Impact of GDUFA II Fee Structure on Generic Drug Change Evaluation

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Executive Summary

GDUFA II will become effective on October 1, 2017, bringing significant changes in the user fee structures that are designed to provide more predictable agency revenue, further reduce review cycle times, and simplify the financial impact on the industry. The new fee structures will either alter or abolish certain fees that may have created impediments to manufacturing changes for generic drug companies, thus revising the assessment process for such changes. GDUFA II fee structure changes may now provide incentives for generic drug companies to pursue manufacturing upgrades that may have previously been prohibitive.

Scope

This paper addresses upcoming changes to the fee structures under GDUFA II and their potential impact to generic drug manufacturers who are evaluating potential Quality changes to their products.

This discussion focuses on generic drugs in the US market, both those to be submitted for approval to the FDA, and marketed generic drugs which may require major post-approval changes. This discussion does not cover issues related to regulatory assessment of proposed changes to either pending or approved ANDAs.

Glossary of Terms

ADUFA:	Animal Drug User Fee Act	GDUFA:	Generic Drug User Fee Act
AGDUFA:	Animal Generic Drug User Fee Act	MDUFA:	Medical Device User Fee Act
ANDA:	Abbreviated New Drug Application	PDUFA:	Pharmaceutical Drug User Fee Act
BSUFA:	Biosimilar Drug User Fee Act		

Background

When the first Generic Drug User Fee Act (GDUFA I) was implemented in 2013, The US FDA was experiencing a very large backlog of ANDAs and associated post-approval submissions. GDUFA I introduced user fees into the generic drug application process, in much the same way as other user fee acts have been put in place in the US for branded pharmaceuticals and biopharmaceuticals (PDUFA, first passed in 1992[1]), branded animal drugs (ADUFA, 2003[2]), medical devices (MDUFA, 2007[3]), generic animal drugs (AGDUFA, 2008[4]), and biosimilars (BSUFA, 2012[5]). The introduction of user fees has provided the FDA with an increased, reliable revenue source that allows for increased agency resources. In turn, the agency has committed to performance goals to optimize review cycle times and minimize potential review backlogs.

The FDA reported[6] that it expected to receive approximately 750 ANDAs per year under GDUFA I and instead saw about 1,000 per year for at least the first 4 years. In the final year of GDUFA I, the agency projected to spend approximately $430 million, but noted that more than $493 million is needed each year (incorporating an annual inflation adjustment) moving forward to maintain their current performance goals.

As with other FDA user fee acts, GDUFA was designed to require renewal after 5 years. Negotiations between the agency and the generic drug industry attempted to balance the needs of both parties:

- For FDA, a more consistent and reliable source of funding through the user fees to permit them to more accurately predict resource needs each year
- For the generics industry, a more simplified fee structure tied to enhanced agency performance goals to further reduce application review times.

Renewal terms were agreed upon between FDA and the Generic drug industry in 2016, and changes agreed upon for GDUFA II include:

- Modified fee structures based on newly introduced program fees, and providing relief to small businesses
- New performance goals to further reduce backlogs and review times
- Enhanced communication opportunities between generic drug applicants and the FDA

For the purposes of this discussion we'll focus on the fee structure changes.

Modifications to GDUFA Fee Structure

Program Fees

The centerpiece of the GDUFA II fee structure will be a three-tiered annual Program Fee that will be based on the number of approved ANDAs that a company holds with the FDA.

Tier	No. of Approved ANDAs	Fee
Large	> 20	Full Fee
Medium	6-19	40% of full fee
Small	≤ 5	10% of full fee

To assist the industry in this transition, FDA has compiled a list of authorized ANDA holders, listing the number of approved ANDAs held by each entity on record, to their website[7]. The intent is to give generic drug manufacturers the opportunity to confirm their total number of ANDAs, taking different corporate legal entity names into account. This process will give

manufacturers the opportunity to streamline their legal entity names, allowing them to lower the overall cost of the program fees that they will pay.

Program fees under GDUFA II will be based on the number of approved ANDAs held by a given manufacturer. Firms holding only ANDAs that are in review will not be assessed fees until an application is approved.

Application Fees

ANDA sponsors will be eligible under GDUFA II to receive a 75% refund of application fees if an ANDA is withdrawn while it is under review. The intent is to provide an incentive to manufacturers in cases when an ANDA has significant issues, thus saving them and FDA time and resource.

Facility Fees

Facility fees remain in place for both Active Pharmaceutical Ingredient (API) and Finished Dosage Form (FDF) facilities, however there will be some changes under GDUFA II. Contract Manufacturing Organizations (CMOs) will only be required to pay one-third of the FDF fee. In addition, facilities that manufacture both API and FDA will only be assessed the FDA fee, instead of both fees.

Prior Approval Supplement (PAS) Fees

Under GDUFA II, the fee currently assessed for PAS submissions will be eliminated. This was driven by the fact that the number of PAS' filed each year was too unpredictable to allow FDA to accurately forecast revenue from fee collections. In addition, the agency recognized that companies are sometimes required to file a PAS at the FDA's request, which imposed an unwarranted burden on those application sponsors.

Implications for Generic Drug Manufacturers and Change Evaluation

Evaluation of proposed or planned manufacturing changes by any pharmaceutical manufacturer must take numerous business, technical, and regulatory considerations into account. Generic drug manufacturers must especially weigh financial impacts of proposed manufacturing changes and user fees may have an outsized impact on these evaluations.

For generic drug manufacturers evaluating potential Quality changes prior to ANDA submission, the impact of GDUFA fee structure changes should be minimal. The firm may still need to perform additional testing to evaluate the impact of the change, but there should be no impact to the application fee. Depending on the change, there may be an impact to facility fees, and this must be incorporated into the company's evaluation.

The elimination of the PAS fee will have a significant impact on any generics manufacturer considering major post-approval changes to their drug products or related manufacturing processes. The impact will be even more profound in cases where a manufacturer evaluates a change that impacts several different approved drugs. Depending upon the number of affected drug products, the cost savings may be significant, since the PAS fee may have served as a disincentive to change for many manufacturers.

Example: Container Closure Changes

Changing a primary packaging component, an elastomeric closure for instance, particularly when a sterile medicinal product is concerned, would typically be expected to constitute a major regulatory change. For a generic manufacturer, such a change may be a difficult hurdle to tackle. Factoring in the current PAS fee increases the size of that hurdle and may create an insurmountable barrier to change.

This disincentive may lead generic drug manufacturers to maintain the status quo, inhibiting a proactive approach to change evaluation. In cases where a generic drug has employed older packaging components, the risk exists that current regulatory requirements may eventually surpass the component's quality limits and performance capabilities. Such situations carry the risk of inspectional issues and, in worst cases, recalls and shortages.

Easing the financial burden of prior approval supplements on generic drug manufacturers can facilitate a more proactive approach to manufacturing changes for generic drug manufacturers. In the case of a container closure component, incentive increases for the manufacturer to pursue changes to more modern components that are more likely to maintain regulatory compliance over time.

Conclusions

When GDUFA II becomes effective on October 1, 2017, it will usher in a significantly revised fee structure that is intended to simplify the generic drug submission and approval process while providing a consistent source of revenue for the FDA. The upcoming fee structure changes will include elimination of fees for submission of Prior Approval Supplements (PAS), which should create a significant impact on the generic drug industry with respect to managing manufacturing process changes.

With the elimination of a significant financial hurdle to post approval change, it should now be more feasible for generic manufacturers to pursue enhancements to their drug products and manufacturing processes. Manufacturers may be encouraged to pursue quality enhancements more proactively under GDUFA II. The result can be a greater shift from reactive to proactive methodologies can benefit both the generics industry and the patient populations depending on their medicinal products.

References

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