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Phone: +1 646 783 7100 | Fax: +1 646 783 7161 | customerservice@law360.com

Dissecting The Rules Of Generic Drug User Fee Amendments

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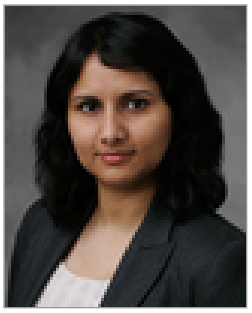

Suchira Ghosh

The Generic Drug User Fee Amendments (GDUFA), which were enacted as part of the comprehensive U.S. Food and Drug Administration Safety and Innovation Act (FDASIA) in July 2012, changed the practice of generic drug sponsors in a multitude of ways, most notably, the requirement of various types of fees associated with the filing of an application for approval of a generic drug with the FDA.

The GDUFA also sets forth various other requirements intended to improve the efficiency and quality of the generic drug approval process. Certain requirements directed at manufacturers of drug substances used in generic drug products should be anticipated by generic drug sponsors because they may impact whether an abbreviated new drug application (ANDA) will be filed by the FDA.

These requirements should be top of mind for ANDA filers because they may ultimately impact a generic applicant's eligibility for the coveted six-month marketing exclusivity.

GDUFA Requirements for Type II API DMFs

Specifically, the GDUFA subjects manufacturers of active pharmaceutical ingredients (API) used in generic drug products to requirements related to the filing of drug master files (DMFs). DMFs are typically submitted by manufacturers of API, packaging materials and excipients, and contain confidential information related to manufacturing processes, controls, components or study data. The GDUFA applies only to "Type II API" DMFs, which describe API manufacturing and controls that are referenced in generic drug submissions.

Under the GDUFA, type II API DMF holders are required to pay a one-time fee when an ANDA or prior approval supplement references their DMF for the first time after Oct. 1, 2012. That fee is $21,340 for fiscal year 2013 and can be paid by the DMF holder or ANDA applicant.

The GDUFA also requires that a DMF referenced in an ANDA be "available for reference," meaning that it has both paid a DMF fee and passed a "completeness assessment." The FDA identifies all DMFs that are available for reference in support of a generic drug submission on a publicly available website, which the agency updates generally at the end of each week.
This published information encourages potential ANDA applicants to utilize the API sourced from one of these suppliers and may also suggest that an ANDA filing based upon one of these API may be imminent.

The completeness assessment is not a complete review of the DMF, which still must be completed successfully in order for an applicant to receive final FDA approval of its ANDA. But the completeness assessment is more than simply an administrative review of parts. It is an initial review — akin to an ANDA filing review — performed by a DMF chemistry reviewer in the Office of Generic Drugs to ensure that the DMF contains the required administrative and scientific elements to permit a complete scientific review (as set out in an October 2012 FDA guidance on type II API DMFs).

Any deficiencies identified by the FDA during a completeness assessment that must be remedied are communicated to the DMF holder via a DMF incomplete letter. Given the newness of this initial DMF assessment — which did not exist prior to the GDUFA — and the possibility that DMF holders did not regularly provide such information as part of their earlier filings, there are some risks in an ANDA applicant assuming that another company's compliance with these GDUFA requirements will be quick or easy.

Timing the DMF and ANDA filings

The timing of successful completion of the completeness assessment is critical to an ANDA applicant. The agency will refuse to receive the ANDA for technical reasons if the DMF has not passed the completeness assessment by the time the agency makes a decision on whether or not to accept filing of the ANDA, which usually occurs within 60 days of submission of the ANDA, resulting in a partial refund (75 percent) of the application fee. An applicant may refile its ANDA, paying the application fee in full again, but the applicant may have potentially lost "first applicant" status by that point.

Where a drug product upon which the ANDA relies, i.e., the reference-listed drug, is associated with Orange Book-listed patents, the first generic applicant to file a substantially complete ANDA containing a paragraph IV certification to at least one of the listed patents will be considered a "first applicant" eligible for the six-month generic marketing exclusivity under the Hatch-Waxman Act.

During this period, no other ANDA applicant will be permitted to market its ANDA product with the exception of any other first applicants. Thus, first applicant status is critical to generic sponsors and hinges upon being one of the first to file a complete ANDA with the FDA.

Once an ANDA is submitted to the FDA, the agency will initially review the ANDA to determine whether it is sufficiently complete to undertake a substantive review. If so, the application is deemed acceptable for filing, with an official filing date assigned that is usually the date the application was submitted if the application was deemed complete at the time it was filed. This official filing date determines which applicants are first to file for exclusivity purposes.

Accordingly, a generic applicant that relies on a type II API DMF in its submission must ensure that the DMF holder has satisfied GDUFA requirements to be assured that their ANDA will even be received by the FDA. Although the agency has stated that fees, including the DMF fee, are incurred on the date that the first generic drug submission referencing the DMF is submitted, the DMF fee should nevertheless be paid in advance of this if the DMF is not already available for reference.

This is because the DMF fee must be paid in order to even put the DMF in queue for a completeness assessment, and the completeness assessment must be successfully completed by the time the FDA renders a filing review decision in order for the ANDA applicant to receive filing acceptance.

There is no guarantee that a completeness assessment can be satisfactorily completed within the ANDA filing review window. An even more risky scenario occurs when the ANDA is filed before a DMF fee has even been paid. In this situation, the applicant runs a greater risk that a completeness assessment may not be successfully finished by the time the ANDA filing review window has closed.

Additionally in this situation, failure to pay the DMF fee within a 20-day grace period following notification by the FDA will result in a refusal to receive the application until the outstanding fees have been paid; payment outside of this grace period will reset, i.e., delay, the official filing date of the ANDA to the date that all outstanding fees were satisfied.

Although there is no time line by which the agency must finish a completeness assessment, the FDA has recommended that the DMF fee be paid at least three months in advance of submitting the ANDA. And while the agency will hasten completeness assessments for expedited applications, the FDA has requested even more advance payment for expedited ANDAs.

Although the FDA has indicated that it intends on coordinating completeness assessments to avoid loss of first applicant status, there is no guarantee that completeness assessments will be completed (with a positive outcome for the DMF holder, no less) within a set time period. Only where a DMF is already available for reference prior to an ANDA filing can the applicant be assured that DMF status will not bar filing acceptance.

Ultimately, an applicant seeking 180-day marketing exclusivity must communicate with its API supplier, early and often, as well as the FDA, in order to properly time the filing of its application to avoid a refusal to receive based on an incomplete or inadequate completeness assessment where the DMF is not already available for reference, as well as to avoid partial loss of the application fee and potential loss of first applicant status.

Where the earliest ANDA filing may only take place on the "new chemical entity-1" date (i.e., the date the four-year period after the FDA has granted new chemical entity exclusivity for a drug product has elapsed), the deadline by which a type II API DMF must be available for reference is clear. In non-NCE situations where the DMF is not already available for reference, ensuring that the DMF undergoes a completeness assessment in timely fashion may require more coordination between the API supplier and ANDA sponsor.

Furthermore, sponsors should not ignore the fact that deficiencies identified by the FDA during a completeness assessment may potentially impact the filing of an ANDA and therefore must be expediently addressed where an ANDA filing is planned. Even where first-applicant status is not relevant, the consequences for referencing an unavailable DMF may be the FDA’s refusal to receive the ANDA and partial loss of the application fee.

Given these reasons, ensuring that a DMF is available for reference is as important to an ANDA sponsor as timing the filing of its own application.

--By Suchira Ghosh, Axinn Veltrop & Harkrider LLP

Suchira Ghosh is an associate in the firm's New York office.