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SBIA CHRONICLES

FEBRUARY 6TH, 2018

FDA Helping the Generic Industry Submit Complete Applications

Listen to our Audio Podcast*!*

Attn NDA and ANDA Holders: One-time marketing report required and due to FDA by Feb. 14th!

Resources:

1. Guidance for Industry: Good ANDA Submission Practices

2. MAPP 5241.3, Good Abbreviated New Drug Application Assessment Practices

Upcoming Events:

1. Coming Soon – SBIA REdI Generic Drugs Forum – April 11-12th in Silver Spring, MD.

2. Evaluating Inclusion and Exclusion Criteria in Clinical Trials – April 16th in Washington D.C.

3. 2018 Clinical Outcome Assessments in Cancer Clinical Trials Workshop – June 22nd in MD

FDA is working to make the Abbreviated New Drug Application (ANDA) submission and assessment process more efficient by providing guidance to industry and establishing internal practices to help reduce the number of review cycles for an ANDA to attain approval. The newly released draft guidance for industry, Good ANDA Submission Practices, and the Manual of Policies and Procedures (MAPP) 5241.3, Good Abbreviated New Drug Application Assessment Practices, apply insights gained through the first five years of the Generic Drug User Fee Amendments (GDUFA) program.

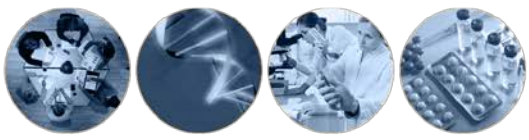
Until now, approximately half of all ANDAs with GDUFA review goals required at least three review cycles to reach approval or tentative approval. The agency and industry found applications often required multiple review cycles to reach approval-- an inefficient and resource-intensive process that could delay access to safe, affordable generic medicines. GDUFA II includes important program enhancements to improve the predictability and transparency of ANDA assessments by fostering the development of high-quality submissions and resubmissions.

Good ANDA Submission Practices Guidance for Industry

The Good ANDA Submission Practices Guidance draft guidance lists common, recurring deficiencies that may lead to a delay in the approval of an ANDA, such as issues with patents and exclusivities, labeling, product quality, and bioequivalence. It also provides recommendations to applicants on how to avoid these deficiencies. Some of the highlights of FDA's recommendations to prevent deficiencies include:

Patent and Exclusivity Deficiencies **–** *Applicants should:*

- Submit to FDA timely written documentation of the sending and receipt of notice of a paragraph IV certification, that the patent owner(s) and/or exclusive patent licensee filed a legal action, or a statement that the patent owner(s) and/or exclusive patent licensee did not file a legal action within 45 days of receipt of the notice of the paragraph IV certification.
- Monitor the Orange Book and address newly-listed patents, revised patents, and exclusivities in a timely manner, as an applicant must not submit a paragraph IV certification to the ANDA for a newly-listed patent "earlier than the first working day after the day the patent is published in [the Orange Book]."
- Submit the required notification of commercial marketing to FDA within the 30-day time frame.



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Labeling Deficiencies - *Applicants should:*

- Ensure that the draft version of container labels and carton labeling "reflect the content as well as an accurate representation of the layout, text size and style, color, and other formatting factors that will be used with the [final printed labeling]."
- Ensure that the color and/or format of container labels and carton labeling is adequately differentiated from other pending and approved products in the applicant's product line.
- Submit labeling in Microsoft Word, Structured Product Labeling, and PDF files, and ensure consistency in the content between the different formats.
- Ensure that for ANDAs of parenteral drug products, the package type is the same as that approved for the reference listed drug (RLD); the strength is clearly displayed and expressed on the container label; and the ferrules and cap overseals of injectable drug products clearly convey cautionary statements that will help prevent imminent, life-threatening situations.

Product Quality Deficiencies -

For the drug substance, drug master file (DMF) holders should:

- Provide complete information in Module 3.2.S.2.2 on their active pharmaceutical ingredient (API) manufacturing process, including a flow chart for every stage.
- Include API characterization information, including information on all potential impurities, justification for their specification for isolated intermediates, and a clear rationale that includes critical quality attributes (CQAs) when establishing drug substance specifications.
- Communicate with ANDA applicants regarding when amendments will be submitted to the DMF, as unsolicited amendments that affect the adequacy of the DMF to support approval of the ANDA may extend GDUFA goals or create new review goals.

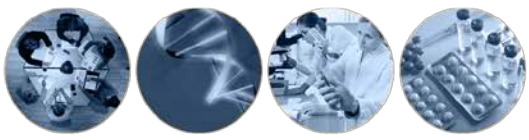
For the drug product, applicants should:

- Include information in their ANDAs evaluating their drug product based on recommendations in the specified International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidances to support the selection and rationale for their CQAs. FDA has also provided recommendations for the identification, control, and qualification of impurities; justification of inactive ingredients exposure level and safety; and validation of analytical methods.
- Submit a complete method development and validation report when an in-house dissolution testing method is used.
- Refer to the Inactive Ingredient Database (IID) to determine the previously approved level of an inactive ingredient in a given drug product. For levels above the maximum listed in the IID, submit controlled correspondence with a justification for the safety of the inactive ingredient at that amount to request information regarding whether the use of the ingredient could be acceptable.
- Provide complete manufacturing facility information in their Form FDA 356h and provide complete facility and process information within Module 3 of the application,
- Communicate with any contract manufacturing facilities about current good manufacturing practices (CGMP)-related roles and changes in inspection status.

Bioequivalence Deficiencies - *Applicants should:*

- Provide complete bioanalytical study reports and bioanalytical methodology validation data, and accurate and complete information in their model summary tables.
- Provide justification if there is a deviation from a relevant product-specific guidance, as well as data to support this deviation.
- Provide justification and documentation for any differences permissible under FDA regulations between the formulation of the proposed generic drug product and the RLD.

The guidance does not include a comprehensive list of *all* deficiencies identified during ANDA assessment. It is each applicant's responsibility to submit a high-quality, complete application that meets the standards for approval in the first cycle.



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MAPP - Good Abbreviated New Drug Application Assessment Practices

In addition to providing guidance to applicants, FDA has established a Manual of Policies and Procedures (MAPP) with good ANDA assessment practices for the Office of Generic Drugs (OGD) and the Office of Pharmaceutical Quality (OPQ). The goal of the MAPP is to increase operational efficiency and effectiveness while decreasing the number of cycles to approval for ANDAs that meet the requirements for approval.

To reinforce the policy and procedural changes set forth in this MAPP, OGD and OPQ will use the term *assessment* in place of *review*. *Assessment* refers to the process of evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval, and documenting that determination. Specifically, the MAPP:

- Establishes that assessment teams should, when available, use templates and assessment tools provided by the sub-disciplines that focus the primary assessment of quality, bioequivalence, or labeling data or information on the critical attributes of the application.

- Clarifies the roles and responsibilities of primary assessors, secondary assessors, and division directors, ultimately reducing duplicative and unnecessary work, and increasing FDA's efficiency and effectiveness.

- Establishes that OGD and OPQ will clearly communicate to applicants what deficiencies must be corrected for their ANDAs to be approved, enabling applicants to develop high-quality re-submissions and to reduce the number of subsequent cycles to approval.

The changes are expected to expand access to generic medicines and enable FDA experts to focus more of their attention on novel or challenging scientific and policy issues associated with the development and assessment of generic drug products. FDA remains committed to increasing competition in the prescription drug marketplace, and facilitating the entry of safe, effective, high-quality and affordable generic drugs.

Cheers,
Renu Lal, Pharm.D.
CDER Small Business and Industry Assistance

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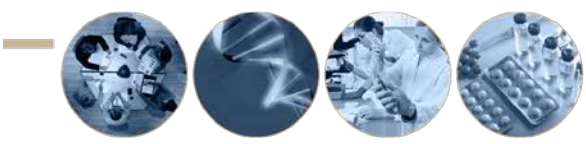

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