FDA Regulatory & Compliance Monthly Recap
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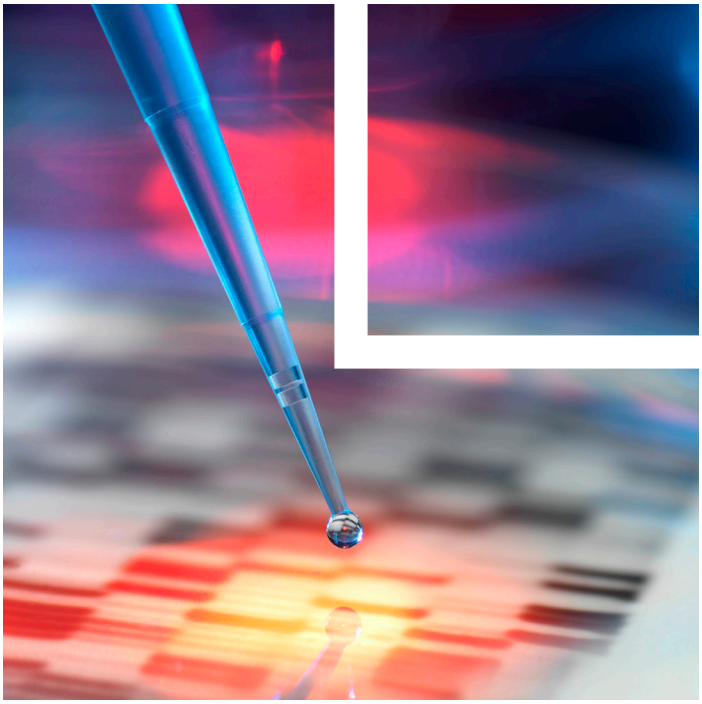

FDA issues final guidance on complex innovative trial designs for drug, biologic sponsors

The FDA issued a final guidance providing sponsors and applicants recommendations on their interactions with the agency regarding complex innovative trial design (CID) proposals for drugs and biologic products. The guidance explores the use of novel trial designs in the development and regulatory review of drugs and biologics. The guidance also discusses how sponsors can receive feedback from the FDA on technical issues related to modeling and simulation, as well as the types of quantitative and qualitative information that should be submitted for review.

The guidance provides recommendations for sponsors as to the type of information that should be included when submitting a novel design proposal to the agency for review. While the specific documentation required is dependent on the type of proposal submitted by the sponsor, there are certain common elements that should be included in most proposals. These include, but are not limited to:

- A discussion on the choice of trial design and how it fits into the overall drug development plan
- A detailed description of vital aspects of the design, such as plans for possible adaptations, implementation details for interim analyses and decision criteria
- If necessary, details regarding the source and choice of prior information borrowed, its relevance to the proposed design and an explanation of steps taken to ensure all relevant information is accounted for
- A rationale for borrowing and an explanation of how the prior distributions were constructed from the prior information, when necessary
- A detailed evaluation of the design's operating characteristics, including chance of producing erroneous conclusions and the reliability of treatment effect estimates

When opting to submit complex adaptive and other novel designs, sponsors should include a rationale for the borrowing of certain details in regard to how they avoided bias in the selection of the borrowed information. Additionally, Bayesian proposals should include a detailed discussion of the prior distribution, as well as any data or external information used to form the prior distribution. Sponsors should also propose decision criteria in study protocols for all intended primary and secondary endpoints to be included in product labeling if approved.

If sponsors plan to use simulations to estimate trial operating characteristics or to optimize design parameters, such as the number and timing of interim analyses, the guidance notes that it can be advantageous to discuss plans for trial simulations at meetings with the FDA. The discussions would ideally take place during End of Phase 2 meetings, which often occur at a stage in development where preliminary plans for Phase 3 trails are being discussed. Structuring part of the End of Phase 2 discussion around such simulations can help the sponsor and the agency consider relevant scenarios to be explored in the simulations and the core trial assumptions, including accrual rate and likely control group outcomes.

FDA issues guidance regarding controlled correspondence for generic drug manufacturers

The FDA issued a guidance outlining the process by which generic drug manufacturers can submit controlled correspondence with the agency in regard to the development of generic drugs, as well as the FDA's process for providing communications related to such correspondence. The guidance also outlines the types of inquiries that are considered controlled correspondence, as well as exceptions to the definition of controlled correspondence.

Under the guidance, standard controlled correspondence is defined as correspondence submitted to the FDA, by or on behalf of a generic drug manufacturer or related industry, requesting information on a specific aspect of generic drug development. The guidance defines complex controlled correspondence as correspondence involving evaluation of clinical content, bioequivalence (BE) review protocols and evaluation of alternative BE approaches.

In regard to controlled correspondence related to a pending citizen petition, a petition for stay of action or a petition for administrative reconsideration of action, the FDA will notify the requester if it determines that the controlled correspondence is related to an issue raised in a pending petition. The agency will begin consideration of the correspondence once it issues its response. In regard to requests related to matters still under consideration, the FDA will advise the requester that it is still considering its decision and will keep the request open until it issues a response.

However, there are some instances in which controlled correspondence may not be the preferred mechanism to secure the agency's feedback on a topic. These mechanisms can include pre-ANDA meetings for discussing issues such as methods of characterization for complex products or clinically critical BE considerations. Other, more general topics, such as the proposed use of in vitro data to support BE demonstration, would be better considered as part of the Regulatory Science Initiative. In these instances, the FDA will notify the requestor of the recommended alternative mechanism and close the request.

The guidance also highlights three exceptions to its definition of controlled correspondence:

1. **BE Guidance Requests**: In accordance with the process described in the FDA's Bioequivalence Recommendations for Specific Products guidance, as well as the agency's good guidance practices regulation, the FDA will publish BE recommendations in product-specific guidances. This allows the agency to be proactive in developing and publishing guidance for new drug products without waiting on inquiries on BE methodologies from individual requestors.
2. **Clinical Protocol Requests**: The agency will continue to exclude these requests from controlled correspondence if the reference listed drug product is not subject to risk evaluation and mitigation strategies with elements to assure safe use. Generally, these requests are not considered controlled

correspondence because they are more resource- and time-intensive than other requests.

3. **Pre-ANDA Meeting Requests**: These requests will not be considered controlled correspondence because the purpose of controlled correspondence is to provide a process for a direct inquiry on the FDA's position regarding a particular element of generic drug manufacturing. Meanwhile, the pre-ANDA process was designed to initiate a dialogue with the agency on a particular matter for which controlled correspondence is not suitable.

The guidance also provides recommendations to requestors regarding what information should be included in controlled correspondence. Apart from standard identification information, such as the name of the company making the request and the FDA-assigned control number and submission date, the agency also recommends that requesters include relevant prior research and supporting materials on the specific element of generic drug development about which it seeks the FDA's input.

FDA issues draft guidance relating to cross-labeling oncology drugs in combination regimens

The FDA issued a draft guidance regarding the cross-labeling of oncology medications used in various combination regimens. The document is in response to the increased number of applications proposing cross-labeling for such regimens. The guidance is intended to outline the agency's current recommendations regarding the information that should be included on the labels of oncology drugs approved for combination regimens.

The guidance defines cross-labeling as the inclusion of information in approved product labeling of two or more oncology drugs approved in combination regimens for a specific indication. According to the FDA, cross-labeling is intended to ensure that the information present on the labels of such drugs is complementary and consistent, without inclusion of redundant information in labeling for each drug in the combination regimen.

The agency also provides recommendations for the content of labeling that applicants should consider when submitting a cross-labeling application. These include:

- **Indications and Usages**: The indication for the combination regimen should be the same for all approved drugs for use in the combination regimen. The applicant's drug should be listed first in the combination regimen, and the established name or proper name should be used for the other drugs included in the regimen.
- **Dosage and Administration**: Generally, applicants need only include the recommended dosage for the applicant's drug with respect to the regimen. Any dose modification instructions should be limited to the applicant's drug unless there are adverse reactions that would require dose modifications for other drugs in the regimen.
- **Clinical Studies**: Applications should also include a description of clinical studies for the combination regimen, which should be similar on the labeling of all drugs included in the regimen.
- **Warning and Precautions**: This section should include information unique to the combination regimen based on synergistic or novel adverse reactions and/or risks. This information should be limited to the applicant's drug only, and information regarding warnings and precautions for other drugs in the regimen should not be included.
- **Adverse Reactions**: Applications should also include adverse reactions observed during the trial or trials supporting approval of the regimen.
- **Patient Counseling Information**: Finally, applications should include information regarding the regimen that a health care provider should convey to patients and/or caregivers. This information should be limited to unique toxicities and unique preparation and administration instructions relevant to the regimen.

FDA issues two guidances regarding proprietary naming for prescription, non-prescription drugs

The FDA issued a pair of draft guidances relating to the selection of proprietary names for prescription and non-prescription drugs. The documents provide best practices for developers and are designed to mitigate name-related medication errors and to prevent the adoption of proprietary names that contribute to FDCA violations. The guidances also outline how the FDA uses its Phonetic Orthographic Computer Analysis (POCA) software to evaluate the similarities between proposed proprietary names and the names of other drugs.

Both the guidance for prescription drugs and the guidance for non-prescription drugs recommend that sponsors screen proposed proprietary names for a number of different attributes. This screening process is recommended as a first step before proceeding with a full assessment as to whether a proposed name is likely to contribute to medication errors or otherwise contribute to FDCA violations. The attributes are:

- **Obvious similarities in spelling/pronunciation**: Sponsors should avoid proposed proprietary names that are similar in spelling and pronunciation to existing proprietary names, established names or names of ingredients or other products.
- **Inert or inactive ingredients**: Proprietary names should not incorporate any reference to these types of ingredients, as doing so may create a misleading impression of an ingredient's importance within the medication.
- **Combinations of active ingredients**: The FDA recommends that the proprietary names of fixed combination drugs not include or suggest the name of one or more of its active ingredients because such names can mislead end users by implying the product only contains the ingredients included in the name.
- **U.S. adopted name (USAN) stems**: Sponsors should also avoid names that incorporate USAN stems, because they are intended to indicate specific pharmacological or chemical traits and could be applicable to multiple drug products.
- **Brand-name extension**: This refers to a naming strategy that uses a proprietary name that is already associated with one or more marketed drug products. The guidance recommends against using a brand-name extension, as it could lead to the use of a product for the wrong indication.
- **Reuse of proprietary names**: Sponsors should refrain from using the proprietary name of products that are no longer being marketed, because there is a risk that end users could continue to associate the name with the discontinued product.

The guidances also recommend that sponsors consider other important attributes during the development of a proprietary name, such as names referencing product-specific attributes, medical abbreviations, modifiers as components of a proprietary name, dual proprietary names, proprietary names of drug products marketed outside the U.S. and incorporation of the sponsor's name.

Additionally, the documents provide suggestions for possible methods to evaluate the risk of medication error posed by similarity of a proposed proprietary name to the names of other products. The agency notes that it uses these methods when evaluating a proposed proprietary name but recommends that sponsors also use them prior to submitting a proposed proprietary name for review. The first such recommendation is the use of name simulation studies, which tests how health care professionals respond to a proposed name. The second method is to obtain medication error data for names already associated with marketed products. Other recommendations include the use of computation methods to identify names with potential orthographic, spelling and phonetic similarities, and a safety determination of names with potentially similar orthographic, spelling and phonetic qualities.

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