Guidance for Industry

ANDAs: Impurities in Drug Substances

DRAFT GUIDANCE

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For questions regarding this draft document, contact M. Scott Furness, (301) 827-5845.

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

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Revision 1

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ANDAs: Impurities in Drug Substances

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If you plan to submit comments on this draft guidance, we recommend that you note the following suggestions to help expedite FDA review of your comments:

- *Clearly explain each issue/concern. You may include a proposed revision for FDA consideration, along with a rationale or justification for the revision.*
- *Identify specific comments by line numbers.*
- *If possible, use the pdf version of the document.*
- *If possible, e-mail an electronic copy (Word) of the comments you have submitted to the docket to cummingsd@cder.fda.gov.*

I. INTRODUCTION

This guidance provides revised recommendations on what chemistry, manufacturing and controls (CMC) information to include regarding the reporting, identification, and qualification of impurities in drug substances produced by chemical synthesis when submitting:[1]

- Original abbreviated new drug applications (ANDAs)
- Drug master files (DMFs) including type II DMFs
- ANDA supplements for changes in drug substance synthesis or process

The guidance also provides recommendations for establishing acceptance criteria for impurities in drug substances. The guidance, when finalized, will replace a 1999 guidance of the same name.

This guidance does not apply to DMFs referenced in ANDAs or ANDA supplements if the FDA has already accepted a DMF for that dosage form, route of administration, and daily intake prior to publication of the final version of this guidance. This guidance also does not apply to

[1] See 21 CFR 314.94(a)(9).

applications for peptide, oligonucleotide, radiopharmaceutical, fermentation, and semisynthetic products derived from herbal products or crude products of animal or plant origin.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency'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.

II. BACKGROUND

We are revising the guidance for industry titled *ANDAs: Impurities in Drug Substances*, published in November 1999, for the following reasons:

1. To update information on listing of impurities, setting acceptance criteria, and qualifying impurities (thresholds and procedures) in ANDAs in conformance with the revision of the guidance for industry (February 2003) on *Q3A Impurities in New Drug Substances (Q3A)(R).*

2. To remove those sections of the 1999 guidance containing recommendations that are no longer needed because they are addressed in the more recent *Q3A(R)* (See the list below).

The *Q3A(R)* was developed by the International Conference on Harmonisation (ICH) to provide guidance on impurities in drug substances for new drug applications (NDAs). However, the Agency believes that many of the recommendations provided on impurities in drug substances also apply to ANDAs. Please refer to the following specific sections in the *Q3A(R)* for these recommendations:

- Section I, Introduction
- Section II, Classification of Impurities
- Section III, Rationale for the Reporting and Control of Impurities
- Section IV, Analytical Procedures
- Section V, Reporting Impurity Content of Batches
- Attachment 1, Threshold Levels (for reporting, identification, and qualification)

III. LISTING OF IMPURITIES AND SETTING ACCEPTANCE CRITERIA FOR IMPURITIES IN DRUG SUBSTANCE SPECIFICATIONS

A. Listing of Impurities in Drug Substance Specifications

We recommend that the specifications for a drug substance include a list of impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product. It is important that the list of impurities for the drug substance specification be based on impurities found in the batch(es) manufactured by the proposed commercial process.

We recommend that you include in your submission a rationale for the inclusion or exclusion of impurities in the drug substance specification. It is important that the rationale include a discussion of the impurity profiles observed in the batch(es) under consideration together with a consideration of the impurity profile of the batch(es) manufactured by the proposed commercial process.

Individual impurities with a specific acceptance criterion that are included in the specification for a drug substance are referred to as *specified impurities* in this guidance. Specified impurities can be *identified* or *unidentified*.

We recommend that *identified* specified impurities be included in the list of impurities along with *unidentified* specified impurities that are estimated to be present at a level greater than the identification threshold given in *Q3A(R)*. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, we recommend that the quantitation and/or detection limit of the analytical procedures correspond to the level at which the impurities are expected to be controlled.

For *unidentified* impurities to be listed in the drug substance specification, we recommend that you clearly state the procedure used and assumptions made in establishing the level of the impurity. It is important that *unidentified* specified impurities be referred to by an appropriate qualitative analytical descriptive label (e.g., unidentified A, unidentified with relative retention of 0.9). We recommend that you also include general acceptance criteria of not more than the identification threshold (see *Q3A(R)* in Attachment 1) for any unidentified impurity and acceptance criteria for total impurities.

We recommend that the drug substance specification include, where applicable, a list of the following types of impurities:

- Organic impurities
  - Each identified specified impurity
  - Each unidentified specified impurity
  - Any unspecified impurity with an acceptance criterion of not more than (≤) the figure in the identification threshold in Attachment 1, *Q3A(R)*
  - Total impurities
- Residual solvents
- Inorganic impurities

B. Setting Acceptance Criteria for Impurities

We recommend that the acceptance criterion be set no higher than the qualified level (see section IV, Qualification of Impurities). In establishing impurity acceptance criteria, the first critical consideration is whether an impurity is specified in the United States Pharmacopeia (USP). If there is a monograph in the USP that includes a limit for an identified specified impurity, we recommend that the acceptance criterion be set no higher than the official compendial limit.

However, if the level of the impurity is above the level specified in the USP, we recommend qualification. Then, if appropriate qualification has been achieved, an applicant may wish to petition the USP for revision of the impurity's acceptance criterion.

If the acceptance criterion for a drug substance impurity does not exist in the USP and this impurity can be qualified by comparison with an FDA-approved human drug product, it is important that the acceptance criterion be consistent with the level observed in the approved human drug product. In other circumstances, the acceptance criterion may need to be set lower than the qualified level to ensure drug substance quality. For example, if the level of the metabolite impurity is too high, other quality attributes, like potency, could be seriously affected. In this case, we would recommend that the impurity acceptance criterion be set lower than the qualified level.

We recommend that ANDA sponsors develop robust formulations and manufacturing processes that are based on sound state-of-the-art scientific and engineering principles and knowledge. Although routine manufacturing variations are expected, significant variation in batch-to-batch impurity levels or an unusually high level of impurity may indicate that the manufacturing process of the drug substance is not adequately controlled or designed.

IV. QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) being considered. When appropriate, we recommend that applicants provide a rationale for establishing impurity acceptance criteria that includes safety considerations.

An impurity is considered qualified when it meets one or more of the following conditions:

- When the observed level and proposed acceptance criterion for the impurity do not exceed the level observed in an FDA-approved human drug product.
- When the impurity is a significant metabolite of the drug substance.
- When the observed level and the proposed acceptance criterion for the impurity are adequately justified by the scientific literature.

- When the observed level and proposed acceptance criterion for the impurity do not exceed the level that has been adequately evaluated in comparative *in vitro* genotoxicity studies.

Although Quantitative Structure Activity Relationships (QSAR) programs may be used for prediction of toxicity of an individual impurity or a given impurity profile, the results are not generally considered conclusive for qualification purposes.

A. Qualification Thresholds

Recommended qualification thresholds[2] based on the maximum daily dose of the drug substance are provided in ICH *Q3A(R)*. When these qualification thresholds are exceeded, we recommend that impurity levels be qualified. In some cases, it may be appropriate to increase or decrease the threshold for qualifying impurities. For example, when 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. Conversely, when the concern for safety is low, a higher threshold for qualifying impurities may be appropriate. The FDA will consider proposals for applications for alternative qualification thresholds on a case-by-case basis after considering issues such as patient population, drug class effects, and historical safety data.

B. Qualification Procedures

The decision tree in Attachment 1 describes considerations for the qualification of an impurity when the usual qualification threshold recommended in ICH *Q3A(R)* is exceeded. In some cases, decreasing the level of the impurity below the threshold rather than providing additional data can be the simplest course of action. Alternatively, adequate data could be available in the scientific literature to qualify the impurity. The studies considered appropriate to qualify the impurity will depend on a number of factors, including the patient population, daily dose, and route and duration of drug administration. Such studies can be conducted on the drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate. The following are descriptions of methods for qualifying impurities.

1. Comparative Analytical Studies

An impurity present in a drug substance covered by an ANDA can be qualified by comparing the analytical profiles of the drug substance with those in an approved human drug product using the same validated, stability-indicating analytical procedure (e.g. comparative HPLC studies). This approved human drug product is generally the reference listed drug (RLD). However, you may also compare the profile to a different drug product with the same route of administration and similar characteristics (e.g., tablet versus capsule) if samples of the reference listed drug are unavailable or for an ANDA submitted pursuant to a suitability petition. We recommend that

[2] *Qualification threshold* is defined as a limit above (>) which an impurity should be qualified.

you conduct the stability studies on comparable samples (e.g., age of samples) to get a meaningful comparison of the impurity profiles.

An impurity present in the ANDA drug substance is considered qualified if the amount of identified impurity in the ANDA drug substance reflects the levels observed in the corresponding approved human drug product.

2. Scientific Literature and Significant Metabolites

If the level of the identified specified impurity is adequately justified by the scientific literature, no further qualification is considered necessary. In addition, an impurity that is also a significant metabolite of the drug substance is generally considered qualified.

3. Genotoxicity Studies

Comparative *in vitro* genotoxicity tests are the least preferred method to qualify impurities because they are the most time consuming and costly of the methods described. We recommend the tests be used only when impurities cannot be qualified by either of the above procedures (section IV.B.1 or 2). The tests are designed to detect compounds that induce genetic damage directly or indirectly by various mechanisms. If performed, such studies should be conducted on the drug product or drug substance containing the impurities to be controlled, although studies using the isolated impurities may also be used.

232 **ATTACHMENT 1: IDENTIFICATION AND QUALIFICATION OF IMPURITIES IN**
233 **DRUG SUBSTANCES**
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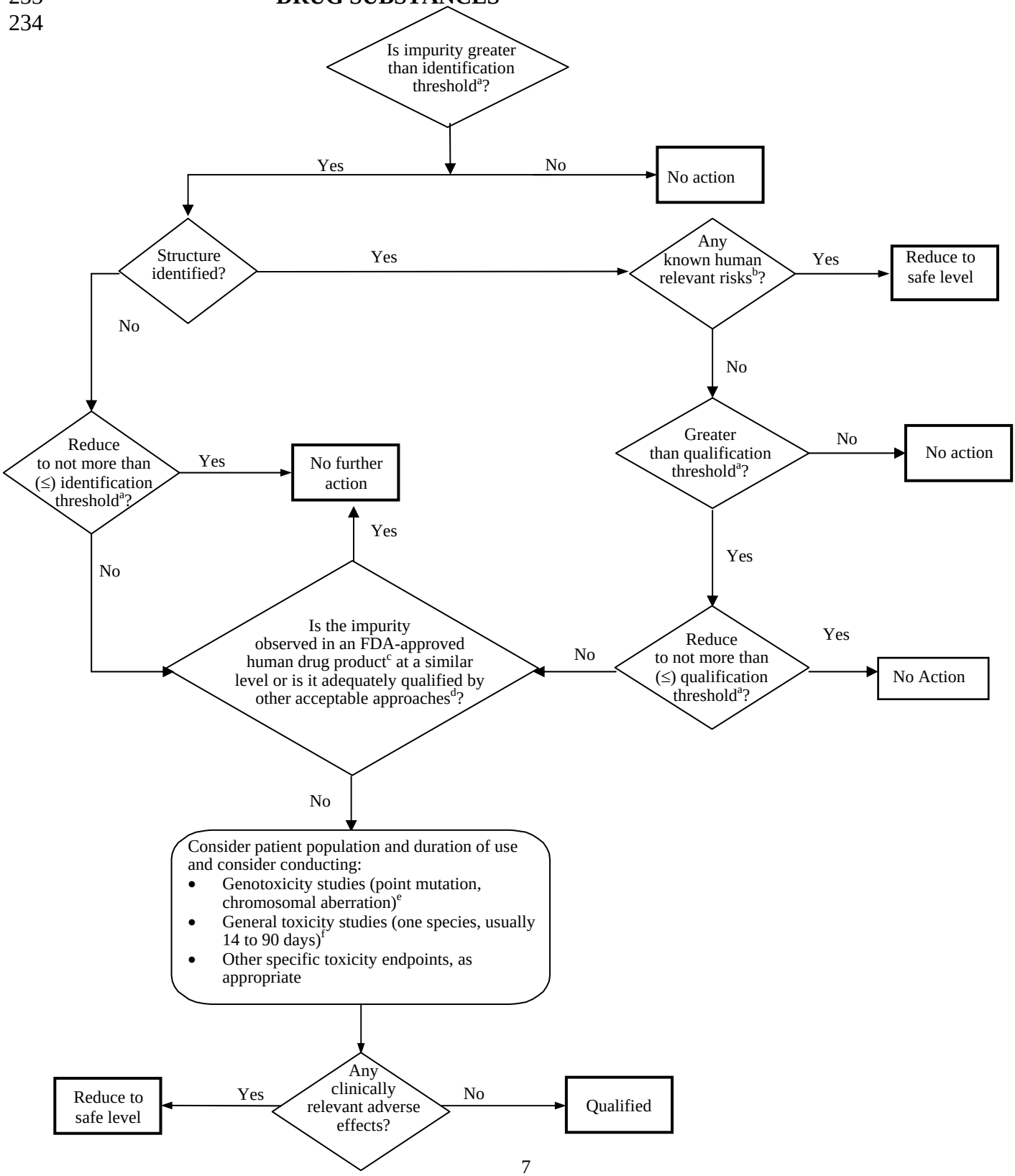

Notes on Attachment 1

[a] Lower thresholds can be appropriate if the impurity is unusually toxic.

[b] For example, do known safety data for this impurity or its structural class preclude human exposure at the observed level?

[c] In this context, an FDA-approved human drug product generally refers to the reference listed drug. It may also include a different drug product with the same route of administration and similar characteristics such as tablet versus capsule.

[d] An impurity is considered qualified for ANDAs when one or more of the following conditions are met:

- When the observed level and proposed acceptance criterion for the impurity do not exceed the level justified by an FDA-approved human drug product.
- When the impurity is a significant metabolite of the drug substance.
- When the observed level and the proposed acceptance criterion for the impurity are adequately justified by the scientific literature.
- When the observed level and proposed acceptance criterion for the impurity do not exceed the level that has been adequately evaluated in comparative *in vitro* genotoxicity studies.

[e] If appropriate, a minimum screen (e.g., genotoxic potential) should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are considered an appropriate minimum screen.

[f] If general toxicity studies are appropriate, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential for detecting the toxicity of an impurity. On a case-by-case basis, single dose studies can be appropriate, especially for single dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.