ANDA Submissions — Refuse to Receive for Lack of Proper Justification of Impurity Limits

Guidance for Industry

DRAFT GUIDANCE

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

September 2014
Generic Drugs

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist applicants preparing to submit to the Food and Drug Administration (FDA) 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* an ANDA.[3,4] A refuse-to-receive decision indicates that FDA determined that an ANDA is not sufficiently complete to permit a substantive review.[5]

Typical deficiencies leading to a refuse-to-receive decision include: (1) failing to provide adequate justification for proposed limits in drug substances and drug products for ***specified identified impurities*** that are above qualification thresholds; (2) failing to provide adequate justification for proposed limits for ***specified unidentified impurities*** that are above

[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 not covered in this guidance because there are currently no specifically defined identification and qualification thresholds for impurities: (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. See FDA's guidances for industry *ANDAs: Impurities in Drug Substances*, *ANDAs: Impurities in Drug Products*, *Q3A(R) Impurities in New Drug Substances* (ICH Q3A(R)), and *Q3B(R) Impurities in New Drug Products* (ICH Q3B(R)). The guidances referenced in this document are available on FDA's drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check FDA's drugs guidance Web page.

[5] 21 CFR 314.101(b)(1).

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 to a refuse-to-receive determination by FDA. Instead, this guidance clarifies that a failure to provide proper justification for proposed impurity limits may lead FDA to refuse to receive an ANDA. It also makes recommendations to ensure that appropriate justification for impurities are submitted in ANDAs. This guidance is being issued concurrently with the guidance for industry *ANDA Submissions – Refuse to Receive Standards*.

FDA's guidance documents, including this guidance, 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 refuse-to-receive standards are important because the practice of submitting an ANDA that is not sufficiently complete and then "repairing" it in the course of an extended review period that needs several cycles of FDA response and applicant repair is inherently inefficient and wasteful of resources. In addition, ANDAs that are not sufficient to permit a substantive review generate extra reviews and letters.

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

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[6] At various points in this guidance, it is noted that when a particular type of deficiency in an ANDA is seen, FDA *will* refuse to receive the ANDA. It is important to understand that these statements do not create legal obligations, on applicants, or on FDA, but are included for purposes of transparency. This means that FDA, in the normal course, will refuse to receive 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 refuse to receive 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).

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

- 21 CFR 314.50
- 21 CFR 314.94
- 21 CFR 320.21
- 21 CFR 320.22

This guidance focuses on when FDA expects to refuse to receive an ANDA because it lacks proper justification for proposed impurity limits.

III. JUSTIFYING IMPURITY LIMITS IN DRUG SUBSTANCES AND PRODUCTS

All ANDAs must contain a description of the composition, manufacture and specification 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[12] (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 of the impurities in their drug substances and drug products.

A. Refusal to Receive for Lack of Impurities Information

FDA may refuse to receive an ANDA that is not sufficiently complete because it does not on its face contain information required under §314.50, which includes a demonstration of the purity of the drug substance and drug product and information on impurities and residues (§314.101(d)(3)) (see also *Final Rule on Abbreviated New Drug Applications* 57 FR 17950 at 17959).[13]

Accordingly, FDA may refuse to receive an ANDA for: (1) failing to provide adequate justification for proposed limits in drug substances and drug products for specified ***identified***

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

[12] 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.

[13] "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).

impurities that are above qualification thresholds; (2) failing to provide adequate 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) above identification thresholds.

B. Providing Proper Justification for Impurity Limits

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 chemistry, manufacturing, and controls (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 the criteria for justifying appropriate impurity limits[14] in the drug substance and drug product.[15]

If a generic product contains ***specified identified impurities*** that exceed the qualification thresholds[16] or ***specified unidentified impurities***[17] that exceed identification thresholds,[18,19,20] the ANDA should propose impurity limits and include supporting data to demonstrate that:

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[14] The term *impurity limit* as used in this draft guidance and *acceptance criterion* used in the FDA guidances referenced in note 16 are synonymous.

[15] The referenced guidances apply to drug substance and drug products, generally. However, if FDA has issued a product-specific guidance, the more stringent impurity identification or qualification threshold applies. 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%.

[16] See guidances for industry *ANDAs: Impurities in Drug Substances*, *ANDAs: Impurities in Drug Products*, ICH Q3A(R), and ICH Q3B(R). Identification and qualification thresholds should be based on maximum daily dose (MDD) of the drug and total daily intake of impurities. These thresholds should be reported as a percentage, and percentages should be based on lower total daily intake (TDI) of impurities per ICH guidance tables for all impurities.

[17] See supra note 15. 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).

[18] See supra note 15. 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, these changes will not be evaluated during the filing review but will be addressed during the technical review of the ANDA.

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

[20] Acceptance criteria for unspecified impurities should be set not to exceed the identification threshold in ICH Q3A(R), even in the case when higher acceptance criteria for unspecified (other) impurities are listed in the United States Pharmacopeia (USP) monograph. If the acceptance criteria for unspecified (other) impurities in the USP

(1) the observed impurity levels and proposed impurity limits do not exceed the level observed in the reference listed drug product;
(2) the impurity is a significant metabolite of the drug substance;[21]
(3) the observed impurity levels and proposed impurity limits are adequately justified by the scientific literature; or
(4) the observed impurity levels and proposed impurity limits do not exceed the level that has been adequately evaluated in toxicity studies.

FDA will refuse to receive 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. FDA will refuse to receive an ANDA under §314.101(d)(3) with proposed limits for ***unspecified impurities*** that exceed identification thresholds.[22]

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.

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

[21] 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, like potency, could be significantly affected. In this case, it is recommended that the acceptance criterion be set lower than the qualified level.

[22] See guidances for industry *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products.* FDA may refuse to receive an ANDA for any unspecified and unidentified impurities that exceed the recommended identification thresholds found in current guidances referenced.