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FDA User Fee Act Full of Surprises for Pharma and Biotech

FDA user fee reauthorization law expands fees to include generic and biosimilar applications, and includes a new emphasis on drug supply chain safety and incentives for development of new therapies.

The enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) stands to have significant impact on the pharmaceutical and biologics industries. Signed into law by President Obama on July 9, FDASIA reauthorizes and amends the existing user fee statute for drugs, the Prescription Drug User Fee Act (PDUFA), and establishes two new statutes, the Generic Drug User Fee Act (GDUFA) and the Biosimilar User Fee Act (BsUFA), that set out fee structures for generic drugs and biosimilars, respectively.

The following identifies a few of the more significant potential effects of FDASIA on industry.

User Fees

Pharmaceutical User Fee Reauthorization

Under FDASIA, the drug industry will pay an estimated $700 million to support FDA's review of drug applications for fiscal years 2013-2017.

Biosimilars Product Development Fees: Could Affect Timing of Biosimilar Product Development

Through BsUFA, FDASIA authorizes the collection of fees for biologic products licensed through the new biosimilars pathway. The rates for application, product, and establishment fees are equal to the PDUFA rates for those fees. A separate biosimilar product development fee equal to 10% of the PDUFA application fee also was added.

The structure and timing of the product development fees are particularly interesting and may affect the strategic planning of smaller companies with less access to funding. An initial product development fee is due by the earlier of (i) five days of being given a date by FDA for a meeting involving the review or discussion of clinical data or (ii) submission of an Investigational New Drug Application (IND). Once the initial product development fee is paid, an annual biosimilar biological product development fee must be paid each year until the product application is filed, unless the development of the product is terminated and any INDs are withdrawn (not made inactive). Companies that fail to pay the requisite development fees can be placed on "financial hold" (distinguished from clinical hold). This status will become public information and could affect the valuation of a company.

This new fee payment schedule could impact the timing for initiation of the development process and cause companies to delay contacting FDA until adequate and sustainable revenues are available. The payments could also affect the triggering of payment milestones in licensing transactions and the timing of venture capital investment in biosimilar companies. The new fees for meetings and IND submissions, which are not currently in place for New Drug Applications (NDAs) or Biologics License Applications (BLAs), may signal a potential new source of revenue for FDA in future user fee statute negotiations with industry.

Generic Drug User Fees

FDASIA provides for the collection of user fees for engaging in "human generic drug activities," which include issuance of approval letters, complete response letters, review of active ingredient drug master files, inspections, research monitoring, postmarket safety (AEs) and postapproval studies or REMS, or regulatory science activities (this last activity is not defined). Under GDUFA, the generic drug industry would pay approximately $1.5 billion over five years in exchange for FDA's faster and more predictable review of generic applications and increased inspections of generic drug facilities. Of particular interest, GDUFA establishes fees for the following:

- Owners of drug master files (a one-time fee) (see below)
- Abbreviated New Drug Applications (ANDAs) and ANDA prior-approval supplements
- Facilities that manufacture both finished drug products and active pharmaceutical ingredients used in generic drugs (an annual fee)

Drug Master File Fees Could Affect Timing of ANDA Filings

As part of GDUFA there are now fees for review of Type II Drug Master Files (DMFs) for active ingredients referenced in ANDAs. The law provides a somewhat expanded definition of "active pharmaceutical ingredient" (API), providing that API also includes "a substance intended for final crystallization, purification or salt formation or any combination of these activities to become the final API." This expansion may mean that manufacturers of late-stage intermediates will have to pay a facility fee for the intermediate and for the Type II DMF, if applicable.

There are a number of new requirements that accompany the Type II DMF user fees, including the following:

- Each person that owns a Type II DMF that is referenced on or after October 1, 2012, in a generic drug submission by any initial letter of authorization will pay an annual fee.
- In order to be referenced in an ANDA, each Type II DMF holder will need to have paid the user fee and not failed an initial completeness assessment of the DMF as defined by FDA.
- Facilities that produce both active ingredients subject to DMFs and finished dosage forms must pay both user fees.
- FDA intends to list publicly all DMFs that have satisfied an initial completeness assessment and paid the relevant fees.
- DMF fees must be paid no later than the date on which the first generic drug submission is submitted that references the DMF.

The new DMF fees may cause substantial disruption and/or consolidation in the API industry and affect the timing of the generic drug development and review process. API supply contracts should be reviewed and revised to reflect requirements for prompt fee payments.

The penalties for noncompliance with these new user fee requirements are significant, and have the potential to impact a company's full line of products. For instance, failure to pay Type II DMF fees will result in a determination that the DMF is not available for reference by ANDAs, effectively blocking formal receipt by FDA of any ANDA referencing that DMF. Likewise, failure to pay an application fee under GDUFA within 20 calendar days of the due date will result in the application not being formally filed by FDA until the fee is paid. Worse still, failure to pay facility fees under GDUFA can result in all products at the relevant facility (including both drugs and APIs manufactured in the facility or containing an ingredient manufactured in such facility) being deemed misbranded. By establishing this new fee requirement for Type II DMFs, FDA may be setting a precedent for a potential new source of revenue in future user fee negotiations (i.e., user fee statute reauthorizations in the future may include fees for other types of DMFs).

Emphasis on Safety of Supply Chain, Inspection, and Enforcement

Registration and listing requirements are expanded under FDASIA. The law now requires the following:

- Registrants must provide a unique facility identifier and point-of-contact email address for each facility.
- Foreign facilities must register and list with FDA or face a determination that their products are misbranded (and thus not eligible for U.S. import).
- Establishments manufacturing drug excipients must register and list.
- All drug importers must register.

FDASIA also empowers FDA to require electronic submission of drug information for importers as a condition of granting entry of their products into the United States, and requires FDA (once the agency has specified a unique facility identifier system) to ensure that its databases are adequate to facilitate risk-based inspections.

This broadened emphasis on more effective inspection imposes more robust record-keeping requirements on manufacturers, requiring that establishments provide (in either electronic or physical form), in advance or in lieu of inspection, records that FDA has requested. As a component of each request to manufacturers, FDA must "include a sufficient description of the records requested," arguably leaving room for manufacturers to tailor responses to such requests as narrowly as possible.

Enhanced Enforcement Powers to Detect and React Quickly Against Adulterated or Counterfeit Drugs

FDASIA expands FDA's tools for inspection and related enforcement, allowing FDA to take the following actions:

- Destroy counterfeit or adulterated imported products.
- Detain (i.e., through administrative detention) drugs found during inspection to be adulterated or misbranded.
- Bar entry of imported drugs from an establishment deemed to have delayed, limited, or denied an inspection.
- Take into account the results of inspections conducted by parallel foreign regulatory authorities.
- Deem failures of quality controls in manufacturing and assurance of raw material safety to be violations of good manufacturing practices (GMPs) and a basis for an adulteration violation.
- Require notification if a regulated party (which could include distributors) knows that the use of a drug could lead to serious injury or death, or if a drug is stolen or has been counterfeited.
- Assess higher penalties for (1) knowingly and intentionally adulterating a drug, where that drug has a reasonable probability of causing serious adverse health consequences or death (up to 20 years' imprisonment or a fine of up to $1 million); (2) engaging in activities related to knowingly and intentionally forging and/or counterfeiting drugs, including selling and dispensing (up to 20 years' imprisonment or a fine of up to $4 million); and (3) trafficking counterfeited drugs (criminal penalties).

Improving Patient Access and Incentivizing Innovation for Serious Diseases

FDASIA includes provisions intended to spur innovation and emphasize FDA's continued focus on serious or life-threatening diseases, orphan populations, and patient access, by doing the following:

- Providing priority review vouchers to sponsors of drugs for rare pediatric diseases. These vouchers may be of considerable commercial value to biotech and small drug companies, as the vouchers can be used for a subsequent application and are transferrable by the sponsor.
- Mandating consultation with stakeholders from the rare disease community and with external scientific and medical experts.

- Broadening the qualification for designation as "fast-track products" by including products intended for a "serious or life-threatening **disease** or condition" (not just those intended for a "serious or life-threatening condition," as was previously provided).
- Expanding the scope of available endpoints that can be used to support accelerated approval.
- Requiring that FDA establish a program to encourage the development of surrogate and clinical endpoints (e.g., biomarkers) that can help to predict a product's clinical benefit in treating serious or life-threatening conditions for which significant unmet medical needs exist.
- Allowing FDA to withdraw expedited approval of fast-tracked products for a variety of violations, including the dissemination of false and misleading promotional materials about such a product.
- Reauthorizing the Orphan Products Grant Program through 2017.
- Providing for limited reporting of certain information related to product shortages.

The valuation and marketing of priority review vouchers will introduce new negotiating opportunities and leverage into corporate transactions and licensing deals. Likewise the introduction of consumer stakeholders into the FDA consideration of product approvals is likely to prompt discussions about and media attention on product cost and potential reimbursement (topics FDA normally does not consider and sponsors avoid during the approval stage).

Pediatric Studies and Exclusivity Are Here to Stay

FDASIA permanently reauthorizes the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), which, prior to FDASIA's enactment, were subject to reauthorization every five years. Thus, the additional six months of exclusivity granted under BPCA, and FDA's ability to require pediatric studies, have been made permanent. It also requires studies in neonates or a rationale why such studies are not necessary. Failure to meet pediatric study or reporting requirements will result in the product being misbranded.

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