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# Impurity Deficiencies: How FDA Can Refuse-to-Receive an ANDA

Posted 24 August 2016 | By [Zachary Brennan](#)



The US Food and Drug Administration (FDA) on Wednesday finalized guidance that will assist abbreviated new drug application (ANDA) submitters seeking approval of a new strength of a drug.

The guidance, for applicants preparing to submit to FDA ANDAs and prior approval supplements to ANDAs, highlights serious deficiencies in impurity information that may cause FDA to refuse-to-accept (RTR) an ANDA.

Specifically, FDA says the deficiencies include: “(1) Failing to provide justification for proposed limits for specified identified impurities in drug substances and drug products that are above qualification thresholds; (2) failing to provide justification for specified unidentified impurities that are above identification thresholds; and (3) proposing limits for unspecified impurities (e.g., any unknown impurity) that are above identification thresholds.”

## Background

The finalization of the guidance comes almost two years after the draft was first published in September 2014, with the title "ANDA Submissions--Refuse to Receive for Lack of Proper Justification of Impurity Limits."

“Upon review of the comments submitted to the draft guidance, FDA removed the word ‘proper’ from the title to emphasize that this guidance does not apply to the technical review of impurity limit justifications submitted in an ANDA,” FDA said in the Federal Register on Wednesday.

FDA also notes the importance of enhanced RTR standards because in cases where an ANDA submission is not sufficiently complete to permit a substantive review, the ANDA has to be “repaired” via several cycles of applicant resubmission and FDA response, which FDA calls “inherently inefficient and wasteful of resources.”

## Details

FDA may RTR an ANDA that is not sufficiently complete because it does not contain certain required information, including a demonstration of the purity of the drug substance and drug product and information on impurities and residues.

FDA will also RTR an ANDA if it “lacks supporting data or information to justify the proposed limits for specified identified and/or specified unidentified impurities that exceed qualification thresholds and/or identification thresholds.” ANDA applicants can also expect an RTR if proposed limits for unspecified impurities exceed identification thresholds.

“FDA expects applicants to develop and use appropriate analytical methods to detect all observed impurities. Applicants are encouraged to review the draft guidance for industry [ANDA Submissions – Content and Format of Abbreviated New Drug Applications](#) [from June 2014] for more information on the characterization of impurities for drug substances and drug products,” the guidance says.

However, if a generic contains specified identified impurities that exceed the qualification thresholds or specified unidentified impurities that exceed identification thresholds, FDA says the ANDA should propose impurity limits and include supporting data to demonstrate:

- The observed impurity levels and proposed impurity limits do not exceed the level observed in the reference listed drug (RLD) product.
- The impurity is a significant metabolite of the drug substance.
- The observed impurity levels and proposed impurity limits are adequately justified by the scientific literature.
- The observed impurity levels and proposed impurity limits do not exceed the level that has been adequately evaluated in toxicity studies.

[ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits Guidance for Industry](#)

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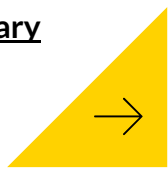
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