Guidance for Industry

ANDAs: Impurities in Drug Substances

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

June 2009
Office of Generic Drugs

Revision 1

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Contains Nonbinding Recommendations

Guidance for Industry[1]
ANDAs: Impurities in Drug Substances

This guidance represents 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 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[2]:

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

The guidance also provides recommendations for establishing acceptance criteria for impurities in drug substances.

The following types of drug substances are not covered in this guidance:

- Biological/biotechnological
- Peptide
- Oligonucleotide
- Radiopharmaceutical
- Fermentation products
- Semisynthetic products derived from fermentation products
- Herbal products
- 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

[1] This guidance was prepared by the Office of Generic Drugs, Office of Pharmaceutical Science, in the Center for Drug Evaluation and Research at the Food and Drug Administration.

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

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

In November 1999, FDA published the first version of this guidance. As a result of changes to recommendations on impurities in drug substances for new drug applications (NDAs), which the International Conference on Harmonisation (ICH) included in the guidance for industry on *Q3A Impurities in New Drug Substances* (Revision 1) (Q3A(R)) in 2003, we began an effort to revise this guidance for ANDAs.[3] On January 31, 2005 (70 FR 4857), FDA announced the availability of a draft revision for public comment. The comment period closed on June 6, 2005. A number of comments were received, which the agency considered carefully as it began the process of finalizing the guidance.

FDA believes that much of the content of the Q3A(R) guidance applies to ANDAs. See especially sections I through V and the Attachment, Thresholds.[4]

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

Applicants submitting ANDAs, DMFs, including type II DMFs, and ANDA supplements for changes in the synthesis or processing of a drug substance are required to submit the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance.[5] Submissions should list impurities and set acceptance criteria for those impurities in the drug substance specifications.

A. Listing 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.

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[3] CDER guidance documents can be found on the Internet 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 the CDER guidance Web site.

[4] Please note that in June 2008, FDA published a second revision of ICH Q3A(R) that updated an attachment that is not needed in the ANDA guidance.

[5] 21 CFR 314.50(d)(1)(i).

Applicants should also include in their 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.

In this guidance, individual impurities with a specific acceptance criterion that are included in the specification for a drug substance are referred to as *specified impurities*. Specified impurities can be *identified* or *unidentified*. We recommend that specified identified impurities be included in the list of impurities along with specified unidentified 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.

When specified unidentified impurities are listed in the drug substance specification, we recommend that applicants also describe the identification efforts attempted and clearly state the procedure used and assumptions made in establishing the level of the impurity. It is important that specified unidentified 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 for any unspecified impurity and the acceptance criteria for total impurities (see Attachment 1, Q3A(R)).

Where applicable, the drug substance specification should include a list of the following types of impurities:

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

B. Setting Acceptance Criteria for 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 a specified impurity, we recommend that the acceptance criterion be set no higher than the official compendial limit.

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

If a limit for a specified impurity does not exist in the USP, we recommend that you qualify the impurity by comparing it to the observed amounts of the impurity in the reference listed drug product (RLD). Your acceptance criterion should be similar to the level observed in the RLD. Alternatively, the acceptance criterion may be set based on a qualified level that is justified by scientific literature, metabolite data, or toxicity studies.

In some 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 a metabolite impurity is too high, other quality attributes, like potency, could be seriously affected. In this case, we recommend that the impurity acceptance criterion be set lower than the qualified level.

Acceptance criteria for unspecified impurities in ANDAs should be set not to exceed the identification threshold in Attachment 1, Q3A(R), even in the case when higher acceptance criteria for unspecified (other) impurities are listed in the USP monograph. If the acceptance criteria for unspecified (other) impurities in the USP monograph are lower than the identification threshold in Attachment 1, Q3A(R), the acceptance criteria for unspecified impurities should be set to the USP level.

IV. QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data that establish 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:

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

Although Quantitative Structure Activity Relationships (QSAR) programs may be used for predicting the 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*[6] based on the maximum daily dose of the drug substance are provided in 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, a higher threshold for qualifying impurities may be appropriate when the concern for safety is low. Therefore, we will consider proposals 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 the Attachment to this guidance describes what to consider for the qualification of an impurity when the usual qualification threshold recommended in 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 the RLD using the same validated, stability-indicating analytical procedure (e.g., comparative HPLC studies).

A specified impurity present in the ANDA drug substance is considered qualified if the amount of the impurity in the ANDA drug substance is similar to the levels observed in the RLD.

2. Scientific Literature and Significant Metabolites

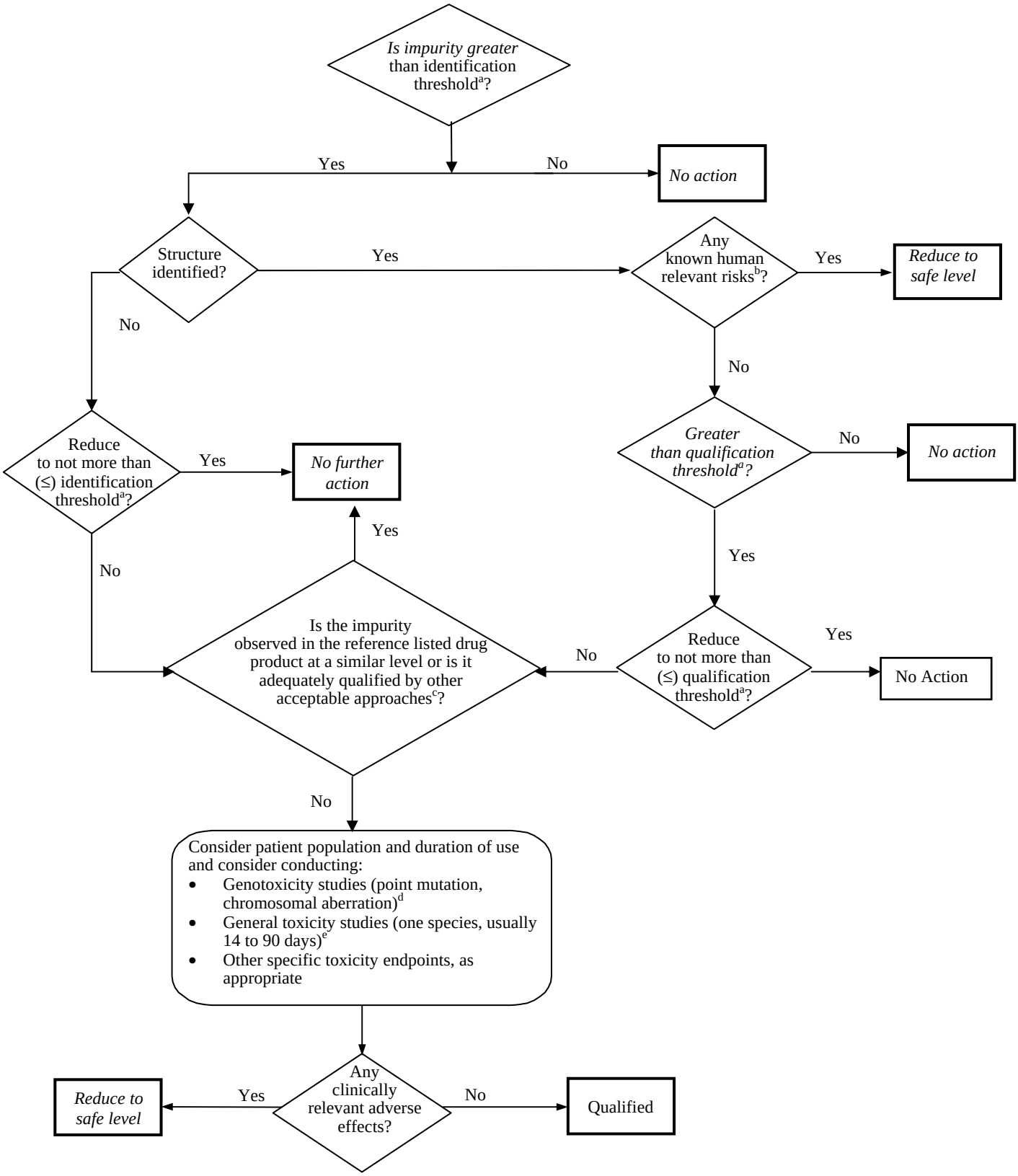
If the level of the specified identified impurity is adequately justified by the scientific literature, no further qualification is considered necessary. In addition, an impurity that is also a significant metabolite of the drug substance is generally considered qualified.

3. Toxicity Studies

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

Toxicity tests are the least preferred method to qualify impurities. 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 general toxic or genotoxic effects in experimental systems. If performed, such studies should be conducted on the drug product or drug substance containing the impurities to be controlled, although studies using isolated impurities may also be used.

ATTACHMENT: IDENTIFICATION AND QUALIFICATION OF IMPURITIES IN DRUG SUBSTANCES



Notes on the Attachment

[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 require no human exposure at the observed level?

[c] A difference from Q3A(R), Attachment 3, is that an impurity is considered qualified for an ANDA when one or more of the following conditions are met:

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

[d] 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.

[e] 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.