ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2016
Generics

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Contains Nonbinding Recommendations

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ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants preparing to submit to the Food and Drug Administration (FDA) original abbreviated new drug applications (ANDAs) and prior approval supplements (PASs) to ANDAs for which the applicant is seeking approval of a new strength of the drug product.[2] The guidance highlights deficiencies in relation to information about impurities that may cause FDA to refuse to receive (RTR) an ANDA.[3,4] An RTR decision indicates that FDA determined that an ANDA is not sufficiently complete to permit a substantive review.[5]

Typical deficiencies leading to an RTR decision include: (1) failing to provide justification for proposed limits in drug substances and drug products for ***specified identified impurities*** that are above qualification thresholds; (2) failing to provide justification for proposed limits 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.

This guidance is not meant to be a comprehensive list of deficiencies in relation to impurity information that may or will lead FDA to make an RTR determination. Rather, this guidance clarifies that a failure to provide justification for proposed impurity limits may lead FDA to RTR

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
[2] For purposes of this guidance, the use of the term *ANDA* will mean ANDAs **and** new-strength PAS submissions.
[3] This should not be confused with a *refuse-to-approve determination.*
[4] The following types of products are currently excluded from this guidance: (1) biological/biotechnologicals; (2) peptides; (3) oligonucleotides; (4) radiopharmaceuticals; (5) fermentation products; (6) semisynthetic products derived from fermentation products; (7) herbal products; (8) crude products of animal or plant origin; and (9) enantiomeric impurities. For additional information on the applicability to ANDAs, see guidances for industry *ANDAs: Impurities in Drug Substances*; *ANDAs: Impurities in Drug Products*; See also, guidances for industry *Q3A(R) Impurities in New Drug Substances* (Q3A(R)); and *Q3B(R2) Impurities in New Drug Products* (Q3B(R2)).
[5] 21 CFR 314.101(b)(1).

an ANDA. It also makes recommendations to ensure that applicants include appropriate justification for impurities in their ANDA submissions.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.[6]

II. BACKGROUND

Pursuant to the enactment of the Generic Drug User Fee Amendments of 2012 (GDUFA),[7] the Office of Generic Drugs (OGD) is tasked with a number of activities, including the development of "enhanced refusal to receive standards for ANDAs and other related submissions by the end of year 1 of the program…."[8] Enhanced RTR standards are important because the practice of submitting an ANDA that is not sufficiently complete to permit a substantive review, which then is "repaired" via several cycles of applicant resubmission and FDA response, is inherently inefficient and wasteful of resources.

FDA evaluates each submitted ANDA individually to determine whether it can be received for Agency review. FDA's receipt of an ANDA means the Agency has made a threshold determination that the ANDA is sufficiently complete to permit a substantive review.[9] FDA's regulations at 21 CFR 314.101 provide the regulatory authority by which FDA may in certain cases, and will in others, RTR an ANDA.[10]

Generally, FDA will not receive an ANDA for substantive review unless it contains the information required under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and in 21 CFR 314.101 and other regulations, for example:[11]

- 21 CFR 314.50
- 21 CFR 314.94
- 21 CFR 320.21

[6] At various points this guidance notes that when FDA sees a particular type of deficiency in an ANDA it *will* RTR the ANDA. It is important to understand that such statements do not impose legal obligations on applicants or on FDA, but are included for purposes of transparency. This means that FDA, in the normal course, will RTR an ANDA on the grounds described in this guidance. This guidance does not preclude the possibility that an ANDA applicant may be able to demonstrate, in particular circumstances, that the regulatory requirements for receiving an ANDA have been met even when, as described in this guidance, FDA would in the normal course find the application not sufficiently complete and RTR it.

[7] Generic Drug User Fee Amendments of 2012 (GDUFA), Public Law 112-144, Title III.

[8] See Generic Drug User Fee Act Program Performance Goals and Procedures (the Commitment Letter): http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

[9] See 21 CFR 314.101(b)(1).

[10] See 21 CFR 314.101(d) -(e).

[11] In certain cases, other statutes or regulations may apply.

- 21 CFR 320.22

This guidance focuses on when FDA expects to RTR an ANDA because it lacks justification for proposed impurity limits.[12]

III. JUSTIFYING IMPURITY LIMITS IN DRUG SUBSTANCES AND PRODUCTS

All ANDAs must contain a description of the composition, manufacture, and specifications of the drug substance and the drug product (see 21 CFR 314.94(a)(9) and 314.50(d)(1)). Applicants are required to submit a full description of the drug substance including, but not limited to: its method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance (§314.50(d)(1)(i)). Applicants are also required to submit a list of all components used in the manufacture of the drug product[13] (regardless of whether they appear in the drug product) and a statement of the specifications for each component and the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product (§314.50(d)(1)(ii)(a)). To ensure purity, applicants should propose and justify appropriate limits on the impurities in their drug substances and drug product.

A. Refusal to Receive for Lack of Impurities Information

FDA may RTR an ANDA that is not sufficiently complete because it does not on its face contain information required under §314.94, which includes a demonstration of the purity of the drug substance and drug product and information on impurities and residues (§§314.101(d)(3), 314.94(a)(9) (requiring ANDA to contain the information required under § 314.50(d)(1)) (see also *Final Rule on Abbreviated New Drug Applications*, 57 FR 17950 at 17959 (Apr. 28, 1992)).[14]

Accordingly, FDA may RTR an ANDA for: (1) failing to provide justification for proposed limits in drug substances and drug products for ***specified identified impurities*** that are above qualification thresholds; (2) failing to provide justification for proposed limits for ***specified unidentified impurities*** that are above identification thresholds; and (3) proposing limits for

[12] At the time of filing, FDA reviews the content of an ANDA to determine, among other things, whether the ANDA applicant has provided a complete justification for proposed impurity limits. FDA does not conduct a thorough review of the justification of the proposed impurity limits until after filing, during technical review of the ANDA. To help applicants ensure the appropriate purity of their drug substance (§314.50(d)(1)(i)) and drug product (§314.50(d)(1)(ii)(a)), FDA has published the following guidances for industry: *ANDAs: Impurities in Drug Substances; ANDAs: Impurities in Drug Products;* and *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* .

[13] Impurities that are monitored in the drug product are classified as degradation products. Process impurities from the drug substance synthesis are normally controlled during drug substance testing, and therefore are not generally included in drug product specifications, unless they are also degradation products.

[14] "As for possible impurities or residues in the ANDA product, ANDA applicants would be required to provide information on the drug substance and the drug product as part of the chemistry, manufacturing, and controls section of the application. This would include information on impurities and residues." 57 FR 17950 at 17959.

unspecified impurities (e.g., any unknown impurity) above 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* for more information on the characterization of impurities for drug substances and drug products.

B. Providing Justification for Impurity Limits

As stated in Section II, to help applicants ensure the appropriate purity of their drug substance (§314.50(d)(1)(i)) and drug product (§314.50(d)(1)(ii)(a)), FDA has published two guidances for industry: *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products*. These guidances provide recommendations on what CMC information applicants should include regarding the reporting, identification, and qualification of impurities in drug substances and impurities that are classified as degradation products in drug products. These guidances provide recommendations for justifying appropriate impurity limits[15] in a drug substance or drug product.[16]

If a generic product contains ***specified identified impurities*** that exceed the qualification thresholds[17] or ***specified unidentified impurities***[18] that exceed identification thresholds,[19,20,21] the ANDA should propose impurity limits and include supporting data to demonstrate that:

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[15] The terms "impurity limit" as used in this guidance and "acceptance criterion" as used in the FDA guidances referenced above in this paragraph and in note 4 are synonymous.

[16] The referenced guidances apply to drug substances and drug products, generally. However, if FDA has issued a product-specific guidance, the most stringent impurity identification or qualification threshold would apply. For example, the guidance for industry *Nasal Spray and Inhalation Solution Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* states that unspecified impurities (degradation products) at levels of 0.1% or greater should be specified. Therefore, for these specific products, the limits for unspecified impurities (degradation products) should not exceed 0.1%.

[17] See guidances for industry Q3A(R) and Q3B(R2). Identification and qualification thresholds should be based on the maximum daily dose (MDD) of the drug and total daily intake of impurities, which refers to the publicly available drug product dosage labeling. These thresholds should be reported as a percentage, and percentages should be based on lowest total daily intake (TDI) of impurities per ICH guidance tables for all impurities.

[18] See supra, note 16. When specified unidentified impurities are listed in the specification, FDA recommends that applicants describe the identification efforts attempted and clearly identify the procedure used and assumptions made in establishing the level of the impurity. It is important that specified unidentified impurities are referred to by an appropriate qualitative analytical descriptive label (e.g., unidentified A, unidentified with relative retention of 0.9).

[19] See supra, note 16. In some cases, it may be appropriate to decrease the threshold for qualifying impurities. For example, if there is evidence that an impurity in certain drug classes or therapeutic classes has previously been associated with adverse reactions in patients, it may be important to establish a lower qualification threshold. When such circumstances arise, and when these circumstances have not already been contemplated in a product-specific guidance, these changes will not be evaluated during the filing review but will be addressed during the technical review of the ANDA.

[20] See guidances for industry Q3A(R) and Q3B(R2) for definitions of an *identified impurity*, *identification threshold*, *qualification*, and *qualification threshold*.

[21] Acceptance criteria for unspecified impurities should not exceed the identification threshold in the guidances for industry Q3A(R) and Q3B(R2), even in the case when higher acceptance criteria for unspecified (other) impurities are listed in the U.S. Pharmacopeia (USP) monograph. If the acceptance criteria for unspecified (other) impurities

(1) the observed impurity levels and proposed impurity limits do not exceed the level observed in the reference listed drug (RLD) product;[22]
(2) the impurity is a significant metabolite of the drug substance;[23]
(3) the observed impurity levels and proposed impurity limits are adequately justified by the scientific literature;[24]

or

(4) the observed impurity levels and proposed impurity limits do not exceed the level that has been adequately evaluated in toxicity studies.[25]

FDA will RTR an ANDA under §314.101(d)(3) if the ANDA 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, respectively, as described above. Also, FDA will RTR an ANDA under §314.101(d)(3) with proposed limits for ***unspecified impurities*** that exceed identification thresholds.

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in the USP monograph are lower than the identification threshold in Q3A(R) and Q3B(R2), the acceptance criteria for unspecified impurities should be set to the USP level.

[22] In the event that the RLD is no longer marketed, thereby preventing the ANDA applicant from obtaining samples to conduct a comparative analysis, an applicant is required to provide a justification of the proposed impurity limits based on other criteria delineated in this guidance (e.g., metabolite, scientific literature, or toxicity studies) in order for that ANDA to be received. An applicant that wishes to use an alternative approach is encouraged to submit a controlled correspondence to determine the acceptability of the approach prior to ANDA submission.

[23] The guidances for industry *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products* state that a significant metabolite of the drug substance is considered qualified. However, if the level of the significant metabolite impurity is too high, other quality attributes, such as potency, could be significantly affected. In this case, FDA recommends that the acceptance criterion be set lower than the qualified level.

[24] If the applicant relies on published literature, complete and legible copies of each publication should be included in the ANDA submission.

[25] The toxicity assessment should also include an evaluation of potentially genotoxic impurities (PGI) that may include in silico, in vitro and/or in vivo analyses.