FDA Regulatory & Compliance Monthly Recap
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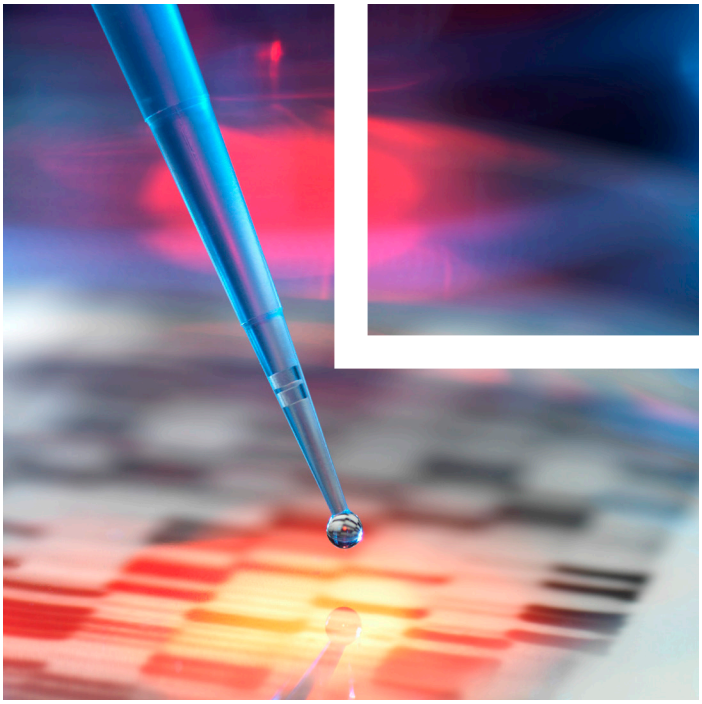

FDA issues guidance outlining potential insanitary conditions for compounding facilities

The FDA issued a final guidance providing compounding facilities and state regulatory agencies with several examples as to what the agency considers insanitary conditions that could result in the contamination of drug products. The examples provided potential insanitary conditions for the production of both sterile and non-sterile drugs. The guidance also provides recommendations for actions undertaken to prevent the occurrence of such conditions.

The guidance was published after the FDA investigated several outbreaks of infections and deaths caused as a result of contaminated drug products, particularly in 2012 when injectable drug products produced by a compounding facility caused a fungal meningitis outbreak that resulted in more than 750 infections and 60 deaths. Since that outbreak, the FDA has identified numerous insanitary conditions at many compounding facilities that the agency routinely inspects. However, there are also numerous state-licensed pharmacies engaged in compounding, repackaging drugs, or mixing, diluting or repackaging biological products that do not register as outsourcing facilities with the FDA. The guidance was designed to ensure these facilities are able to identify and correct insanitary conditions to the same level as the FDA.

The guidance provides examples of potential insanitary conditions that could cause both sterile and non-sterile drugs to become contaminated. While sterility is not a requirement for non-sterile drugs, the guidance highlights that it is still possible for these products to become contaminated with micro organisms that could lead to patient harm. Examples of insanitary conditions applicable to both sterile and non-sterile drug products include:

- Vermin, such as insects and rodents, or other animals. This includes any evidence of their presence, such as urine or feces, in the production or adjacent areas;
- Visible microbial contamination, such as bacteria or mold in the production or adjacent areas;
- Foreign matter, such as rust, glass shavings, hairs or paint chips, in the production area;

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- Producing drugs while construction is ongoing in a nearby area without adequate controls to prevent contamination of the production area or product;
- Standing water or evidence of water leakage in the production or adjacent areas;
- Handling drug substances or products that are hazardous, sensitizing or highly potent without adequate cross-contamination controls;
- Processing of beta-lactams without complete and comprehensive separation from non-beta-lactam products; and
- Using active ingredients, inactive ingredients or processing aides that have higher levels of impurities compared to equivalents.

The guidance also provides a list of possible insanitary conditions specifically applicable to sterile drugs only, including, but not limited to:

- Engaging in aseptic processing wearing non-sterile gown components;
- Donning gowning apparel in a way that may cause it to become contaminated;
- Failing to disinfect or change gloves frequently enough to prevent contamination;
- Engaging in aseptic processing after leaving the cleanroom and re-entering from a non-classified area without replacing gowning apparel first; and
- Failure to detect or address a change in air quality of any classified area before a loss of environmental control that may impact drug sterility.

Upon identifying insanitary conditions, the FDA recommends compounding facilities should immediately assess the impact of the condition on the drugs produced. This assessment should include an evaluation of how widespread the conditions are and the period of time during which the conditions have existed, as well as the lots of drug product remaining on the market that could be affected. The facility should also determine whether to stop production of drug products until the conditions have been addressed and whether to initiate a recall of potentially affected products.

FDA issues final guidance to generic drugmakers on how to identify RLDs on ANDAs

The FDA issued a final guidance to clear any confusion on the part of stakeholders in the basis of submission and reference standard and how they should be applied in abbreviated new drug applications (ANDAs), as well as how to indicate reference listed drugs (RLDs). The guidance addresses this confusion by explaining what the terms mean and by clarifying the differences between them. The document also provides recommendations on how applicants can use the terms accurately in ANDAs and how they can request FDA designation of an RLD.

For the purposes of an ANDA, the guidance defines an RLD as a drug currently listed in the FDA's Orange Book upon which the applicant relies in seeking approval of its ANDA. The FDA identifies in the Orange Book which listed drugs have already been designated as RLDs. Furthermore a listed drug that has been approved for safety and effectiveness under the FDCA may be eligible to be an RLD, as can a listed drug that appears in the Discontinued Section of the Orange Book, unless the drug was discontinued for reasons of safety or effectiveness.

ANDA applicants are required to choose an RLD. If the agency has yet to designate an RLD for the drug product an applicant intends to duplicate, the applicant may submit controlled correspondence to the FDA identifying the drug it intends to copy and request the agency designate it as an RLD. In the event an applicant selects a listed drug as an RLD, but plans to refer to a different listed drug that was approved for safety and effectiveness and is a pharmaceutical equivalent to the RLD drug, the applicant may also request the FDA designate the second drug as an RLD. If an RLD appears in the Orange Book's discontinued section and the agency has yet to publish whether the drug was withdrawn from sale for reasons of safety or effectiveness, the applicant must submit a citizen petition seeking a safety and effectiveness determination for the listed drug at the same time as the ANDA submission. This submission must include all available evidence concerning the reason the drug was withdrawn from sale.

The guidance also examines "reference standards," which it defines as a drug product selected by the FDA that must be used by ANDA applicants in conducting in vivo bioequivalence studies required for approval. The agency commonly selects a single reference standard to ensure the most consistency between a generic drug and its RLD. As a result, the RLD is usually selected as the reference standard. In the event the agency cannot select the RLD as the reference standard, the FDA will usually select a previously approved ANDA that referred to, and is the therapeutic equivalent to, the RLD as the reference standard. If there are multiple such drugs, then the FDA will usually select the market leader, based on commercial data, as the reference standard.

FDA issues final guidance on increasing diversity in clinical trial participants

The FDA issued a final guidance discussing ways for sponsors to increase the diversity of clinical trial participants. In the guidance, the FDA recommends sponsors employ inclusive trial practices, suggesting design and methodological changes that promote diversity of study populations based on demographic (sex, race, ethnicity, age, residency) and non-demographic (patients with organ dysfunction, comorbid conditions, disabilities, those at the extremes of the weight range, and populations with diseases or conditions with low prevalence) factors.

The FDA explains that past guidance, which encouraged sponsors to diversify study groups to better reflect the target population for a particular drug, has not had the desired effect. Challenges to broadening cohorts to account for demographic and non-demographic factors remain, so this final guidance aims to address the under-representation of certain groups in clinical trials. There are three ways the FDA proposes to do this, by broadening eligibility criteria, introducing study design and methodology changes, and providing a framework for eligibility in clinical trials for orphan drugs. The FDA recognizes that certain individuals should be excluded from certain trials if the benefit of their inclusion would be outweighed by possible adverse effects from the agent. Other groups typically not part of clinical studies include pregnant or lactating women, or patients with complex medical issues or comorbidities.

To introduce more inclusivity in enrollment, the guidance suggests that drug sponsors:

- Ensure criteria for eligibility reflects the target population for the proposed medication and to focus exclusions only on those groups that could be most harmed by the trial. For example, patients with impaired organ function may still be considered for a trial cohort if their dysfunction is not severe enough to create an unreasonable risk;
- Consider whether more restrictive exclusion criteria in Phase 2 trials are necessary as the drug candidate moves forward to Phase 3. The guidance states even high-risk patients may be considered if the test sites have expertise in treating their specific condition; and
- Enroll participants that represent the age, sex, race, and ethnicity of the population at large. Differing demographic factors may elicit diverging results during clinical trials and lead to generalizations about product safety and effectiveness that are not correct for all groups. The FDA recommends clinically-relevant populations be introduced into studies for drugs and biologics no later than Phase 2.

In addition, the guidance suggests various design and methodological changes to promote diversity, such as characterizing drug metabolism and clearance across populations early in development to prevent exclusions later on and allow for dose adjustments. Sponsors are also urged to consider non-clinical factors that contribute to a broader enrollment, such as reducing the frequency of study visits, replacing some physical visits with electronic communications, or using mobile medical professionals to travel to a participant's location. Finally, to aid in enrollment, the agency recommends sponsors working on rare disease treatments work with patient advocacy groups, experts, and patients early in the process and consider launching open-label extension studies with broader inclusion criteria after early-phase studies.

FDA issues guidance relating to electronic formatting for drug regulatory submissions

The FDA issued a revised guidance relating to the presentation of drug regulatory submissions in an electronic format to modify exemptions to the electronic submission requirements for standardized study data. As well, the revision clarifies a section of the original guidance governing the timetable for the submission of standardized study data.

The FDA's revised guidance updates two sections of the original document which concern the types of submissions which are exempt from the requirement for electronic submission of standardized study data, as well as protocols governing the timelines for electronic data submission. Under Section II B of the revised guidance, the FDA includes a change from "noncommercial products" to "noncommercial IND" on the list of submissions that are exempt from the electronic submission requirements for standardized study data. The agency defines "noncommercial IND" as an investigational new drug (IND) that is not intended for commercial distribution. These can include investigator-sponsored or expanded access INDs. Despite the exemption, the FDA will accept voluntary submissions of data in an electronic format.

The guidance also clarifies the information required to assess whether study data requirements are in compliance with FDA regulations and provided a sample timetable that indicates submission timelines. A number of standards for drug studies are available, including Exchange Format Standards, Study Data Standard, or the Controlled Terminology Standard. Examples of the latter are The National Drug File (NDF) - Reference Terminology for drug classification, CDISC Controlled Terminology and Medical Dictionary for Regulatory Activities (MedDRA). The guidance specifies the electronic format for submissions of standardized clinical and non-clinical study data under the FDCA, whether they are new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), or investigational new drug applications (INDs), that are required by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).

The FDA notes that the initial 24- and 36-month implementation deadlines under the initial timetable passed and that periodically, it publishes version updates which account for content or structural changes, or typographical errors. It provides examples of when drug sponsors will be required to adopt version updates into their submissions as well as which format is acceptable for it to process, review, and archive the request. Furthermore, the FDA may introduce new documentation standards while the drug is still in clinical trials, necessitating their implementation within a specified transition date.

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