

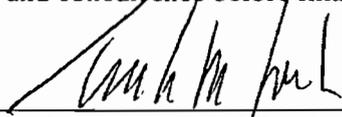
**Report to Congress**

**FDA Amendments Act of 2007  
Section 914(b) Public Law 110-85**

**Encouraging Early Submission of  
Citizen Petitions and  
Petitions for Stay of Agency Action**

**Department of Health and Human Services  
Food and Drug Administration  
February 2009**

Submit to HHS for review and concurrence before final signature:

  
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Acting Commissioner of Food and Drugs

Date 02/09/2009

## **Statutory Requirement**

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). Section 914(b) of Title IX of FDAAA, entitled Encouraging Early Submission of Citizen Petitions and Petitions for Stay of Agency Action states the following:

Not later than 1 year after the date of enactment of this Act, the Secretary of Health and Human Services shall submit a report to the Congress on ways to encourage the early submission of petitions under Section 505(q).

### **I. BACKGROUND**

#### **A. Citizen Petitions and Petitions for Stay of Agency Action**

Citizen petitions are a vehicle that stakeholders outside of the Food and Drug Administration (FDA or the agency) can use to ask the FDA to take (or refrain from taking) an action. Citizen petitions can pertain to any products regulated by FDA but for purposes of this report, we refer only to citizen petitions pertaining to prescription drugs. Citizen petitions can ask the agency to take a broad range of actions, for example to:

- remove a drug from the market;
- disapprove a drug product application;
- add warnings to a drug's label; or
- change products from prescription to over-the-counter status.

FDA regulations provide the opportunity for any interested person to file a citizen petition requesting FDA "to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action" (21 CFR 10.25 and 10.30). A petition can also be submitted to stay (delay) the effective date of any administrative action (21 CFR 10.35). Both citizen petitions and petitions for stay of agency action will be collectively referred to as "petitions" throughout this report.

FDA responds to each petition it receives with a letter to the petitioner. FDA also responds to more than one related petition in the same letter. Responses to petitions are considered final agency action that can be challenged in court (21 CFR 10.45). Therefore, to successfully defend its action, FDA must have adequate administrative records to demonstrate that its decision to deny or grant the petition has not been arbitrary or capricious.

#### **B. Section 505(q) Petitions**

Section 914 of FDAAA added Section 505(q) to the Federal Food, Drug, and Cosmetic Act to govern FDA's treatment of certain petitions and related applications for drug approval.

- Under Section 505(q), FDA cannot delay approval of a pending abbreviated new drug application (ANDA) or 505(b)(2) application because of the issues raised in a petition, unless FDA determines that a delay is necessary to protect the public health.
- Even if such a determination is made, FDA must take final action on a 505(q) petition within 180 days of submission and cannot extend this deadline for any reason.
- FDA may deny a 505(q) petition at any time if it determines the petition was submitted with the primary purpose of delaying approval of an ANDA or 505(b)(2) application *and* the petition does not obviously raise valid scientific or regulatory issues.
- In addition, 505(q) petitioners must include certifications regarding the inclusion of all information upon which the petition is based, the inclusion of unfavorable data and information, steps taken to ensure unfavorable information was disclosed to the petitioner, the timing of receipt of information upon which the petition is based, and the persons or organizations who paid the petitioner for filing the petition.

### **C. Petitions That Have the Effect of Delaying Approval of Applications**

FDA welcomes the submission of material information that can help inform its decision on the appropriate standards to employ in the review of a particular ANDA or 505(b)(2) application. The agency believes it is the desire of Congress that this information be submitted in a timely manner, i.e., as early as possible so that relevant information can be considered in the review of applications while not necessarily delaying the approval of ANDAs and 505(b)(2) applications. By enacting 505(q), Congress has clearly indicated a desire that subject citizen petitions not be employed as a means to delay approval of these applications. Of particular concern to FDA are petitions falling under 505(q) that contain no new important and material evidence, especially when these are submitted shortly before the FDA would otherwise be ready to approve an ANDA or 505(b)(2) application.

Over the years, FDA has received numerous petitions asking the agency not to approve particular ANDAs or 505(b)(2) applications (or ANDAs and 505(b)(2) applications for an entire class of drug products), unless certain criteria set forth in the petition are met. In most cases, the petitions raise scientific issues relating to the standards for approval of the applications. For example, a citizen petition may suggest an alternative method for determining bioequivalence. When submitted early, such as at the time FDA is developing bioequivalence recommendations for generic drugs, or before FDA has received the first ANDA, a citizen petition containing material information may assist the agency in establishing standards for ANDAs.

Prior to the passage of FDAAA, FDA reviewed several years of data regarding petitions. Between October 1, 2003, and September 30, 2006, (fiscal years (FY) 2004 to 2006), FDA's Center for Drug Evaluation and Research (CDER) received a total of 213

petitions.<sup>1</sup> Of these, approximately one third were petitions that presented a scientific or legal challenge to the approval of ANDAs or 505(b)(2) applications.<sup>2</sup> As part of its review, FDA looked at *first-time generic drug approvals* — a high priority for the agency and frequent target of challenging petitions — during FY 2005 and identified a number of examples of petitions that were submitted shortly before the date on which approval of a relevant ANDA was otherwise anticipated (i.e., due to expiration of patent or exclusivity for the innovator drug):

- On January 28, 2005, FDA approved the first ANDA for a fentanyl transdermal patch. Four petitions were submitted in the 5 months preceding this action — the last on December 7, 2004.
- On April 18, 2005, FDA approved seven ANDAs for anagrelide capsules. Two petitions were submitted in the 8 months preceding these actions.
- On May 13, 2005, FDA approved three ANDAs for doxycycline hyclate. The innovator submitted six petitions between July 10, 2002, and November 19, 2004.
- On September 13, 2005, FDA approved the first ANDA for leflunomide tablets. The innovator submitted a petition on March 31, 2005.

In all of these cases, the innovators opposed approval of the relevant ANDA based on arguments relating to bioequivalence. Many of the petitions contained data that had been available to the petitioner well before the date of the petition and involved theoretical arguments offered without full knowledge of the data actually submitted in the ANDAs. The contents of pending applications are confidential. All of these petitions were denied. The associated ANDAs were approved at the same time the agency issued responses denying the citizen petitions. The petition responses explained the reasons for the denials, including the basis for the agency's conclusions that the related applications met the applicable statutory and regulatory requirements for approval.

## II. INITIATIVES TO ENCOURAGE EARLY SUBMISSION OF 505(q) PETITIONS

Prior to the passage of FDAAA, FDA developed several initiatives that may be useful for either encouraging the early submission of 505(q) petitions directed at approval of ANDAs or possibly reducing the number of such petitions. Some of these initiatives have been implemented, but others are still under consideration.

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<sup>1</sup> This total does not include ANDA suitability petitions and petitions pertaining to over-the-counter monographs. It should be noted that not all petitions included in this review would necessarily have qualified as "505(q)" petitions had they been submitted after the passage of FDAAA.

<sup>2</sup> FDA also reviewed petition *responses* issued from FY 2002 to FY 2006. Each response may address more than one petition. Of the 45 responses issued during that period, 35 were denied. Seven were granted, but did not alter the course the agency would have otherwise taken. Only three petitions actually resulted in a change by the agency in its criteria for reviewing affected ANDAs; these petitions were similar in that they contained new scientific data.

## **A. Petitions Raising Bioequivalence Issues**

Approximately 50 percent of the citizen petitions that were submitted between FY 2004 and FY 2006 seeking to delay or block the approval of an ANDA raised issues associated with bioequivalence studies that are required for approval of most ANDAs. In the past, such petitions have frequently been submitted long after ANDA applicants have conducted their bioequivalence studies for the drug under consideration.

### ***Recently Implemented Process for Product-Specific Bioequivalence Recommendations***

FDA believes that if the type of information related to bioequivalence criteria that has been included in these petitions seeking to block or delay the approval of an ANDA had been made available to the agency earlier, it could have been considered in the development of bioequivalence recommendations when it would have been most useful to industry and would not delay action on applications. Therefore, FDA has developed a process for seeking public comment on product-specific bioequivalence recommendations.

On May 31, 2007, FDA announced in the *Federal Register* the availability of a new draft guidance document that describes its new procedures to streamline the process for making guidance available to the public on how to design product-specific bioequivalence studies. Product-specific bioequivalence recommendations are now being developed and posted in draft on the CDER Internet Web site.

When FDA issues a draft guidance on how to conduct a bioequivalence study for a particular drug, FDA welcomes comments on the draft guidance. These draft guidances provide a public forum where issues pertaining to the bioequivalence standards for a particular drug product may be raised. The Internet site for these draft guidances is: <http://www.fda.gov/cder/guidance/bioequivalence/default.htm>. If anyone has concerns about a draft guidance, FDA anticipates that these concerns will be raised by the submission of comments to the draft guidance. In this way, concerns may be raised early in the development process of generic drugs. FDA considers comments on product-specific bioequivalence recommendations in developing final bioequivalence recommendations. It is hoped that persons who, in the past, may have submitted citizen petitions as a means of raising bioequivalence issues will use the guidance procedures under 21 CFR 10.115. FDA believes that these product-specific bioequivalence recommendations are a very important means to permit the timely and full consideration, including the opportunity for public comment, of scientific issues that are often raised in petitions submitted late in the application review process that may delay ANDA approvals.

### ***Brief Response to Petition Raising Bioequivalence Issues***

One potential additional approach to encouraging the early submission of petitions would be for FDA to consider issuing only a brief response to a petition raising bioequivalence

issue(s) for a particular drug product when the specific criteria addressed in the petition relate to issues addressed in product-specific bioequivalence guidance issued by the agency. For example, if appropriate, FDA may issue a brief response to a petition raising a bioequivalence issue if:

- a draft bioequivalence guidance was published for that drug product and the issue(s) raised in the petition was/were not submitted as comment(s) to the draft guidance, or
- the petition is submitted more than a certain number of days after FDA publishes final guidance on bioequivalence studies for that drug product.

The rationale for such an approach is that the petitioner already had an opportunity to raise these issues in the context of a proposed product specific guidance. Whether or not anyone raises an issue in the context of a bioequivalence guidance, where someone disagrees with FDA's bioequivalence recommendations issued in a final guidance and chooses to raise those issues in a petition, the objections can be raised shortly after the publication of a final guidance because the petitioner should have been aware of both the draft and the final guidance. An exception to this could be if the petition contains material new information not previously considered by the agency.

#### **B. Petitions Submitted After Filing of a Paragraph IV Certification**

The petitioner often has notice of the submission of an ANDA or 505(b)(2) application for a particular drug when the applicant submits a paragraph IV certification, i.e., a certification with respect to a particular patent that the patent is invalid, unenforceable, or will not be infringed by the applicant's ANDA or 505(b)(2) application. An applicant must notify the new drug application (NDA) holder (and patent owner) of any paragraph IV certification. The notice is required to contain a detailed description of the legal and factual basis for the assertion by the applicant that the patent is invalid, unenforceable, or not infringed. FDA statistics from FY 2004 to FY 2006 indicate that over 40 percent of all petitions challenging the approval of an ANDA (1) pertain to ANDAs containing a paragraph IV certification and (2) were submitted after notification of the paragraph IV certification. Often, these petitions are not filed until well after there is notice of a paragraph IV certification and have the effect of delaying approval of the ANDA or 505(b)(2) application while the agency assesses the merit of the petition and develops its response.

#### ***Web Site with Information on Paragraph IV Certifications***

FDA has already made important information about paragraph IV certifications available on its Web site: <http://www.fda.gov/cder/ogd/ppiv.htm>. On this site, applicants and innovators can find a list of all drugs for which a paragraph IV certification has been filed and the date the first substantially complete ANDA containing such a certification was filed.

### ***Agency Response Based on Timely Filing of Petition After the First Paragraph IV Certification***

Another possible means to encourage the early submission of 505(q) petitions that involve ANDAs with paragraph IV certifications — or more precisely, discourage their late submission — is to establish a policy under which FDA may, if appropriate, issue only a brief response to a petition that raises any issues pertaining to the approval of an ANDA if the petition is submitted more than a certain number of days after the filing of the first substantially complete ANDA using a particular listed drug as the basis of its submission and containing a paragraph IV certification. Again, a possible exception that FDA could invoke would be situations where the agency determines that a petition contains material new information not previously considered.

### **III. POTENTIAL STATUTORY IMPEDIMENTS TO IMPLEMENTATION OF SUGGESTIONS**

In section II of this report, FDA suggests possible approaches for issuing brief responses to petitions that the agency believes may be developed to encourage the early submission of petitions. It is also noted that Section 505(q) describes specific circumstances in which FDA may issue a summary denial of a petition and recognizes that this provision is not likely to be applicable often.

As described in section I.B of this report, Section 505(q)(1)(E) describes situations where FDA may summarily deny a petition submitted with the primary purpose of delaying approval of an ANDA or 505(b)(2) application (i.e., if the agency determines the petition was submitted with the primary purpose of delaying approval of an application *and* the petition does not obviously raise valid scientific or regulatory issues). We believe the statutory language requires that both preconditions be present. Therefore, FDA may summarily deny a petition subject to Section 505(q)(1)(E) only if the petition does not on its face raise valid scientific or regulatory issues. FDA believes this statutory standard would be extremely difficult to meet. Although a petition may not raise persuasive scientific or regulatory issues when those issues have been reviewed by FDA, a petition can easily raise valid scientific or regulatory issues.

FDA could issue guidances describing petitions filed under certain circumstances that would give rise to the presumption that a petition was filed with the primary purpose to delay approval of an ANDA or 505(b)(2) application. However, given the statutory standard in 505(q)(1)(E) for summary denial of petitions, the agency does not believe issuing a guidance on delay would allow the summary denial of petitions under this provision. Without any significant impediment to filing a late petition, such as summary denial, it may be difficult to encourage the early submission of petitions under 505(q).

Finally, if FDA was able to issue a summary denial or brief response to a petition, the agency would still want to have an adequate internal record that the merits of any

relevant substantive issues had been addressed in the consideration of affected applications.

#### IV. CONCLUSION

FDA has had 1 year of experience implementing Section 505(q) of FDAAA. The agency believes it is too soon to determine whether petitions that may delay approval of an ANDA or 505(b)(2) application are being discouraged overall. The requirement to respond to petitions within 180 days may have this effect without further action. This provision may also have some unintended consequences. For example:

- Many 505(q) petitions have been filed by companies that hold ANDA applications or have applications pending before FDA, rather than by innovator companies that hold the NDA referenced by an ANDA or 505(b)(2) applicant. These petitions raise issues about the standards for approval for applications that, if approved, might compete with the petitioner's approved or pending application.
- Petitions that are filed early may not be subject to 505(q) and its 180-day response deadline because, when the petition is submitted, an ANDA or 505(b)(2) application may not be pending.
- Early response to one petition may give rise to a new petition raising additional issues or a petition for reconsideration. These new petitions could cause additional work and delay approval of ANDAs or 505(b)(2) applications.

Therefore, FDA intends to closely monitor the petitions filed under Section 505(q). The agency's goal is to develop a legally sustainable approach to discourage petitions that do not raise new and material scientific issues and that have the effect of delaying approval of ANDAs or 505(b)(2) applications.

Section 505(q)(3) also requires FDA to submit an annual report to Congress providing relevant data on petitions covered by the new Section 505(q) provisions and whether these petitions have delayed approval of pending ANDAs or 505(b)(2) applications. The agency intends to submit the annual report required by Section 505(q)(3) separately in the next few months so that the report can contain data covering the entire FY 2008.