Guidance for Industry

Q3A Impurities in New Drug Substances

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

June 2008
ICH

Revision 2

Guidance for Industry

Q3A Impurities in New Drug Substances

Additional copies are available from:

Office of Training and Communication
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Bldg. 51, Room 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

and/or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
Fax: 1-888-CBERFAX or 301-827-3844
(Tel) 800-835-4709 or 301-827-1800

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

June 2008
ICH

Revision 2

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]
Q3A Impurities in New 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. An alternative approach may be used if such 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 (1)

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. Impurities in new drug substances are addressed from two perspectives:

- Chemistry aspects include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures

- Safety aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

This is the second revision of the Q3A guidance, which was published in 1996 and revised in 2003. In revision 2, Attachment 2 is retitled "Illustration of Reporting Impurity Results for Identification and Qualification in an Application" and includes clarifying information and an additional example.

[1] This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process (October 2006). At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, October 2006.

This guidance is not intended to apply to new drug substances used during the clinical research stage of development. The following types of drug substances are not covered in this guidance:

- biological/biotechnological
- peptide
- oligonucleotide
- radiopharmaceutical
- fermentation products and semisynthetic products derived therefrom
- herbal products
- crude products of animal or plant origin

II. CLASSIFICATION OF IMPURITIES (2)

Impurities can be classified into the following categories:

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

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

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

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

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

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Q3C on Residual Solvents).

Excluded from this document are: (1) extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as good manufacturing practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

III. RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES (3)

A. Organic Impurities (3.1)

The applicant should summarize the actual and potential impurities most likely to arise during the synthesis, purification, and storage of a new 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 new drug substance, and possible degradation products. This discussion can be limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the applicant should summarize the laboratory studies conducted to detect impurities in the new drug substance. This summary should include test results of batches manufactured during the development process and batches from the proposed commercial process, as well as the results of stress testing (see ICH Q1A(R) on stability) used to identify potential impurities arising during storage. The impurity profile of the drug substance batches intended for marketing should be compared with those used in development, and any differences discussed.

The studies conducted to characterize the structure of actual impurities present in a new drug substance at a level greater than (>) the identification threshold given in Attachment 1 (e.g., calculated using the response factor of the drug substance) should be described. Note that any impurity at a level greater than (>) the identification threshold in any batch manufactured by the proposed commercial process should be identified. In addition, any degradation product observed in stability studies at recommended storage conditions at a level greater than (>) the identification threshold should be identified. When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. Where attempts have been made to identify impurities present at levels of not more than (≤) the identification thresholds, it is useful also to report the results of these studies.

Identification of impurities present at an apparent level of not more than (≤) the identification threshold is generally not considered necessary. However, analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold**.** All impurities should be qualified as described later in this guidance.

B. Inorganic Impurities (3.2)

Inorganic impurities are normally detected and quantified using pharmacopoeial or other appropriate procedures. Carry-over of catalysts to a new drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in a new drug substance specification should be discussed. Acceptance criteria should be based on pharmacopoeial standards or known safety data.

C. Solvents (3.3)

The control of residues of the solvents used in the manufacturing process for a new drug substance should be discussed and presented according to ICH *Q3C Impurities: Residual Solvents*.

IV. ANALYTICAL PROCEDURES (4)

A registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities (see ICH Q2A and Q2B on analytical validation). Technical factors (e.g., manufacturing capability and control methodology) can be considered as part of the justification for selection of alternative thresholds based on manufacturing experience with the proposed commercial process. The use of two decimal places for thresholds (see Attachment 1) does not necessarily reflect the precision of the analytical procedure used for routine quality control purposes. Thus, the use of lower precision techniques (e.g., thin-layer chromatography) can be appropriate where justified and appropriately validated. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed in the registration application. The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold.

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 new drug substance itself. Reference standards used in the analytical procedures for control of impurities should be evaluated and characterized according to their intended uses. The drug substance can be used as a standard to estimate the levels of impurities. In cases where the response factors of a drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated. Acceptance criteria and analytical procedures used to estimate identified or unidentified impurities can be based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in registration applications.

V. REPORTING IMPURITY CONTENT OF BATCHES (5)

Analytical results should be provided in an application for all batches of a new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process. Quantitative results should be presented numerically, and not in general terms such as “complies” or “meets limit.” Any impurity at a level greater than (>) the reporting threshold (see Attachment 1) and total impurities observed in these batches of the new drug substance should be reported with the analytical procedures indicated. Below 1.0 percent, the results should be reported to two decimal places (e.g., 0.06 percent, 0.13 percent); at and above 1.0 percent, the results should be reported to one decimal place (e.g., 1.3 percent). Results should be rounded using conventional rules (see Attachment 2). A tabulation (e.g., spreadsheet)

of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor (e.g., retention time). If a higher reporting threshold is proposed, it should be fully justified. All impurities at a level greater than (>) the reporting threshold should be summed and reported as total impurities.

When analytical procedures change during development, reported results should be linked to the procedure used, with appropriate validation information provided. Representative chromatograms should be provided. Chromatograms of representative batches from analytical 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 applicant should ensure that complete impurity profiles (e.g., chromatograms) of individual batches are available, if requested.

A tabulation should be provided that links the specific new drug substance batch to each safety study and each clinical study in which the new drug substance has been used.
For each batch of the new 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 procedure used

VI. LISTING OF IMPURITIES IN SPECIFICATIONS (6)

The specification for a new drug substance should 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. The selection of impurities in a new drug substance specification should be based on the impurities found in batches manufactured by the proposed commercial process. Those individual impurities with specific acceptance criteria included in the specification for a new drug substance are referred to as *specified impurities* in this guidance. Specified impurities can be identified or unidentified.

A rationale for the inclusion or exclusion of impurities in a specification should be presented. The rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of batches manufactured by the proposed commercial process. Specified identified impurities should be included along with specified unidentified impurities estimated to be present at a level greater than (>) the identification threshold given in Attachment 1. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the impurities should be controlled. For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated. Specified, unidentified impurities

should be referred to by an appropriate qualitative analytical descriptive label (e.g., "unidentified A," "unidentified with relative retention of 0.9"). A general acceptance criterion of not more than (≤) the identification threshold (see Attachment 1) for any unspecified impurity and an acceptance criterion for total impurities should be included.

Acceptance criteria should be set no higher than the level that can be justified by safety data and should be consistent with the level achievable by the manufacturing process and the analytical capability. Where there is no safety concern, impurity acceptance criteria should be based on data generated on batches of a new drug substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels can indicate that the manufacturing process of the new drug substance is not adequately controlled and validated (see ICH Q6A guidance on specifications, Decision Tree #1, for establishing an acceptance criterion for a specified impurity in a new drug substance). The use of two decimal places for thresholds (see Attachment 1) does not necessarily indicate the precision of the acceptance criteria for specified impurities and total impurities.

In summary, a new drug substance specification should include, where applicable, the following list 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
- Total impurities

Residual Solvents
Inorganic Impurities

VII. QUALIFICATION OF IMPURITIES (7)

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) specified. The applicant should provide a rationale for establishing impurity acceptance criteria that includes safety considerations. The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified. Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified. A level of a qualified impurity higher than that present in a new drug substance can also be justified based on an analysis of the actual amount of impurity administered in previous relevant safety studies.

If data are unavailable to qualify the proposed acceptance criterion of an impurity, studies to obtain such data can be appropriate when the usual qualification thresholds given in Attachment 1 are exceeded.

Higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects and clinical experience. For example, qualification can 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 can be appropriate. Conversely, a higher qualification threshold can be appropriate for individual drugs when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, clinical considerations). Proposals for alternative thresholds would be considered on a case-by-case basis.

The "Decision Tree for Identification and Qualification" (see Attachment 3) describes considerations for the qualification of impurities when thresholds are exceeded. In some cases, decreasing the level of impurity to not more than the threshold can be simpler than providing safety data. Alternatively, adequate data could be available in the scientific literature to qualify an impurity. If neither is the case, additional safety testing should be considered. The studies considered appropriate 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 can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate.

Although this guidance is not intended to apply during the clinical research stage of development, in the later stages of development, the thresholds in this guidance can be useful in evaluating new impurities observed in drug substance batches prepared by the proposed commercial process. Any new impurity observed in later stages of development should be identified if its level is greater than (>) the identification threshold given in Attachment 1 (see the “Decision Tree for Identification and Qualification” in Attachment 3). Similarly, the qualification of the impurity should be considered if its level is greater than (>) the qualification threshold given in Attachment 1. Safety assessment studies to qualify an impurity should compare the new drug substance containing a representative amount of the new impurity with previously qualified material. Safety assessment studies using a sample of the isolated impurity can also be considered.

GLOSSARY

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

Enantiomeric Impurity: A compound with the same molecular formula as the drug substance that differs in the spatial arrangement of atoms within the molecule and is a non-superimposable mirror image

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

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 can also be present.

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

Identification Threshold: A limit above (>) which an impurity should be identified

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

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

Intermediate: A material produced during steps of the synthesis of a new drug substance that undergoes further chemical transformation before it becomes a new drug substance

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

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.

Polymorphic Forms: Different crystalline forms of the same drug substance. These can include solvation or hydration products (also known as pseudo-polymorphs) and amorphous forms.

Potential Impurity: An impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the new 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 level(s) specified

Qualification Threshold: A limit above (>) which an impurity should be qualified

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

Reporting Threshold: A limit above (>) which an impurity should be reported. Reporting threshold is the same as reporting level in Q2B.

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

Specified Impurity: An impurity that is individually listed and limited with a specific acceptance criterion in the new drug substance specification. A specified impurity can be either identified or unidentified.

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

Unidentified Impurity: An impurity for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time)

Unspecified Impurity: An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug substance specification

ATTACHMENT 1: THRESHOLDS

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

[1] The amount of drug substance administered per day
[2] Higher reporting thresholds should be scientifically justified
[3] Lower thresholds can be appropriate if the impurity is unusually toxic

ATTACHMENT 2: ILLUSTRATION OF REPORTING IMPURITY RESULTS FOR IDENTIFICATION AND QUALIFICATION IN AN APPLICATION

The attachment is only illustrative and is not intended to serve as a template for how results on impurities should be presented in an application file. Normally, raw data are not presented.

Example 1: **0.5 g Maximum Daily Dose**
Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 0.15%

"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 0.15% exceeded?)
0.044	Not reported	0.2	None	None
0.0963	0.10	0.5	None	None
0.12	0.12[1)]	0.6	Yes	None[1]
0.1649	0.16[1)]	0.8	Yes	Yes[1]

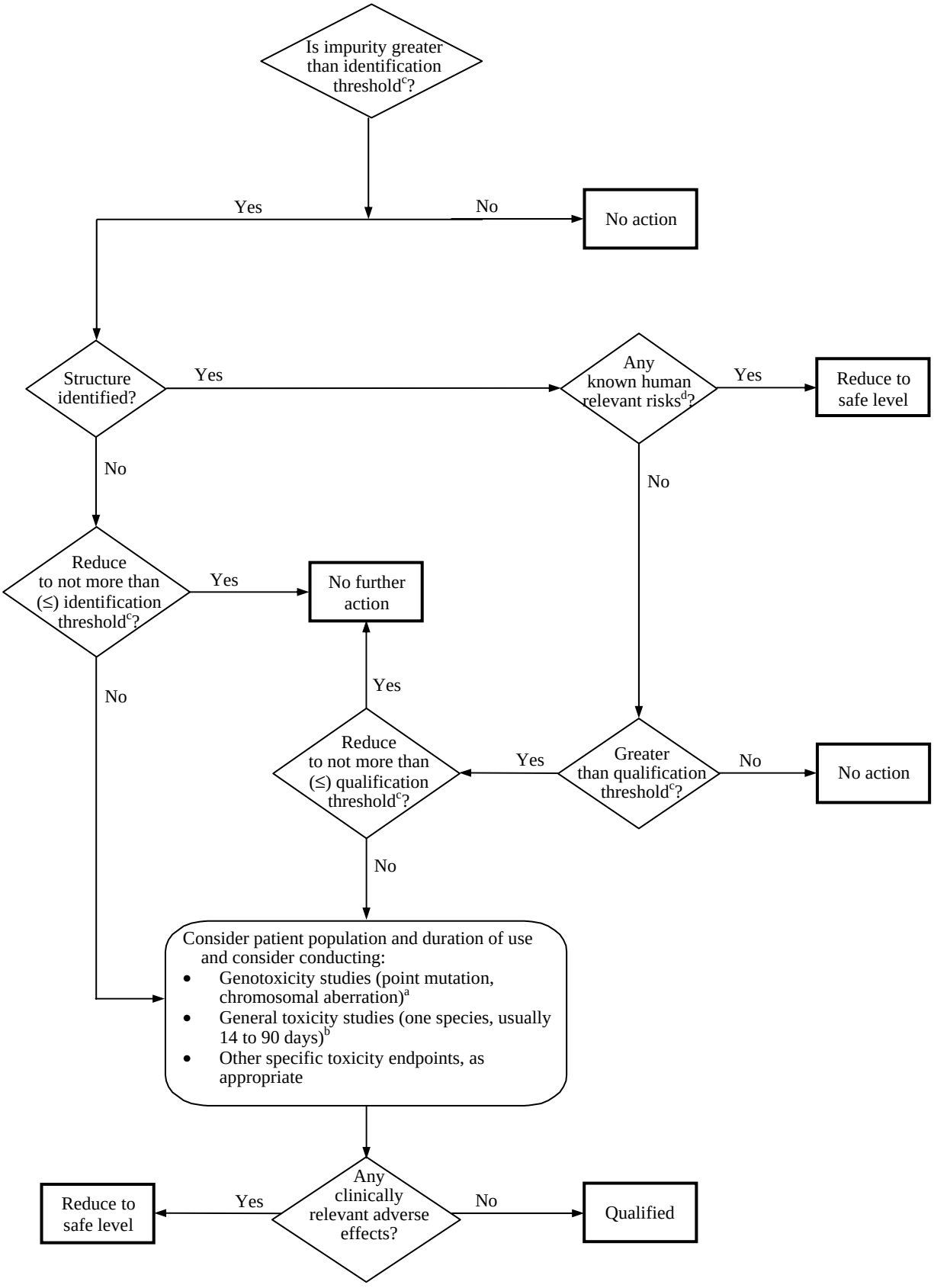
Example 2: **0.8 g Maximum Daily Dose**
Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 1.0 mg TDI

"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 1.0 mg TDI exceeded?)
0.066	0.07	0.6	None	None
0.124	0.12	1.0	Yes	None[1, 2]
0.143	0.14	1.1	Yes	Yes[1]

[1] After identification, if the response factor is determined to differ significantly from the original assumptions, it may be appropriate to remeasure the actual amount of the impurity present and reevaluate against the qualification threshold (see Attachment 1).

[2] To verify if a threshold is exceeded, a reported result should be evaluated against the thresholds as follows: When the threshold is described in %, the reported result rounded to the same decimal place as the threshold should be compared directly to the threshold. When the threshold is described in TDI, the reported result should be converted to TDI, rounded to the same decimal place as the threshold, and compared to the threshold. For example, the amount of impurity at 0.12% level corresponds to a TDI of 0.96 mg (absolute amount), which is then rounded up to 1.0 mg; so the qualification threshold expressed in TDI (1.0 mg) is not exceeded.

ATTACHMENT 3: DECISION TREE FOR IDENTIFICATION AND QUALIFICATION



Notes on Attachment 3

a) 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.

b) If general toxicity studies are desirable, 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 to detect 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.

c) Lower thresholds can be appropriate if the impurity is unusually toxic.

d) For example, do known safety data for this impurity or its structural class preclude human exposure at the concentration present?