BIOPROCESS ONLINE

Guest Column | August 11, 2020

CBER Takes On More Oversight Of Biologic & Biosimilar Master Files

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The Drug Master File (DMF) is one of the most effective ways for companies to protect proprietary information while still collaborating with partners. A DMF is a snapshot of the manufacturing process that is submitted to the FDA to review the suitability of a drug for clinical trials (INDs) or commercialization (NDAs or BLAs).

When a DMF is submitted to the FDA, its contents are confidential. The proprietary information may only be cross-referenced — not accessed — by a partner. Under this model, the company that cross-references another company's DMF is not expected to understand and/or be able to defend the partner's process and process controls.

This year saw a significant change in the process for submitting master files for biologic products: as of March 23, 2020, biologic-related master files are now administered by the FDA's Center for Biologics Evaluation and Research (CBER).

DMFs were introduced in 1939, and both biologic and drug master files have been regulated by the FDA's Center for Drug Evaluation and Research (CDER), while CBER focused oversight on vaccines, gene therapies, and blood, tissue, and cell-derived products. This oversight was not surprising, as CDER has been responsible for overseeing well-characterized therapeutic proteins — technically biologics — since 2003.

The impetus for this change was the Biologics Price Competition and Innovation Act (BCPIA) of 2009. This statute was enacted to stimulate the development of biosimilars available at lower prices, as was successfully seen with generic drugs under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act). Although the FDA was slower than the European Medicines Agency (EMA) to adopt biosimilars, 26 products have been approved to date.

The transition of responsibility to CBER presents a number of challenges for sponsors accustomed to working under CDER.

The Process Is The Product For Biologics And Biosimilars

Except for some well-defined exceptions, biologic manufacturers may no longer cross-reference another company's DMF for drug substance, drug substance intermediate, or drug product. While this change limits opportunities for partnering, it increases potential profits if a company does not need to share revenues with a partner. The FDA expects a biologic sponsor to understand and control the entire manufacturing process. As the saying goes "the process is the product" for biologics due to the intricacies of three-dimensional molecules, where subtle differences in amino acid sequence, glycosylation, and folding of the molecule can have profound effects on efficacy and safety. The FDA's use of the term "biosimilar" indicates that large molecules cannot be replicated exactly without access to the innovator company's equipment, procedures, and intellectual property. To date, the FDA has not approved any interchangeable biosimilars permitting pharmacy-level substitution for patient-administered biosimilars.

Reclassification

Another consequence of implementing the BPCI Act is that a number of biological products previously approved as NDAs were reclassified as approved BLAs (referred to as "Deemed to be a License" products). The FDA has identified 89 products to date where oversight responsibility is being transferred from CDER to CBER.

Going forward with new products and master file submissions, communication with the FDA will be especially important given the extent of these changes. Sponsors should reach out to the FDA to confirm that a master file is appropriate for the product's intended use. For example, proprietary cell culture media can still be submitted through a Type II master file with CBER. Cross-referencing a packaging manufacturer's existing DMF may still be appropriate for a biologic drug substance or product. However, an entire drug substance manufacturing process would not be appropriate.

New Administration

For submissions, MF numbers for biologics are no longer issued through CDER's NextGen portal; instead, sponsors must submit an email request through CBER's Regulatory Information Management Staff at CBERRIMS@fda.hhs.gov, with the following information:

- Sponsor name and address
- Primary point of contact information (name, phone #, email, etc.)
- Anticipated submission date
- Biologic product name and indication
- CBER Review Office (e.g., Office of Tissue and Advanced Therapies (OTAT))

It is important to approach the right center to keep your project on track and to meet your company's goals. With open communication with the agency and careful regulatory planning, it is possible for every sponsor of biologic-related master files to successfully complete the submission.

What The DMF?! Industry And FDA

Ultimately, the change of oversight from CDER to CBER will affect all past, present, and future biologic-related master files and marketing applications/approvals. It will be interesting to observe how much CBER will honor past CDER reviews and approvals, and how much sponsors will have to re-defend already approved submissions and regulatory strategies. It also remains to be seen what the impact to approval time will be.

Fortunately, the FDA already tracks timelines to product approval as a Prescription Drug User Fee Act (PDUFA) metric. Sponsors will need to analyze this data, as well as their own experience, to provide the agency with feedback on any impact to the master file submission and BLA approval processes. This collective effort would be a great opportunity for an industry organization (e.g., PhRMA, DIA, BIO, ISPE, etc.) to step in and take the lead on federating and documenting efforts. Feedback to the FDA will allow for course correction as necessary to support continued timely approval of safe and efficacious therapies.

References:

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About The Author:

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