Guidance for Industry

ANDAs: Impurities in Drug Products

DRAFT GUIDANCE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)

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Revision I

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ANDAs: Impurities in Drug Products

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- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale and/or justification for the proposed revision.*
- *Identify specific comments by line numbers; use the pdf version of the document whenever possible.*
- *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 recommendations on what chemistry, manufacturing and controls (CMC) information sponsors should include regarding the reporting, identification, and qualification of impurities that are classified as *degradation products* in drug products when submitting:[1, 2]

- Original abbreviated new drug applications (ANDAs)
- ANDA supplements for changes that may affect the quantitative or qualitative degradation product profile

The guidance also provides recommendations for establishing acceptance criteria for degradation products (specifically, degradation products of the active ingredient or reaction products of the active ingredient with an excipient(s) and/or immediate container/closure system) in generic drug products. The guidance will replace an existing 1998 draft guidance of the same name.

This guidance does not apply to an ANDA or ANDA supplement that has been reviewed prior to the publication of the final guidance.

[1] The recommendations in this guidance are limited to drug products that are manufactured from drug substances produced by chemical synthesis.

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

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We are revising the draft guidance for industry titled *ANDAs: Impurities in Drug Products*, issued in December 1998, for the following reasons:

1. To update information on listing of degradation products, setting acceptance criteria, and qualifying degradation products (thresholds and procedures) in ANDAs in conformance with the revision of the guidance for industry (November 2003) on *Q3B(R) Impurities in New Drug Products*.

2. To remove those sections of the 1998 draft guidance containing recommendations that are no longer needed because they are addressed in the more recent *Q3B(R)* (see the list below).

The *Q3B(R)* was developed by the International Conference on Harmonisation (ICH) to provide guidance on impurities in drug products for new drug applications (NDAs). However, the Agency believes that many of the recommendations provided on impurities in drug products also apply to ANDAs. Please refer to the following specific sections in the *Q3B(R)* for these recommendations:

- Section I, Introduction
- Section II, Rationale for the Reporting and Control of Degradation Products
- Section III, Analytical Procedures
- Section IV, Reporting Degradation Products, Content of Batches
- Attachment 1, Thresholds for Degradation Products

III. LISTING OF DEGRADATION PRODUCTS AND SETTING ACCEPTANCE CRITERIA FOR DEGRADATION PRODUCTS IN DRUG PRODUCT SPECIFICATIONS

A. Listing of Degradation Products

We recommend that the specification for a drug product include a list of degradation products. Stability studies, chemical development studies, and routine batch analyses can be used to predict the degradation profile for the commercial product. It is important that the list of degradation products for the drug product specification be based on degradation products 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 degradation products in the drug product specification. It is important that the rationale include a discussion of the degradation profiles observed in stability studies and in the degradation profiles observed in the batch(es) under consideration together with a consideration of the degradation profile of the batch(es) manufactured by the proposed commercial process.

Individual degradation products with specific acceptance criteria that are included in the specification for the drug product are referred to as "*specified degradation products*" in this guidance. Specified degradation products can be *identified* or *unidentified.*

We recommend that specified identified degradation products be included in the list of degradation products along with specified unidentified degradation products that are estimated to be present at a level greater than the identification threshold given in Q3B(R). For degradation products 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 degradation products are expected to be controlled.

For unidentified degradation products to be listed in the drug product specification, we recommend that you clearly state the procedure used and assumptions made in establishing the level of the degradation product. It is important that *specified unidentified* degradation products 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 *Q3B(R),* Attachment 1) for any unspecified degradation product and acceptance criteria for total degradation products.

We recommend that the drug product specification include, where applicable, a list of the following types of degradation products:

- Each specified identified degradation product
- Each specified unidentified degradation product
- Any unspecified degradation product with an acceptance criterion of not more than (≤) the figure in the identification threshold in Attachment 1, *Q3B(R)*
- Total degradation products

B. Setting Acceptance Criteria for Degradation Products

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

If the level of the degradation product 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 degradation product's acceptance criterion.

If the acceptance criterion for a specified degradation product does not exist in the USP and this degradation product can be qualified by comparison to an FDA-approved human drug product, the acceptance criterion should 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 product 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 degradation product 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 degradation product levels or an unusually high level of degradation products may indicate that the manufacturing process of the drug product is not adequately controlled or designed.

IV. QUALIFICATION OF DEGRADATION PRODUCTS

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

A degradation product is considered qualified when it meets one or more of the following conditions:

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

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

A. Qualification Thresholds

Recommended qualification thresholds[3] for degradation products based on the maximum daily dose of the drug are provided in ICH *Q3B(R)*. When these qualification thresholds are exceeded, we recommend that degradation product levels be qualified. In some cases, it may be

[3] *Qualification threshold* is defined as a limit above (>) which a degradation product should be qualified.

appropriate to increase or decrease the qualification threshold for qualifying degradation products. For example, when there is evidence that a degradation product 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 degradation products 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 degradation products when the usual qualification threshold recommended in ICH *Q3B(R*) is exceeded. In some cases, decreasing the level of the degradation product 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 degradation product. The studies considered appropriate to qualify the degradation product 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 product containing the degradation product to be controlled, although studies using isolated degradation products can sometimes be appropriate. The following are descriptions of methods for qualifying degradation products.

1. Comparative Analytical Studies

A degradation product present in a drug product covered by an ANDA can be qualified by comparing the analytical profiles of a generic drug product 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 in the case of an ANDA submitted pursuant to a suitability petition. It is essential that maximum daily doses of the degradation product and routes of administration should be taken into account for qualification by comparative analytical studies. The qualified threshold of a degradation product in a dosage form may not be applicable to all drug products containing that degradation product if the maximum daily doses or the routes of administration are different. We recommend that you conduct the stability studies on comparable samples (e.g., age of samples) to get a meaningful comparison of degradation profiles.

A degradation product present in the generic drug product is considered qualified if the amount of identified degradation product in the generic drug product reflects the levels observed in the corresponding approved human drug product.

2. Scientific Literature and Significant Metabolites

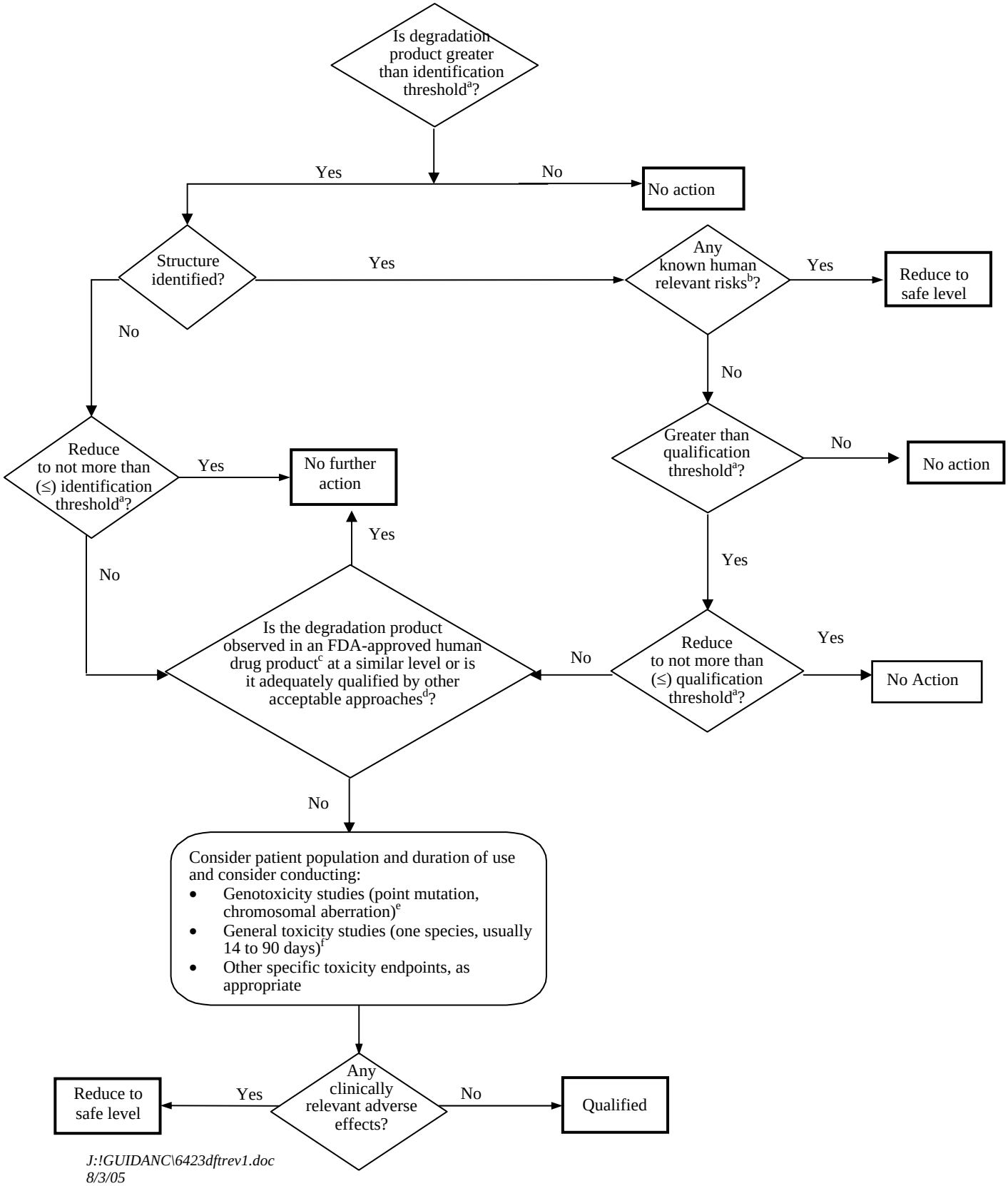
If the level of the specified identified degradation product is adequately justified by the scientific literature, no further qualification is considered necessary. In addition, a degradation product that is also a significant metabolite of the drug substance is generally considered qualified.

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

3. Toxicity Studies

Toxicity tests are the least preferred method to qualify degradation products. We recommend the tests be used only when degradation products 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 degradation products to be controlled, although studies using isolated degradation products may also be used.

ATTACHMENT 1: IDENTIFICATION AND QUALIFICATION OF DEGRADATION PRODUCTS IN GENERIC DRUG PRODUCTS



Notes on Attachment 1

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

[b] For example, do known safety data for this degradation product 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

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[d] A degradation product 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 degradation product do not exceed the level justified by an FDA-approved human drug product.
- When the degradation product is a significant metabolite of the drug substance.
- When the observed level and the proposed acceptance criterion for the degradation product are adequately justified by the scientific literature.
- When the observed level and proposed acceptance criterion for the degradation product do not exceed the level that has been adequately evaluated in toxicity studies.

[e] If considered desirable, 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 for genotoxicity.

[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 a degradation product. 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.