FDA is Soliciting Comments on Improving the Quality of ANDA Submissions

Written by Paul T. Kim

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The Food and Drug Administration (FDA) announced the establishment of a public docket for comments regarding Abbreviated New Drug Application (ANDA) submissions to the agency. FDA is specifically looking for input regarding common deficiencies in the following aspects: filing, chemistry, sterility, bioequivalence, fatal flaws, and drug master files. The new docket, FDA-2014-N-0032, will remain open until March 24, 2014, although FDA "welcomes comments at any time."

According to the notice announcing the new docket, the review staff in the Office of Generic Drugs (OGD) routinely note "common, recurring deficiencies" in ANDA submissions. The deficiencies interfere with FDA's ability to meet its review performance goals under the Generic Drug User Fee Act (GDUFA). FDA listed the following deficiencies:

Filing:	Failure to provide a completed Form FDA 356h; unjustified inactive ingredient levels; inadequate dissolution data; packaging less than the recommended threshold amount without justification; inadequate or insufficient stability data; submissions of non-qualitative and non-quantitative (not Q/Q) same formulations; electronic submission and formatting deficiencies; applications containing an incorrect or unfounded basis of submission.
Chemistry:	Poor or inadequate justification of impurities limits; failure to provide a list of potential impurities and their origins; failure to provide adequate verification of analytical procedures for active pharmaceutical ingredient and finished dosage forms, where appropriate; failure to identify the critical manufacturing process parameters or to link in-process controls to development studies; failure to provide appropriate acceptance criteria of manufacturing yields for the critical steps, or providing yield values varying without adequate rationale or explanation.
Sterility assurance for sterile product applications manufactured by aseptic processing:	Failure to describe sterilization and/or depyrogenation of relevant equipment and components that may come in contact with the sterile drug; failure to provide relevant validation data for sterilization and/or depyrogenation of relevant equipment and components that may come in contact with the sterile drug; failure to provide validation data for sterilizing grade filters, if needed; failure to provide process simulation data for the proposed aseptic filling process/line/room.
Bioequivalence:	Inaccurate and/or incomplete information contained in electronic tables; submission of pharmacokinetic repeats; inaccurate and/or incomplete biowaiver requests (e.g., inappropriate method of solubility determination, lack of dissolution data for all strengths, missing standard operating procedures for analytical methods).
Fatal flaws:	Significant flaws in the design of a drug product such that the proposed product will not be able to meet all conditions of use of the reference listed drug.
Drug master files:	Submission contains more than a single drug substance or more than a single drug manufacturing process; failure to update the drug master file following a large number of amendments or time lapse since the original submission; failure to provide a complete description of manufacturing process and controls; failure to justify appropriate starting materials.

FDA posed four questions to help the agency reduce the deficiencies and enhance the quality and completeness of ANDA submissions:

1. What aspects of the ANDA application process are confusing or not well defined?
2. What problems do ANDA applicants encounter when developing a submission that FDA could help address?
3. Prior to GDUFA, were ANDA submissions consistently slowed or stalled at certain recurring review points post-filing? If so, why?

4. How should FDA share suggestions for improving ANDA submissions with industry, beyond issuing regulatory guidance?

The dialog between generic drug companies and FDA is worth following, as it sheds light on the issues confronting companies during the submission process, and discusses the different tools available to FDA when communicating with the industry. The notice is also an indication that submission quality will be a topic of discussion in the next user fee rounds.

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