.S.C. 156(g), is ambiguous with respect to the question of when the application was "initially submitted," such that the FDA, as the administrative agency charged with implementation of this provision, could appropriately advance an interpretation that it believed to be consistent with the statutory purpose. Specifically, the Court endorsed FDA's position that the initial submission requirement was not met until there was an application that contained or referenced all the parts

[3] See, for rules concerning NDA user fees when an application is found not to be sufficiently complete to be filed, FFD&C Act, Section 736(a)(1)(D),(E).

required for approval, even though at that time FDA has already reviewed the various components of the application.

Here, the administrative process for drug application review is different than it is for animal drugs, but there are some similarities. FDA permitted BI to submit its application on a "rolling review" basis, so that segments of the application that would be reviewed by different disciplines within FDA could be submitted when they were ready. It was clearly understood, however, including by BI, that the application itself would not be considered to be submitted to FDA until such time as the last segment of the application was submitted for FDA review so that the complete application was before the agency. Indeed, BI in its petition does not argue that the application was submitted before it provided that last segment.

Thus, the fact that BI had submitted, and FDA had begun to review, modules of the application — and continued to review them after the application was refused for filing based on the promise that the application would be resubmitted -- has no effect on the date that the application is considered to have been "initially submitted" for purposes of 35 U.S.C. 156(g). While, as the Wyeth court found, this statutory provision may be considered ambiguous, the FDA interpretation is clear, and it is binding here. Accordingly, no application is considered to be "initially submitted" if it has not been found to be sufficiently complete to meet the filing requirement for an application.[4]

We note that, in the legislative history, Congress restated the common understanding that once the sponsor submits a *complete application* containing all the required information, that application would still be considered to have been "initially submitted" even if FDA later decided to request additional information. FDA's position here is consistent with that expectation, and minor amendments or changes made to an application that had been found sufficiently complete to be filed would not "reset" the clock for the beginning of the approval phase.

As noted, in determining the regulatory review period for patent term extension purposes, FDA retrospectively reviews the facts to determine the initially submitted date, that is, the date on which the applicant has submitted an application that was sufficiently complete for Agency action. Because, on June 18, 2010, it was determined that the resubmitted Pradaxa NDA could be filed (i.e., it was determined to be sufficiently complete to permit substantive review), FDA determined that the initially submitted date of the Pradaxa NDA was April 19, 2010, the date the Pradaxa NDA was resubmitted after addressing the issues identified in the RTF letter.

[4] We note that this interpretation is consistent with section 506(d)(2) of the FFD&C Act, which states that the time period for review of an application for a "fast-track" product does not start until the date on which the application is complete, even though it is contemplated—see section 505(d)(1)--that FDA will commence review of portions of the application before the application is complete. Pradaxa was not designated as a fast-track drug, but the concept of rolling review for a potentially important drug is the same.

B. Rolling Submission of Application and Substantive Review of the Application

You have argued that FDA "commenced review" of sections of the Pradaxa NDA on a rolling basis as the Agency received them. You reference ongoing review communications between the Agency and the applicant about the individual review modules before and as they were submitted as support of your assertion that the Agency began substantive review of the sections before the December 15, 2009, submission date. As noted, however, it is not the actual review of portions of the application that drives the "initially submitted date" determination, but rather whether or not the application is complete enough to allow for Agency action. Although you claim that your case differs from that in Docket 91E-0491 cited in your request, the critical fact in that case was that the applicant had not submitted enough information for FDA to take action, and the NDA was incomplete upon filing. Similarly, in your case, although the Pradaxa NDA was submitted in modules, and review and communication about the modules occurred before and after the December submission and after the RTF letter, your application was not sufficiently complete for Agency approval action until the complete final module was received April 19, 2010. The Pradaxa application was sufficiently complete on April 19, 2010, to permit a substantive review.

The policy basis for FDA's interpretation of the "initially submitted" provision is stated in our January 27, 1994, response to Fox, Bennett & Turner (Docket 91E-0491):

> FDA finds that limited inquiries by the Agency regarding information contained in an incomplete application do not constitute substantive review and hence will not support a claim that an NDA was "initially submitted" for purposes of patent term extension. This decision reflects important policy considerations. Even an application lacking crucial information required by the statute, regulations, or FDA presubmission communications with the applicant, might contain information capable of some preliminary probing by the agency. If the agency's preliminary discussions with an applicant about material submitted prior to the submission of a complete application were determinative of the "initially submitted" date, applicants would have the incentive to submit deficient applications in order to shorten the testing phase of the regulatory review period. In addition, FDA could be forced to choose between doing business less efficiently (i.e., defer all inquiries regarding information in a submission even when resources are available to make such initial inquiries), or risk affecting patent rights inequitably. Therefore, FDA concludes that it would be a misreading of 21 CFR 60.22(d) to deem an application initially submitted whenever the Agency makes limited inquiries regarding certain information in the submission.

This policy justification for FDA's interpretation applies very clearly here. FDA sought to work with BI to expedite review of this application and, as noted, FDA's continued review of the application modules that were sufficiently complete allows for efficiency in the review process as

intended by the rolling review process.[5] When BI submitted the final, clinical data, module of the application to FDA, FDA found that there were obvious errors in the data submitted. BI did not disagree and subsequently resubmitted the application after it had completed a data quality review to assure that such errors would no longer be found. Accepting that BI was moving as expeditiously as possible to submit the necessary data to FDA, it appears that the first date on which BI was able to provide a clinical data module that had been subjected to the necessary data quality checks was April 19, 2010. Certainly BI should not now benefit from having submitted a clinical data module on which it had failed to complete required data quality checks in December 2009. Because the application that BI submitted prematurely in December 2009 was not sufficiently complete that FDA could have commenced its review of all parts of the application, it is not appropriate to conclude that the application was "initially submitted" within the meaning of 35 U.S.C. 156(g) at that time.

V. CONCLUSION

FDA received your request for reconsideration and revision of the determination of the regulatory review period on June 28, 2012, before the comment period closed July 2, 2012. Consequently, your request for revision and recalculation of the regulatory review period for Pradaxa is considered timely. FDA has reviewed its records and the determination of the regulatory review period for Pradaxa (dabigatran etexilate mesylate) U.S. Patent No. 6,087,380 filed by BIPI under 35 U.S.C. 156 *et seq.* published in the *Federal Register* of May 3, 2012, and FDA affirms that the date of the resubmission of the application correctly represents the NDA "initially submitted" date in the determination of the regulatory review period as previously published. No revision is required.

Sincerely yours,

for Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

[5] Further information about the rolling review process can be found in *Guidance for Industry — Expedited Programs for Serious Conditions — Drugs and Biologics,* May 2014. Available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.