
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)
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*Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-2 IO
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane
Rockville, Maryland 20857
(Tel) 301-827-4573
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ANDAs: Impurities in Drug Substances

I. INTRODUCTION

This guidance provides recommendations for including information in abbreviated new drug applications (ANDAs) and supporting drug master files (DMFs) on the identification and qualification of impurities in drug substances produced by chemical syntheses for both monograph and nonmonograph drug substances.

Impurities in drug substances are addressed from two perspectives:

- Chemistry aspects, including classification and identification of impurities, generating reports, setting specifications, and a brief discussion of analytical procedures; and
- Safety aspects, including comparative studies and genotoxicity testing.

Specific guidance is provided for:

- Qualifying impurities found in a drug substance used in an ANDA by a comparison with impurities found in the related *U.S. Pharmacopeia* (USP) monograph, scientific literature, or innovator material;
- Qualifying impurities found at higher levels in a drug substance used in an ANDA than found in the related USP monograph, scientific literature, or innovator material;
- Qualifying impurities in a drug substance used in an ANDA that are **not** found in the related USP monograph, scientific literature, or innovator material; and
- Threshold levels below which qualification is not needed.

¹This guidance has been prepared under the direction of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the review of impurities in drug substances used in generic drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

This guidance is not applicable to biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation and semisynthetic products derived therefrom, herbal products, or crude products of animal or plant origin. The recommendations in this guidance are effective on publication and should be followed in preparing new applications and supplements for changes in drug substance synthesis or process. However, if the information in a drug substance DMF cited in such an ANDA or ANDA supplement has been reviewed prior to the publication of this final guidance, this guidance does not apply.

This guidance is intended to be a companion document to the International Conference on Harmonization (ICH) guidance *Q3A Impurities in New Drug Substances*.² The ICH Q3A guidance was published in the *Federal Register* on January 4, 1996 (61 FR 371), and issued as a Center for Drug Evaluation and Research (CDER) guidance. ICH Q3A provides recommendations for (1) inclusion of information regarding specified impurities in certain new drug applications (NDAs) (identified and unidentified impurities in new drug substance specifications) and (2) qualification of impurities (the process of acquiring and evaluating data that establishes the biological safety of individual impurities or a given impurity profile at the levels specified). Generic drugs are not covered by ICH Q3A; however, many of the recommendations in ICH Q3A are applicable to drug substances used in generic drug products. To provide, to the extent possible, comparable processes for new and generic drug review, this guidance was developed using the ICH Q3A framework.

At a meeting held June 22, 1993, an FDA Ad Hoc Advisory Committee recommended' that there should be a 0.1 percent threshold above which isolation and characterization of individual impurities should apply to chemically synthesized drug substances including drug substances used in generic drug products. For compendial materials, the USP 23 in *General Notices and Requirements* (p. 7) states that it is manifestly impossible to include in each monograph a test for every impurity that may arise from a change in the source of material or a change in processing. Consequently, few USP monographs have acceptance criteria for individually identified impurities. However, USP has adopted a 0.1 percent threshold for impurity identification via the publication of *Other Impurities in General Notices and Requirements* (Sixth Supplement, p. 3636), which became official on November 15, 1996.

II. CLASSIFICATION OF IMPURITIES

Impurities can be classified into the following categories:

- Organic Impurities (Process and Drug Related)
- Inorganic Impurities
- Residual Solvents

²*New drug substance* is defined in the Glossary.

Organic impurities may arise during the manufacturing process and/or storage of the drug substance. They may be identified or unidentified, volatile or nonvolatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands, and catalysts

Inorganic impurities may derive from the manufacturing process. They are normally known and identified and include:

- Reagents, ligands, and catalysts
- Heavy metals
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

Residual solvents are organic or inorganic liquids used during the manufacturing process. Because these are generally of known toxicity, the selection of appropriate controls is easily accomplished.

Excluded from this document are (1) extraneous contaminants, which should not occur in drug substances and are more appropriately addressed as good manufacturing practice issues; (2) polymorphic form, a solid state property of the drug substance; and (3) enantiomeric impurities.

III. RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

A. Organic Impurities

The DMF holder or the ANDA applicant should summarize those actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the drug substance, and possible degradation products. This discussion may include only those impurities that may reasonably be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the DMF holder or the ANDA applicant should summarize the laboratory studies conducted to detect impurities in the drug substance. This summary should include test results of materials manufactured during the development process and batches from the proposed commercial process, as well as results of intentional

degradation studies used to identify potential impurities that arise during storage. Assessment of the proposed commercial process may be deferred until the first batch is produced for marketing. The impurity profile of the drug substance lots intended for marketing should be compared with those used in development and any differences discussed.

The studies (e.g., NMR, IR, and MS) conducted to characterize the structure of actual impurities present in the drug substance at or above an apparent level of 0.1 percent (e.g., calculated using the response factor of the drug substance) should be described. All recurring impurities at or above an apparent level of 0.1 percent (see section IV) in batches manufactured by the proposed commercial process should be identified. Degradation products observed in stability studies at recommended storage conditions should be similarly identified. When identification of an impurity is infeasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the DMF or application. Where attempts have been made to identify impurities below the 0.1 percent level, it is useful also to report the results of these studies.

Identification of impurities below apparent levels of 0.1 percent is generally not considered necessary. However, identification should be attempted for those potential impurities that are expected to be unusually potent, producing toxic or pharmacologic effects at a level lower than 0.1 percent. In all cases, impurities should be qualified as described later in this guidance. Although it is common practice to round analytical results of between 0.05 and 0.09 percent to the nearest number (i.e., 0.1 percent), for the purpose of this guidance, such values should not be rounded to 0.1 percent in determining whether to identify the impurities.

B. Inorganic Impurities

Inorganic impurities are normally detected and quantitated using pharmacopeial or other appropriate procedures. Carryover of catalysts to the drug substance should be evaluated during development. The necessity for inclusion or exclusion of inorganic impurities in the drug substance specifications should be discussed. Acceptance criteria should be based on pharmacopeial standards or known safety data.

C. Residual Solvents

The control of residues of solvents used in the manufacturing process for the drug substance should be discussed. Any solvents that may appear in the drug substance should be quantified using analytical procedures with an appropriate level of sensitivity. Pharmacopeial or other appropriate procedures should be used. Acceptance criteria should be based on pharmacopeial standards or known safety data, taking into

consideration dose, duration of treatment, and route of administration. Particular attention should be given to quantitation of toxic solvents used in the manufacturing process as described in the ICH guidance *Q3C Impurities: Residual Solvents*.

IV. ANALYTICAL PROCEDURES

The DMF or abbreviated application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantitation of impurities. Differences in the analytical procedures used during development and proposed for the commercial product should be discussed in the DMF or abbreviated application.

Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the drug substance itself. Reference standards used in the analytical procedures for control of impurities should be evaluated and characterized according to their intended uses. It is considered acceptable to use the drug substance to estimate the levels of impurities when the response factors of the drug substance and impurities are close. In cases where the response factors are not close, this practice may still be acceptable, provided a correction factor is applied or the impurities are, in fact, being overestimated. Analytical procedures used to estimate identified or unidentified impurities are often based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in the DMF submission or abbreviated application.

V. REPORTING IMPURITY CONTENT OF BATCHES

Analytical results should be provided for all batches of the drug substance used for stability testing, as well as for batches representative of the proposed commercial process. The content of individual impurities, both identified and unidentified, and total impurities observed in these batches of the drug substance should be reported with the analytical procedures indicated. A tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor, for example, name or retention time. Levels of impurities that are present but are below the validated limit of quantitation (LOQ) need not be reported.

If analytical procedures change during development, reported results should be linked with the procedure used, and appropriate validation information should be provided. Representative chromatograms should be provided. Chromatograms of such representative batches, from methods validation studies showing separation and detectability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles. The ANDA applicant or DMF holder should ensure that complete impurity

profiles (i.e., chromatograms) of stability batches are available if requested. A tabulation should be provided comparing impurity levels between stability and other batches.

For each batch of the drug substance, the report should include:

- Batch identity and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Impurity content, individual and total
- Use of batches
- Reference to analytical procedures used

VI. ACCEPTANCE CRITERIA FOR IMPURITIES

The specification for a drug substance should include acceptance criteria for impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product. The selection of impurities to include in the drug substance specification should be based on the impurities found in the batches manufactured by the proposed commercial process. Those impurities selected for inclusion in the specification for the drug substance are referred to as *specified impurities* in this guidance. Specified impurities may be identified or unidentified and should be individually listed in the drug substance specification (see below).

A rationale for the inclusion or exclusion of impurities in the specification should be presented. This rationale should include a discussion of the impurity profiles observed in batches under consideration, together with a consideration of the impurity profile of material manufactured by the proposed commercial process. Specific identified impurities should be included along with recurring unidentified impurities estimated to be at or above 0.1 percent. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation and/or detection limit of the analytical methods should be commensurate with the level at which the impurities need to be controlled. For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated. Unidentified impurities included in the specification should be referred to by some appropriate qualitative analytical descriptive label (e.g., “unidentified A,” “unidentified with relative retention of 0.9”). Finally, a general acceptance criteria of not more than 0.1 percent for any unspecified impurity should be included.

Acceptance criteria should be set no higher than the level that can be justified (see the Impurities Decision Tree for generic drug substances, Attachment I) either by comparative studies or genotoxicity studies, and unless such data indicate otherwise, no lower than the level achievable

by the manufacturing process and the analytical capability. In other words, where there is no safety concern, impurity acceptance criteria should be based on data generated on actual batches of the drug substance, allowing sufficient latitude to deal with normal manufacturing and analytical variation, and the stability characteristics of the drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels could indicate that the manufacturing process of the drug substance is not adequately controlled and validated.

In summary, the drug substance acceptance criteria should include, where applicable, acceptance criteria for:

- **Organic Impurities:**
 - Each specified identified impurity
 - Each specified unidentified impurity at or above 0.1 percent
 - Any unspecified impurity, with a limit of not more than 0.1 percent
 - Total impurities
- **Residual Solvents**
- **Inorganic Impurities**

A summation of assay value and impurity levels generally may be used to obtain mass balance for the test sample. The mass balance need not add to exactly 100 percent because of the analytical error associated with each analytical procedure. The summation of impurity levels plus the assay value may be misleading, for example, when the assay procedure is nonspecific (e.g., potentiometric titrimetry) and the impurity level is relatively high.

VII. 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 levels specified. The DMF holder or the ANDA applicant should provide a rationale for selecting impurity acceptance criteria based on safety considerations. The level of any impurity present in a drug substance that is in compliance with a USP specification or has been adequately evaluated in comparative or in vitro genotoxicity studies or has been evaluated via an acceptable *Quantitative Structure Activity Relationships* (QSAR) database program is considered qualified for ANDAs. Impurities that are also significant metabolites do not need further qualification.

If data are unavailable to qualify the proposed acceptance criteria of an impurity, studies to obtain such data may be needed when the usual qualification threshold levels given below are exceeded:

Maximum Daily Dose	Qualification Threshold
≤2g/day	0.1 percent or 1 mg per day intake (whichever is lower)
>2g/day	0.05 percent

Higher or lower threshold levels for qualification of impurities may be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects. For example, qualification may be especially important when there is evidence that such impurities in certain drugs or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold level may be appropriate. Technical factors (manufacturing capability and control methodology) may be considered as part of the justification for selection of alternative threshold levels. Proposals from applicants for alternative threshold levels will be considered by the FDA on a case-by-case basis.

The Impurities Decision Tree for generic drug substances (Attachment I) describes considerations for the qualification of impurities when thresholds are exceeded. In some cases, decreasing the level of impurity below the threshold, rather than providing additional data, may be the simplest course of action. Alternatively, adequate data may be available in the scientific literature to qualify an impurity. The studies that should be performed to qualify an impurity will depend on a number of factors, including the patient population, daily dose, and route and duration of drug administration. Such studies are normally conducted on the drug substance containing the impurities to be controlled, although studies using isolated impurities are acceptable.

Levels L1 through L4 are recommendations for the type of information that would be considered to provide assurance that the impurity in question is “innocuous by virtue of having no significant, undesirable biological activity in the amounts present” (*see USP <1086> Impurities in Official Articles*). Only in Level L5, where concern regarding possible toxicity is indicated, is additional testing recommended (e.g., by a battery of in vitro genotoxicity tests).

Level L6 would be for those rare instances where an impurity has not been qualified. In such cases, the ANDA would then fall outside the purview of section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act).

Additional clarification regarding the levels in the Impurities Decision Tree for generic drug substances is provided below:

- First level (L1): Is the impurity in question “above threshold”? See the threshold table in section VII. This level is identical to the corresponding level in the ICH Decision Tree for Safety Studies (Attachment II).
- Second Level (L2): Is the “structure elucidated”? This refers to structural identification or characterization exactly as in the ICH Decision Tree for Safety Studies. However, in those rare cases where it is not possible to identify the impurity by structure, the efforts made should be satisfactorily documented. Once the impurity has been structurally identified, one could go to level L3.
- Third Level (L3a): Compliance with a USP acceptance criterion for a known individual impurity (e.g., see impurity listed in the Clidinium Bromide USP monograph).

Third Level (L3b): A comparison of the impurity profile of the generic drug substance with the process impurities profile on an average of three or more different lots of the innovator’s drug product is recommended. This comparative study should be performed using appropriate discriminating analytical tests such as HPLC or Capillary Electrophoresis. The impurity is qualified if it is found at similar levels (no more than twofold higher, but not to exceed 1 .0% for most drug substances). Twofold higher criteria are justified for several reasons. For example, the innovators’ impurity acceptance criteria are set higher than levels observed in drug substances, and the safety studies that qualified the innovators’ drug substances are carried out at significantly higher levels than the specifications agreed to under FDA’s pharmacology and toxicology evaluations. In certain dosage forms where sensitivity or toxicity concerns arise, the impurity levels should be no higher than the innovator’s level for toxic impurities. In generic drugs, an unidentified impurity may still be considered qualified in cases where the impurity is observed at similar levels in the innovator’s product via a comparative study.

Third Level (L3c): This level looks at an impurity at a “higher level, or a different new impurity.” *New* means one that was not previously seen in the bulk drug substance. The level of the new impurity may be qualified from the scientific literature if it is substantiated that this impurity is an *ordinary impurity* (see USP <1086>) at the levels used. The scientific literature would include recognized scientific publications. Alternatively, the new impurity may be qualified by lowering it to below the ICH threshold level, or by following the next level in the Impurities Decision Tree for generic drug substances.

- Fourth Level (L4): Is the impurity “related to others with known toxicity”? As one approach, the use of a *Quantitative Structure Activity Relationships* (QSAR) database program may be helpful in identifying whether an impurity is related to others of known toxicity. The use of such a program is acceptable to the Office of Generic Drugs (OGD).

Modules currently recommended are: *Rodent Carcinogenicity*, *Developmental Toxicity Potential*, *Ames Mutagenicity* (five strains), and for topicals, *Skin Sensitization*.

If no potential for concern is indicated by QSAR evaluation, the impurity is considered qualified, but it should not exceed a level of 0.5 percent or 500 micrograms per day, whichever is less (equivalent to 0.5 percent of 100 mg of a drug substance), without other supporting data (such as genotoxicity test data). A determination to accept the QSAR data will be made on a case-by-case basis, taking into consideration the therapeutic use of the drug product, its intended duration of administration, and the results of the QSAR analysis.

However, if the QSAR evaluation does not provide sufficient information because the program cannot perform the evaluation due to the lack of relevant information in the database, the manufacturer should lower the impurity level to below the ICH threshold or qualify the new impurity at the L5 level.

- Fifth Level (L5): This level describes evaluation of the toxicity of an impurity via a battery of in vitro genotoxicity tests (see the ICH Decision Tree for Safety Studies regarding genotoxicity studies). If the result of genotoxicity testing raises a concern, the need for additional toxicity testing will be evaluated on a case-by-case basis. Factors to be considered include the therapeutic use of the drug product, its intended duration of use, and results of the QSAR analysis. However, even in those cases where no potential for concern is indicated by the genotoxicity testing, the necessity for further toxicity testing should be evaluated if the impurity level exceeds either 1 percent of the drug substance or 1 mg/day, whichever is lower, at the human therapeutic dose of the drug product.

If toxicity issues are confirmed by these in vitro tests, the DMF holder or ANDA applicant may either purify the drug substance to reduce the impurity to a level below the ICH threshold or go to the next level (L6) in the Impurities Decision Tree for generic drug substances.

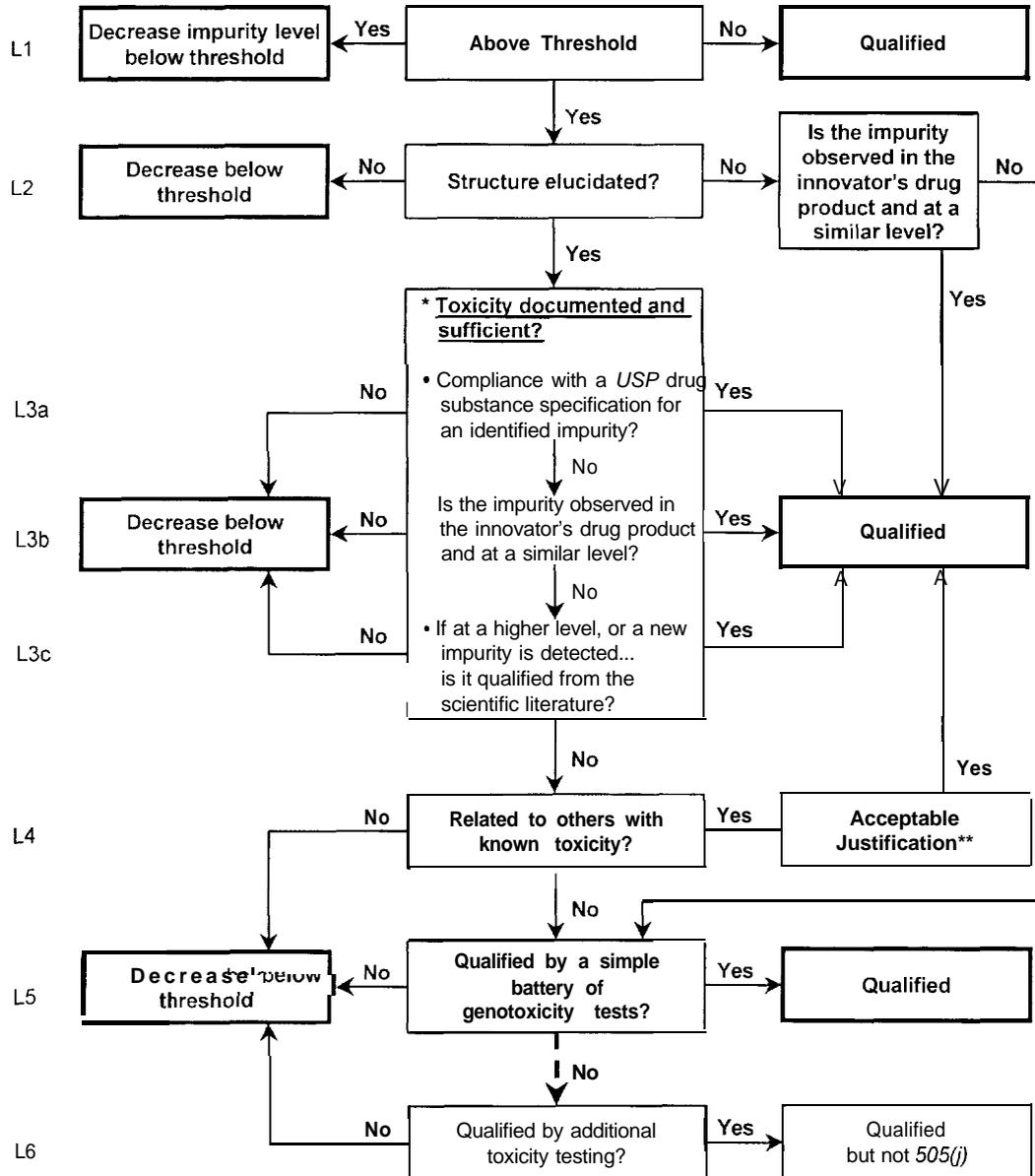
- Sixth Level (L6): This level involves qualification of the impurity “by general toxicity testing” (see Attachment II, items 2 and 3). If this pathway is used, the ANDA would fall under section 505(b) of the Act. General toxicity testing involves animal testing, thus an application would not be deemed acceptable by OGD under section 505(j) of the Act. The drug substance manufacturer as well as the ANDA applicant should be cognizant of this issue before the ANDA applicant commits to extensive studies with the bulk drug substance.

VTII. NEW IMPURITIES

During the course of a drug development program, the qualitative impurity profile of the drug substance may change or a new impurity may appear, for example, as a result of synthetic route changes, process optimization, or scale-up. New impurities may be identified or unidentified. Such changes call for consideration of the need for qualification of the level of the impurity unless it is below the threshold values as noted above. When a new impurity exceeds the threshold, the Impurities Decision Tree for generic drug substances (Attachment I) should be consulted. Studies should compare the drug substances containing a representative level of the new impurity with previously qualified material, although studies using the isolated impurity are also acceptable.

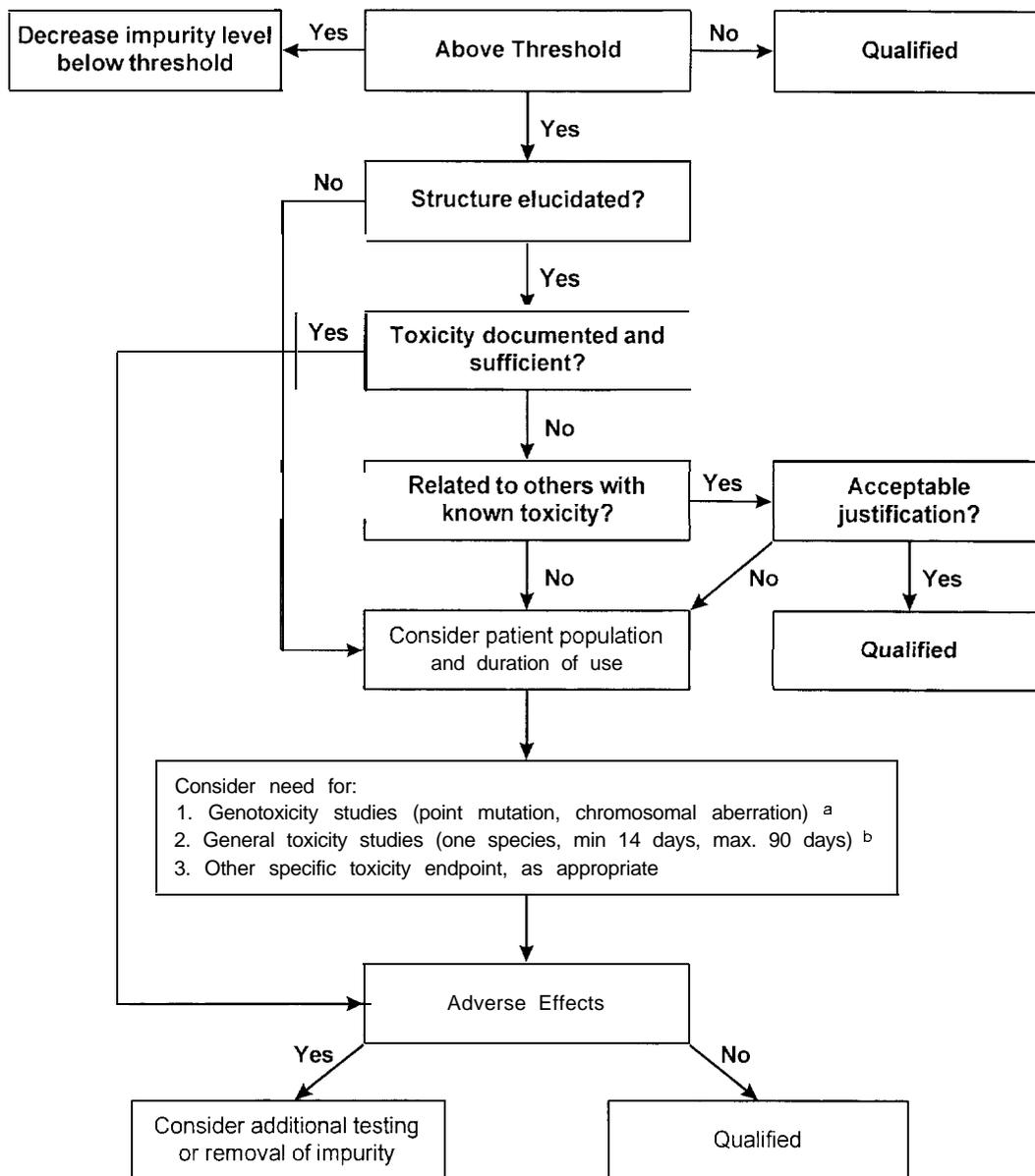
ATTACHMENT I

Impurities Decision Tree (Generic Drug Substance)



* Generic Drug Pathway
** e.g., qualified by QSAR

ICH Decision Tree for Safety Studies



^a If considered desirable, a minimum screen for genotoxic potential should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are seen as an acceptable minimum screen.

^b For NDAs, if general toxicity studies are desirable, study(ies) 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 to detect the toxicity of an impurity. In general, a minimum duration of 14 days and a maximum duration of 90 days will be acceptable.

ATTACHMENT HI

Glossary

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures

Chemical Development Studies: Studies conducted to scale-up, optimize, and validate the manufacturing process for a drug substance

Drug Substance: The designated therapeutic moiety. See also the definition in 21 CFR 314.3.

Enantiomers: Compounds with the same molecular formula as the drug substance, which differ in the spatial arrangement of atoms within the molecule and are nonsuperimposable mirror images

Extraneous Substance: An impurity arising from any source extraneous to the manufacturing process

Genotoxicity Tests: Genotoxicity tests can be defined as in vitro tests designed to detect compounds that induce genetic damage directly or indirectly by various mechanisms. Compounds that are positive in tests that detect such kinds of genetic damage have potential to be human carcinogens and/or mutagens (i.e., may induce cancer and/or heritable damage).

Herbal Products: Medicinal products containing, exclusively, plant material and/or vegetable drug preparations as active ingredients. In some traditions, materials of inorganic or animal origin may also be present.

Identified Impurity: An impurity for which a structural characterization has been achieved

Impurity: Any component of the drug substance that is not the chemical entity defined as the drug substance

Impurity Profile: A description of the identified and unidentified impurities present in a drug substance

Intermediate: A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes the drug substance

Ligand: An agent with a strong affinity to a metal ion

Mass Balance: The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 percent of the initial value, with due consideration of the margin of analytical precision

New Drug Substance: The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphism: The occurrence of different crystalline forms of the same drug substance

Potential Impurity: An impurity that, from theoretical considerations, may arise from or during manufacture. It may or may not actually appear in the drug substance.

Qualification: The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the levels specified

Quantitative Structure Activity Relationship (QSAR): Used for rationalization and prediction of in vivo mammalian toxicity of chemicals on the basis of their overall and/or local properties, as defined by their chemical structure and evaluated by using an appropriate data base and modules

Reagent: A substance, other than a starting material or solvent, used in the manufacture of a drug substance

Safety Information: The body of information that establishes the biological safety of an individual impurity or a given impurity profile at the levels specified

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a drug substance

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. *Conformance to specifications* means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

Specified Impurity: An identified or unidentified impurity that is selected for inclusion in the drug substance specifications and is individually listed and limited to ensure the safety and quality of the drug substance

Starting Material: A material used in the synthesis of a drug substance that is incorporated as an element into the structure of an intermediate and/or of the drug substance. Starting materials normally are commercially available and of defined chemical and physical properties and structure.

Toxic Impurity: Impurities having significant undesirable biological activity

Unidentified Impurity: An impurity that is defined solely by qualitative analytical properties (e.g., chromatographic retention time)

Validated Limit of Quantitation: For impurities at a level of 0.1 percent, the validated limit of quantitation should be less than or equal to 0.05 percent. Impurities limited at higher levels may have higher limits of quantitation.