FDA Regulatory and Compliance Monthly Recap

OCTOBER 2017

KEY FINDINGS

FDA publishes draft guidance on statistical approaches to assessing analytical similarity of biosimilars

The guidance aims to assist sponsors in determining how to demonstrate biosimilarity when developing or submitting a marketing application for a proposed biosimilar product. It outlines the information needed surrounding the structural, physicochemical and functional attributes of a reference product and lists the requirements necessary to establish meaningful similarity acceptance criteria.

The FDA issued a draft guidance document to assist with the marketing application submission for biosimilar products. As part of the application, sponsors must include data from analytical studies demonstrating that the biological product is highly similar to the reference product. When conducting an analytical similarity assessment of quality attributes, the agency recommends using a risk-based approach. This approach consists of determining the quality attributes that characterize the reference product in terms of its structural/physicochemical and functional properties, ranking the quality attributes according to their risk of potential clinical impact, and evaluating the attributes/assays according to one of the following three tiers of statistical approaches:

- **Tier 1:** The agency recommends equivalence testing for quality attributes with the most elevated risk ranking. This should include assays evaluating the clinically relevant mechanisms of action of the product for each indication for which approval is sought.
- **Tier 2:** The agency recommends the use of quality ranges for quality attributes with lower risk rankings.
- **Tier 3:** The agency recommends the use of visual comparisons for quality attributes with the lowest risk ranking.

The guidance notes that sponsors should develop an analytical similarity assessment plan describing the lots available for similarity testing, making efforts to address all factors that could impact whether the proposed biosimilar is determined to be highly similar to the reference product.

The document makes recommendations concerning the quantity and quality of both reference product and biosimilar lots needed to evaluate analytical similarity. The agency recommends a minimum of 10 biosimilar lots be included in the analytical similarity assessment. To establish meaningful similarity acceptance criteria, the agency also recommends that a minimum of 10 reference product lots be sampled, each of which should be selected with the goal of representing the variability of the reference product. Sponsors should account for all the reference product lots available to them and should also select lots with remaining expiry spanning the reference product shelf life.

The FDA notes that applications should include a list of all lots that were evaluated in any manner — regardless of whether a particular lot was used in the final similarity assessment — along with the specific physicochemical, functional, animal and clinical studies for which each lot was used. Furthermore, in the case of biosimilar lots being manufactured with different processes, data should be provided to support comparability of any materials manufactured with the different processes and/or scales.

The FDA recommends that the analytical similarity assessment plan be developed in four stages, corresponding to the development of the risk ranking of the reference product's quality attributes based on the potential impact on the clinical performance categories, the determination of the statistical methods to be used, the development of the statistical analysis plan, and the finalization of the analytical similarity assessment plan.

The guidance goes on to state that analytical similarity acceptance criteria will ideally be derived using data from an analysis of the U.S.-licensed reference product, and the similarity assessment should be based on a direct comparison of the proposed biosimilar product to the U.S.-licensed reference product. Sponsors who wish to use data derived from products approved outside of the U.S. are encouraged to discuss their plans with the FDA prior to submitting a marketing application.

The FDA notes that the draft guidance document is being distributed for comment purposes only.

FDA finalizes guidance clarifying process for classifying combination products as drugs, biologics or medical devices

The guidance details how the FDA makes product classification decisions and addresses issues that may arise in determining whether products should be classified as drugs or devices. It also provides details about the agency's interpretation of the term "chemical action" and addresses the request for designation (RFD) process for securing a formal determination of a product's classification.

The FDA's finalized guidance places a particular focus on cases in which a combination product may be classified as a drug or device. The document stresses the importance of this classification in determining whether the sponsor needs to submit a new drug application (NDA), biologics license application (BLA), or a 510(k) or premarket approval (PMA) application.

The FDA's determination of whether to classify a product as a drug or a device is based on statutory definitions set forth in the Food, Drug, and Cosmetic (FD&C) Act. As the guidance explains, designations are based primarily on whether a product meets the definition of a medical device under Section 201(h) of the FD&C Act, since all FDA-regulated medical products conceptually meet the legislation's broader definition of "drug." The former, more restrictive definition requires that a product:

- Be an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article" that doesn't achieve its primary intended purpose via chemical action within the body. The issue of whether a product may be considered a "similar or related article" under this clause can arise, for example, with regard to products in liquid, semiliquid, gel, gas or powder form. The guidance notes that a product displays chemical actions if it interacts at the molecular level with bodily components (e.g., cells or tissues) to mediate a bodily response, or with foreign entities (e.g., organisms or chemicals) so as to alter that entity's interaction with the body;
- "Does not achieve its primary intended purposes through chemical action within or on the body of man or other animals"; or
- "[Is] not dependent upon being metabolized for the achievement of its primary intended purposes."

The final guidance features an FAQ section and two tables providing examples of products that achieve or fail to achieve their primary intended purpose through chemical action.

The guidance recommends that sponsors contact the Office of Combination Products if they wish to discuss a product for which the appropriate classification is unclear or in dispute. Also outlined is the RFD process for obtaining a formal determination of a product's classification.

The guidance brings together two 2011 draft guidances, Classification of Products as Drugs and Devices & Additional Product Classification Issues and Interpretation of the Term 'Chemical Action' in the Definition of Device Under Section 201(h) of the Federal Food, Drug, and Cosmetic Act.

FDA updates guidance on Center for Devices and Radiological Health (CDRH) appeals process

The guidance clarifies the meaning of "significant decision" within the CDRH's regulatory lexicon and explains how the regulator handles disagreements over such decisions with agency stakeholders.

The guidance notes that the documentation and review procedures required by Section 517A of the FD&C Act apply only to "significant decisions" (or "517A decisions") in the premarket review of device submissions. While the term "significant decision" isn't defined within the Act, the CDRH believes the following types of decisions should be considered as "significant":

- **510(k):** Not substantially equivalent, substantially equivalent
- **PMA/HDE:** Not approvable, approvable with conditions, approval
- **Breakthrough devices:** Granting, denial
- **IDE:** Disapproval, approval
- **Failure to reach agreement** on a protocol under Section 520(g)(7)
- **"Clinical hold" determinations** under Section 520(g)(8)

The FD&C Act also requires that a "substantive summary" of the scientific and regulatory rationale used to reach a "significant decision" for the types of submissions listed above be provided by the CDRH upon request.

According to the guidance, the CDRH considers "substantive summary" to be either the final version of the review memorandum by the lead reviewer or another summary document containing:

- An explanation of the rationale for the regulatory decision;

- An explanation regarding how the least burdensome requirements were considered and applied consistent with Sections 513(i)(1)(D), 513(a)(3)(D) and 515(c)(5) of the FD&C Act;
- Documentation of significant controversies or differences of opinion; or
- References to published literature and consensus standards upon which the decision maker relied.

Finally, the document outlines who is eligible to request documentation of 517A decisions and explains how such requests are processed under the Freedom of Information Act.

The guidance document was developed as a companion to the Appeals Guidance, which outlines the time frames for processing the appeals of significant decisions.

FDA offers final guidance for drugmakers looking to participate in emerging manufacturing technologies program

The guidance outlines the FDA's expectations of drug manufacturers in its Emerging Technology Program. The program encourages drug companies to engage early with the FDA so difficulties can be dealt with more quickly, ensuring faster resolution of challenges and a smoother path to approval.

The FDA issued final guidance aimed at providing drug companies with the criteria for involvement in the agency's Emerging Technology Program. The initiative, launched by the regulator's Center for Drug Evaluation and Research, seeks to promote innovation in drug manufacturing and product design. It is designed to give companies an avenue to present novel technologies to the FDA's Emerging Technology Team before the regulatory submission process begins. This early access gives companies a chance to ask questions and submit proposals to quickly receive and act upon feedback from the regulator regarding investigational drug manufacturing technologies. Drugmakers' meetings with the Emerging Technology Team will allow discussion of product or manufacturing design and development issues, as well as submission content associated with the emerging technology.

The FDA said its focus on drug manufacturing fits with its broader mandate to protect and promote public health, and also intends its efforts in innovative pharmaceutical manufacturing technologies to help prevent drug shortages. Participation in the program requires companies' submissions to contain at least one technological element with which the FDA has limited experience. In addition, the program targets new or innovative technologies that could potentially boost a drug's safety, identity, strength, quality or purity. The program's Emerging Technology Team will partner with the Office of Compliance and Office of Regulatory Affairs to perform on-site evaluations and reviews, and make the final recommendations for approval submissions in the program.

In the final guidance, the FDA outlined three categories in which it would consider emerging pharmaceutical technologies:

- **Small molecules**, including continuous manufacturing (CM) of drug substances, CM of drug products, model-based control strategy for CM, continuous aseptic spray drying, 3D printing and ultra-long-acting oral formulations;
- **Biological molecules**, including controlled ice nucleation for lyophilization processes, advanced process controls, multi-attribute methods, next-generation sequencing, CM for upstream processes and small-manufacturing platforms for continuous bioprocesses ("pharmacy on demand"); and
- **Multiple products**, such as closed aseptic filling systems, isolators and robotic arms for aseptic filling, and novel container and closure systems for injectable products.

Applications to participate in the program should not exceed five pages, the regulator states in the guidance. The regulator also gave five criteria for requests from drugmakers looking to participate in the program, including:

1. A brief description of the proposed emerging technology;
2. A short explanation of why the technology is particularly novel and suitable for the program;
3. A description of how the technology could improve product safety, identity, strength, quality or purity;
4. A summary of the development plan and any potential barriers to implementation; and
5. A timeline for a submission of an IND; original or supplemental ANDA, BLA or NDA; or drug master file (DMF) and its associated application.

The addition of DMF is one of the few changes to the original 2015 draft guidance in the final guidance. The final guidance also specifies that products reviewed by the Center for Biologics Evaluation and Research are ineligible for the Emerging Technology Program.

For more information on any of these FDA regulatory and compliance updates, please contact Scott S. Liebman at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

Loeb & Loeb's FDA Regulatory and Compliance Practice comprises an interdisciplinary team of regulatory, corporate, capital markets, patent and litigation attorneys who advise clients on the full spectrum of legal and business issues related to the distribution and commercialization, including marketing and promotion, of FDA-regulated products. Focusing on the health and life sciences industries, including pharmaceuticals, biologics, medical devices, wellness products, dietary supplements and organics, the practice counsels clients on regulatory issues, compliance-related matters and risk management strategies; advises on laws and regulations related to product advertising and labeling; counsels on FDA exclusivity policies and related Hatch-Waxman issues; and provides representation in licensing transactions and regulatory enforcement actions.