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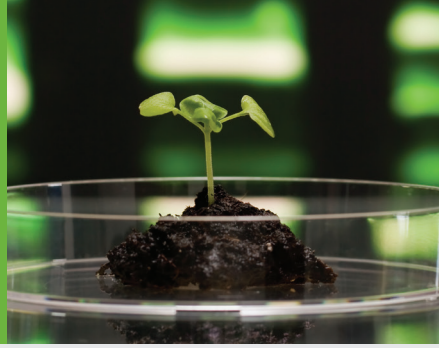
FDA Regulatory and Compliance Monthly Recap



JULY 2015

KEY FINDINGS

FDA finalizes guidance on analytical procedures and methods validation

The regulator issued recommendations to help applicants submit analytical procedures and methods validation data to "support the documentation of the identity, strength, quality, purity and potency of drug substances and drug products" and assemble and present data to support their analytical methodologies.

The recommendations contained in the guidance document concern drug products covered in NDAs, ANDAs, BLAs and supplements to those applications, and complement the ICH guidance "Q2(R1) Validation of Analytical Procedures: Text and Methodology."

Per the guidance, NDAs and ANDAs are required to contain the analytical procedures needed to ensure the identity, strength, quality, purity and potency of a drug substance and drug product. For BLAs, a full description of the manufacturing process must be included, including analytical procedures demonstrating that the manufactured product is up to prescribed standards of identity, quality, safety, purity and potency.

When an analytical procedure gets approved or licensed as part of the NDA, ANDA or BLA, it becomes the FDA-approved procedure for that particular product. A procedure can come from recognized sources, such as a compendial procedure from the USP/NF, or from a validated procedure submitted by a sponsor that the FDA found was acceptable. The document notes that to apply an analytical method to a different drug product, sponsors should consider appropriate validation or verification studies for compendial procedures with the new product's specifications.

In its guidance, the FDA goes over analytical methods development, saying an analytical procedure is developed to test a characteristic

of a drug against an "established acceptance criteria" for that particular characteristic. When it comes to the content of analytical procedures, the FDA recommends that these be described in "sufficient detail" to enable an analyst to reproduce the necessary conditions and get results within the proposed acceptance criteria. The document lists 10 pieces of "essential information" that should be included for an analytical procedure, including principle/scope, apparatus/equipment, operating parameters, reagents/standards, calculations and procedure, among others.

Also covered in the guidance are reference standards and materials, which are defined in a number of ICH guidances. The FDA calls for applicants to include information supporting all reference standards and materials that will be used in an application. While reference standards can be obtained from USP and other organizations listed in the guidance, the FDA notes that a new batch of reference standard materials needs to be qualified/calibrated against the current standards.

In going over analytical method validation, which is defined as the process to show the suitability of an analytical procedure for its intended purpose, the FDA also covered noncompendial and compendial analytical procedures.

Under the noncompendial section, the document notes validation data needs to be generated under a sponsor-approved protocol, and applications should contain details of the validation studies and results, with specificity, linearity, range, accuracy and detection limit among some of the typical characteristics. The FDA points to ICH Q2(R1) as the main reference for recommendations and definition of validation characteristics.

When it comes to compendial analytical procedures, whether an analytical procedure is suitable should be verified under actual conditions of use. Data to show that USP/NF procedures are appropriate for the drug product or substance should be contained in the submission and generated under a verification protocol. The FDA says the protocol should have components including compendial methodology verified with predetermined acceptance criteria and details of the methodology.

The guidance also covers statistical analysis and models, stating statistical analysis of validation data can be used to assess validation characteristics against predetermined acceptance criteria, while other methods might use chemometric or multivariate models.

Also described are life cycle management of analytical procedures, with the FDA stating that over the life cycle of a product, there may be new data and risk assessments warranting a new or alternative analytical method. According to the guidance, if a risk-based evaluation leads to modifications in the analytical procedure or substitution with a new method, applicants should consider revalidation, a new validation exercise, an analytical method comparability study or a combination of those exercises.

FDA provides guidance on orphan drug meetings with OOPD

The regulator issued recommendations for stakeholders seeking meetings with the OOPD, in a bid to provide consistent procedures that promote well-managed meetings.

The guidance document is aimed at assisting stakeholders with requesting, preparing, scheduling, conducting and documenting meetings with the OOPD to address issues related to orphan drug designation requests, humanitarian use device (HUD) designation requests, rare pediatric disease designation requests, funding opportunities via the Orphan Products Grants Program and the Pediatric Device Consortia Grants Program, and orphan product patient-related topics of concern.

Every year, the OOPD staff takes part in meetings with stakeholders who want guidance or clarification. The meetings can be "informal" or "formal," and help build a common understanding of the FDA's thinking concerning orphan products, which may include drugs, biological products, devices, or medical foods for a rare disease or condition.

In its guidance, the regulator:

- clarifies what constitutes an "informal" or "formal" meeting;
- addresses program areas within the OOPD that may be affected by this draft guidance;
- discusses procedures for requesting and scheduling meetings with the OOPD;
- describes what constitutes a meeting package; and
- goes over procedures for the conduct and documentation of meetings with OOPD.

The document notes informal meetings typically take the form of a brief phone conversion, and meeting packages don't need to be provided because the information contained in the meeting request is adequate. During informal meetings, the OOPD can address a number of general questions, including those regarding its policies and procedures, definitions of basic designation terms, and patient group initiatives relating to orphan products, among others.

Formal meetings, which usually consist of in-person meetings or teleconferences, allow the OOPD to address more specific matters, including questions about designation requests and denied requests and questions concerning orphan drug exclusivity, among others. The document says meeting packages must be provided to the OOPD prior to meetings, and notes the meetings aren't forums for stakeholders to get feedback on product development protocols or planned studies. The meetings rather serve to provide stakeholders with clarification from the OOPD and allow them to discuss disagreements about policies, positions and statements.

Programs for which meeting with the OOPD can be requested include the following OOPD designation programs: orphan drug designation, HUD designation and rare pediatric disease designation. The FDA says many questions regarding designations can be answered during informal meetings; those related to exclusivity are usually best addressed at formal meetings. Further, questions concerning orphan drug products grants, pediatric device consortia grants and patient-related issues can also usually be tackled at information meetings.

In discussing procedures for requesting and scheduling meetings, the document refers to the OOPD's website for information and resources that should be consulted prior to requesting a meeting. The FDA goes over several ways stakeholders can go about this, listing a number of components that should be included in requests, such as a brief statement of the meeting purpose, the type of meeting preferred, and suggested dates and times for the meeting.

The FDA notes the OOPD aims to respond to requests within five working days of receipt, upon which it will determine the appropriate meeting type and find a date.

If a meeting is scheduled, the OOPD should get its meeting package at least two weeks prior. The guidance describes what information should be contained in a package, listing elements such as basic information about the product at issue, a proposed meeting agenda and any information, data or material necessary to support the discussion.

The guidance also covers meeting protocol, noting the stakeholder will take the lead following introductions and a statement of the meeting purpose, and closes by addressing documentation, calling for stakeholders to provide a draft summary of meeting minutes to the OOPD within 15 working days after the meeting.

FDA issues guidance for dispensers to explain compliance policy on product tracing requirements and notes limited exemptions

In its document, the regulator explains how dispensers in the pharmaceutical distribution supply chain should comply with the FDCA's product tracing information provisions, which were added by the DSCSA, pushing back compliance from July to November.

Section 202 of the DSCSA, which was signed into law in 2013 and added new sections to the FDCA, laid out new product tracing definitions and requirements. Beginning in 2015, trading partners must provide subsequent purchasers with product tracing information when it comes to transactions that involve certain prescription drugs. They're also required to obtain the tracing information and maintain it for at least six years following the transaction date.

While the product tracing requirements of the FDCA came into effect for dispensers as of July 1, some dispensers voiced concern that electronic systems used for the exchange, capture and maintenance of information couldn't be operational in time. In its guidance, the FDA notes it recognizes that some dispensers may need more time to comply, and thus won't take action before Nov. 1. More specifically, no action will be taken against dispensers who before Nov. 1 accept ownership of product without receiving tracing information prior to or at the time of the transaction or don't collect and maintain the information.

The guidance concludes by advising dispensers to work with previous product owners to receive product tracing information if they've not received it before or at the time of the transaction.

FDA warns ASCEND Therapeutics for excluding from Zazzle card serious risks associated with EstroGel use

The regulator warned the company that its professional EstroGel Zazzle card is misleading and misbrands the menopause treatment because it omits risk information associated with use of EstroGel.

EstroGel is indicated to treat "moderate to severe vasomotor symptoms due to menopause" and "moderate to severe symptoms of vulvar and vaginal atrophy due to menopause," and its use is associated with a several serious risks, the FDA letter states. Boxed warnings are included in the PI, as are a number of other warning and precautions.

According to the letter, while the Zazzle card includes efficacy claims, it omits important risk information associated with the use of EstroGel – causing it to misleadingly suggest the treatment is safer than shown. The FDA cited the Zazzle card's failure to include information from the boxed warning that EstroGel shouldn't be used to prevent cardiovascular disorders or dementia, as an example. ASCEND also omitted conditions for which EstroGel is contraindicated.

The letter notes the company's inclusion of the statements "Please visit www.estrogel.com for additional information" and "See enclosed full PI and boxed warning" fails to mitigate the exclusion of important risks.

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

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