

Despite all the Rhetoric, Time-Consuming FDA Guidelines Make More Work for CMOs but Safe Products for Consumers

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There's been lots of talk lately about increased [safety threats](#) from new drugs hitting the market, prompting even more warning labels. This comes at a time when news outlets are reporting on an [easing of FDA restrictions](#) designed to spur increased innovation and competition, especially among generic drugs.

While new FDA changes may be occurring, it will in no way mean FDA guidelines and restrictions will be simple or less time-consuming for drug manufacturers. In fact, the FDA approval process is one of the most time-consuming, complex processes for Contract Manufacturing Organizations (CMOs) everywhere – and rightly so. FDA scrutiny ensures the safety of drugs and those that consume them and that's not going away anytime soon. This article provides an overview of issues regarding FDA compliance and the reasons it is a complex process.

There really are two major concerns that the FDA requires be proven during clinical trials: That the drug won't hurt anyone, and that the efficacy of the drug is sound. While most products that go through clinical trials are deemed safe by the FDA, there are also plenty of watchdogs, such as patient advocacy groups, politicians and medical professionals who work to ensure that any issues with both brand-name drugs and generics are documented and addressed.

One area that has seen expedited FDA approvals is for drugs seeking [Orphan Drug status](#). For small populations with an imminent need for certain drugs, the regulatory approval process can move more quickly, with smaller clinical trials.

Yet overall, the FDA approval process is still a laborious and costly activity. Tufts University's Tufts Center for the Study of Drug Development published a [report](#) that estimated that it takes \$2.558 billion to bring a new drug to market. This is based on estimated average out-of-pocket costs of \$1.395 billion and time costs of \$1.163 billion. The study also reports that drug development is lengthy—often taking longer than a decade to become commercialized. A key part of these expenses and time is the FDA approval process.

Tighter FDA Restrictions Key to GDUFA

Contrary to easing restrictions, tighter restrictions for FDA approval were established as part of the Generic Drug User Fee Amendments (GDUFA) in 2012. These were designed to speed access to safe and effective generic drugs to the public and reduce costs to the industry.

As part of GDUFA, the FDA requires regulatory filing of new entities be completed electronically in order to be more efficient, reduce costs to the government and eliminate manual, error-prone processes. From registering your site through self-identification, all submissions are done electronically. Yet the ability to navigate FDA electronic submission requirements alone, including using the Electronic Common Technical Document (eCTD) standard, has become increasingly time-consuming and difficult. Additionally, filing each chemical entity can cost from \$41,000 to \$46,000 per Drug Master File (DMF), the primary document in support of an Abbreviated New Drug Application (ANDA).

Complex Reporting Requirements

Aside from inspections and other FDA regulations, reporting alone is a time-consuming and costly process. A critical piece of technical documentation CMOs must provide is the analytical methodology used to test the drug substance. Validation reports for the methods for assay, impurities and residual solvents are included in the open portion of the DMF, along with reports on forced degradation studies performed on the drug substance. These reports demonstrate that the methodology possesses stability-indicating properties.

The DMF also includes reports on various scientific studies essential to the applicant's preparations. The first essential scientific document is a chemical description of the API impurity profile, which includes raw materials and intermediates that have the potential to carry through into the final product, as well as all possible degradants and products of side-reactions that may occur during the process. The second essential document in this category is a well-articulated and scientifically sound rationale for the manufacturing process, with special attention to the selection of the API Starting Material.

A third important report is a justification for the drug substance specifications, especially those for assay, impurities and residual solvents.

Gathering this information must be handled by the CMO, yet given the time and costs involved in submitting the data in-house, many outsource the actual formatting into the FDA-required structure to a third-party. FDA approval through e-filing doesn't end there. Under GDUFA, on the anniversary of a submission, the developer must e-file an annual report each year with updated information on their products.

So, while there may be talk of easing FDA requirements for new chemical entities, the process is by no means an easy one. Smart drug sponsors and CMOs understand that the complex process is meant to ensure safe and effective drugs that by their proven quality, safety and efficacy may not require a long list of safety warnings.

For more information on FDA processes, check out our blog [How to Get Your Organization Prepared for an FDA Inspection](#).