B

Guidance for Industry

Q3B(R) Impurities in New Drug Products

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)

November 2003
ICH

Revision 1

Guidance for Industry

Q3B(R) Impurities in New Drug Products

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

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.
(Tel) Voice Information System at 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)

November 2003
ICH
Revision 1

TABLE OF CONTENTS

I. INTRODUCTION (1.0) 1

II. RATIONALE FOR THE REPORTING AND CONTROL OF DEGRADATION PRODUCTS (2.0) 2

III. ANALYTICAL PROCEDURES (3.0) 3

IV. REPORTING DEGRADATION PRODUCTS, CONTENT OF BATCHES (4.0) 4

V. LISTING OF DEGRADATION PRODUCTS IN SPECIFICATIONS (5.0) 4

VI. QUALIFICATION OF DEGRADATION PRODUCTS (6.0) 6

GLOSSARY 1

ATTACHMENT 1 3

ATTACHMENT 2 5

ATTACHMENT 3 7

Contains Nonbinding Recommendations

Guidance for Industry[1]
Q3B(R) Impurities in New Drug Products

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 it 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 (1.0)[2]

This guidance provides recommendations for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances not previously registered in a region or member state. This guidance revises the ICH guidance of the same title, which was issued in May 1997. The revised guidance clarifies the 1997 guidance and makes some changes.[3] The revision also provides consistency with more recently published ICH guidances (e.g., *Q3A(R) Impurities in New Drug Substances*, *Q3C Impurities: Residual Solvents*, and *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*). This guidance complements the ICH Q3A(R) guidance, which should be consulted for basic principles along with ICH Q3C when appropriate.

This guidance addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system (collectively referred to as *degradation products* in this guidance). Generally, impurities present in a new drug substance need not be monitored or

---

[1] This guidance was developed within the Q3B(R) Expert Working Group 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 was endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 5, 2003. 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.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process.

[3] For example, addressing reporting, identification, and qualification thresholds; listing impurities in specifications and making a clear distinction between ICH Q3B (listing impurities) and Q6A (setting specifications); and deleting the exception to conventional rounding practice (i.e., the provision recommending no rounding up to 0.1 percent for values between 0.05 and 0.09 percent).

specified in new drug product unless they are also degradation products (see ICH Q6A guidance on specifications).

Impurities arising from excipients present in a new drug product or extracted or leached from the container closure system are not covered by this guidance. This guidance also does not apply to new drug products used during the clinical research stages of development. The following types of products are not covered in this guidance:

- Biological/biotechnological products
- Peptides
- Oligonucleotides
- Radiopharmaceuticals
- Fermentation products and semi-synthetic products derived therefrom
- Herbal products
- Crude products of animal or plant origin

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

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. RATIONALE FOR THE REPORTING AND CONTROL OF DEGRADATION PRODUCTS (2.0)

The applicant should summarize the degradation products observed during manufacture and/or stability studies of a new drug product. This summary should be based on sound scientific appraisal of potential degradation pathways in the new drug product and impurities arising from the interaction with excipients and/or the immediate container closure system. In addition, the applicant should summarize any laboratory studies conducted to detect degradation products in the new drug product. This summary also should include test results of batches manufactured during the development process and batches representative of the proposed commercial process. A rationale should be provided for exclusion of those impurities that are not degradation products (e.g., process impurities from the drug substance and impurities arising from excipients). The impurity profiles of the batches representative of the proposed commercial process should be compared with the profiles of batches used in development, and any differences should be discussed.

Any degradation product observed in stability studies conducted at the recommended storage condition should be identified when present at a level greater than (>) the identification thresholds given in Attachment 1. When identification of a degradation product is infeasible, a

summary of the laboratory studies demonstrating the unsuccessful efforts to identify it should be included in the registration application.

Degradation products present at a level of not more than (≤) the identification threshold generally would not need to be identified. However, analytical procedures should be developed for those degradation products that are suspected to be unusually potent, producing toxic or significant pharmacological effects at levels not more than (≤) the identification threshold. In unusual circumstances, technical factors (e.g., manufacturing capability, a low drug substance to excipient ratio, or the use of excipients that are crude products of animal or plant origin) can be considered part of the justification for selection of alternative thresholds based on manufacturing experience with the proposed commercial process.

III. ANALYTICAL PROCEDURES (3.0)

The registration application should include documented evidence that the analytical procedures have been validated and are suitable for the detection and quantitation of degradation products (see ICH Q2A and Q2B guidances on analytical validation). In particular, analytical procedures should be validated to demonstrate specificity for the specified and unspecified degradation products. As appropriate, this validation should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis, and oxidation. When an analytical procedure reveals the presence of other peaks in addition to those of the degradation products (e.g., the drug substance, impurities arising from the synthesis of the drug substance, excipients and impurities arising from the excipients), these peaks should be labeled in the chromatograms and their origin(s) discussed in the validation documentation.

The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold.

Degradation product levels can be measured by a variety of techniques, including those that compare an analytical response for a degradation product 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 degradation products should be evaluated and characterized according to their intended uses. The drug substance can be used to estimate the levels of degradation products. In cases when the response factors are not close, this practice can still be used if a correction factor is applied or the degradation products are, in fact, being overestimated. Acceptance criteria and analytical procedures, used to estimate identified or unidentified degradation products, are often based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in the registration application.

Differences between the analytical procedures used during development and those proposed for the commercial product should also be discussed.

IV. REPORTING DEGRADATION PRODUCTS, CONTENT OF BATCHES (4.0)

Analytical results should be provided in the registration application for all relevant batches of the new drug product used for clinical, safety, and stability testing, as well as batches that are representative of the proposed commercial process. Quantitative results should be presented numerically, and not in general terms such as "complies", "meets limit." Any degradation product at a level greater than (>) the reporting threshold (see Attachment 1), and total degradation products observed in the relevant batches of the new drug product, should be reported with the analytical procedures indicated. Below 1.0 percent, the results should be reported to the number of decimal places (e.g., 0.06 percent) in the applicable reporting threshold; 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. Degradation products 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 degradation products at a level greater than (>) the reporting threshold should be summed and reported as total degradation products.

Chromatograms with peaks labeled (or equivalent data if other analytical procedures are used) from representative batches, including chromatograms from analytical procedure validation studies and from long-term and accelerated stability studies, should be provided. The applicant should ensure that complete degradation product profiles (e.g., chromatograms) of individual batches are available, if requested.

For each batch of the new drug product described in the registration application, the documentation should include:

- Batch identity, strength, and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Immediate container closure
- Degradation product content, individual and total
- Use of batch (e.g., clinical studies, stability studies)
- Reference to analytical procedure used
- Batch number of the drug substance used in the new drug product
- Storage conditions for stability studies

V. LISTING OF DEGRADATION PRODUCTS IN SPECIFICATIONS (5.0)

The specification for a new drug product should include a list of degradation products expected to occur during manufacture of the commercial product and under recommended storage conditions. Stability studies, knowledge of degradation pathways, product development studies, and laboratory studies should be used to characterize the degradation profile. The selection of degradation products in the new drug product specification should be based on the degradation products found in batches manufactured by the proposed commercial process. Those individual

degradation products with specific acceptance criteria included in the specification for the new drug product are referred to as *specified degradation products* in this guidance. Specified degradation products can be identified or unidentified. A rationale for the inclusion or exclusion of degradation products in the specification should be presented. This rationale should include a discussion of the degradation profiles observed in the safety and clinical development batches and in stability studies, together with a consideration of the degradation profile of batches manufactured by the proposed commercial process. Specified identified degradation products should be included along with specified unidentified degradation products estimated to be present at a level greater than (>) the identification threshold given in Attachment 1. For degradation products known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation or detection limit of the analytical procedures should be commensurate with the level at which the degradation products should be controlled. For unidentified degradation products, the procedure used and assumptions made in establishing the level of the degradation product should be clearly stated. Specified unidentified degradation products 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 (Attachment 1) for any unspecified degradation product and an acceptance criterion for total degradation products should also be included. For a given degradation product, its acceptance criterion should be established by taking into account its acceptance criterion in the drug substance (if applicable), its qualified level, its increase during stability studies, and the proposed shelf life and recommended storage conditions for the new drug product. Furthermore, each acceptance criterion should be set no higher than the qualified level of the given degradation product.

Where there is no safety concern, degradation product acceptance criteria should be based on data generated from batches of the new drug product 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 product. Although normal manufacturing variations are expected, significant variation in batch-to-batch degradation product levels can indicate that the manufacturing process of the new drug product is not adequately controlled and validated (see ICH Q6A guidance on specifications, decision tree #2, for establishing an acceptance criterion for a specified degradation product in a new drug product).
In this guidance, the use of two decimal places for thresholds (see Attachment 1) does not necessarily indicate the precision of the acceptance criteria for specified degradation products and total degradation products.

In summary, the new drug product specification should include, where applicable, the following list 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 identification threshold
- Total degradation products

VI. QUALIFICATION OF DEGRADATION PRODUCTS (6.0)

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual degradation product or a given degradation profile at the levels specified. The applicant should provide a rationale for establishing degradation product acceptance criteria that includes safety considerations. The level of any degradation product present in a new drug product that has been adequately tested in safety and/or clinical studies would be considered qualified. Therefore, it is useful to include any available information on the actual content of degradation products in the relevant batches at the time of use in safety and/or clinical studies. Degradation products that are also significant metabolites present in animal and/or human studies are generally considered qualified. Degradation products could be considered qualified at levels higher than those administered in safety studies based on a comparison between actual doses given in the safety studies and the intended dose of the new drug product. Justification of such higher levels should include consideration of factors such as: (1) the amount of degradation product administered in previous safety and/or clinical studies and found to be safe; (2) the increase in the amount of the degradation product; and (3) other safety factors, as appropriate. If the qualification thresholds given in Attachment 1 are exceeded and data are unavailable to qualify the proposed acceptance criterion of a degradation product, additional studies to obtain such data may be appropriate (see Attachment 3).

Higher or lower thresholds for qualification of degradation products may be appropriate for some individual new drug products 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 degradation products in certain new drug products or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold may be appropriate. Conversely, a higher qualification threshold may be appropriate for individual new drug products when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, and clinical considerations). Proposals for alternative thresholds would be considered on a case-by-case basis.

The Decision Tree for Identification and Qualification of a Degradation Product (Attachment 3) describes considerations for the qualification of degradation products when thresholds are exceeded. In some cases, reducing the level of degradation product (e.g., use of a more protective container closure or modified storage conditions) 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 a degradation product. If neither is the case, additional safety testing should be considered. The studies considered appropriate to qualify a degradation product will depend on a number of factors, including the patient population, daily dose, and route and duration of new drug product administration. Such studies can be conducted on the new drug product or substance containing the degradation products to be controlled, although studies using isolated degradation products 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 may be useful in

evaluating new degradation products observed in new drug product batches prepared by the proposed commercial process. Any new degradation product observed in later stages of development should be identified (see the Decision Tree for Identification and Qualification of a Degradation Product in Attachment 3) if its level is greater than (>) the identification threshold given in Attachment 1. Similarly, qualification of the degradation product should be considered if its level is greater than (>) the qualification threshold given in Attachment 1. Safety studies should provide a comparison of results of safety testing of the new drug product or drug substance containing a representative level of the degradation product with previously qualified material, although studies using the isolated degradation products can also be considered.

GLOSSARY

Degradation Product: An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the new drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system

Degradation Profile: A description of the degradation products observed in the drug substance or drug product

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

Identification Threshold: A limit above (>) which a degradation product should be identified

Identified Degradation Product: A degradation product for which a structural characterization has been achieved

Impurity: Any component of the new drug product that is not the drug substance or an excipient in the drug product

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

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 substance.

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

Qualification Threshold: A limit above (>) which a degradation product should be qualified

Reporting Threshold: A limit above (>) which a degradation product should be reported

Specified Degradation Product: A degradation product that is individually listed and limited with a specific acceptance criterion in the new drug product specification. A specified degradation product can be either identified or unidentified

Unidentified Degradation Product: A degradation product for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time)

Unspecified Degradation Product: A degradation product that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug product specification

ATTACHMENT 1

THRESHOLDS FOR DEGRADATION PRODUCTS IN NEW DRUG PRODUCTS

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 1 mg	1.0% or 5 μg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 μg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

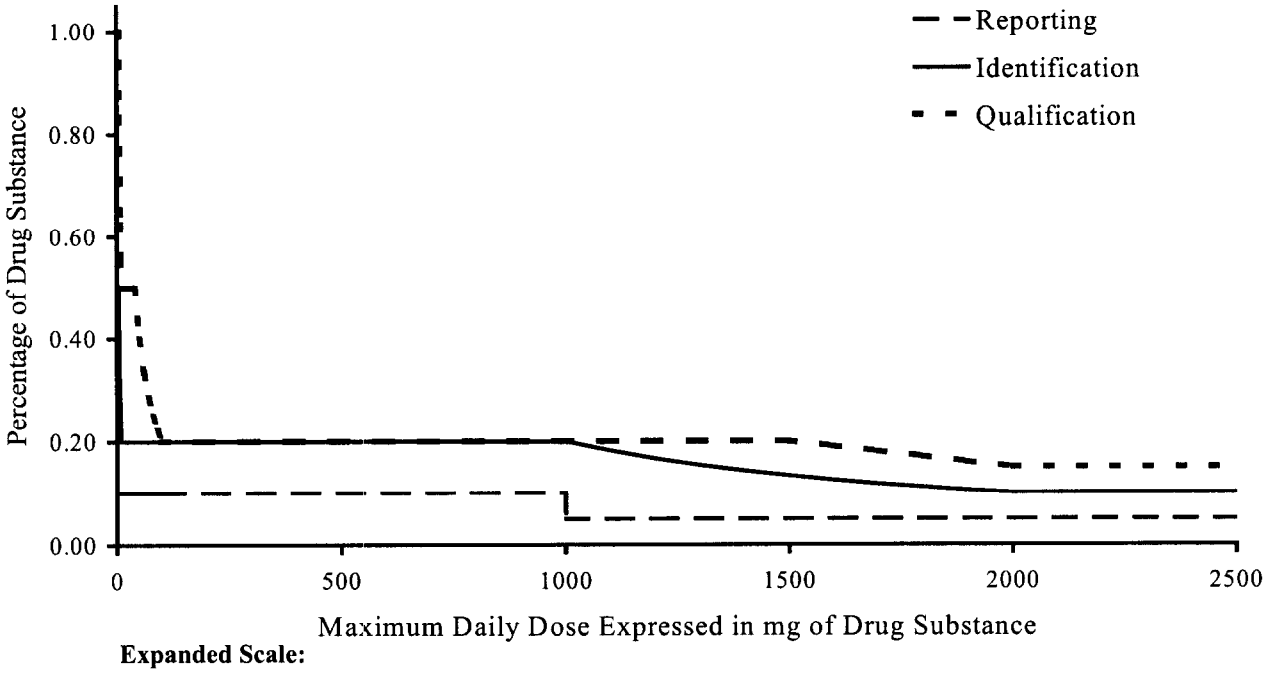
Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 μg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 μg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

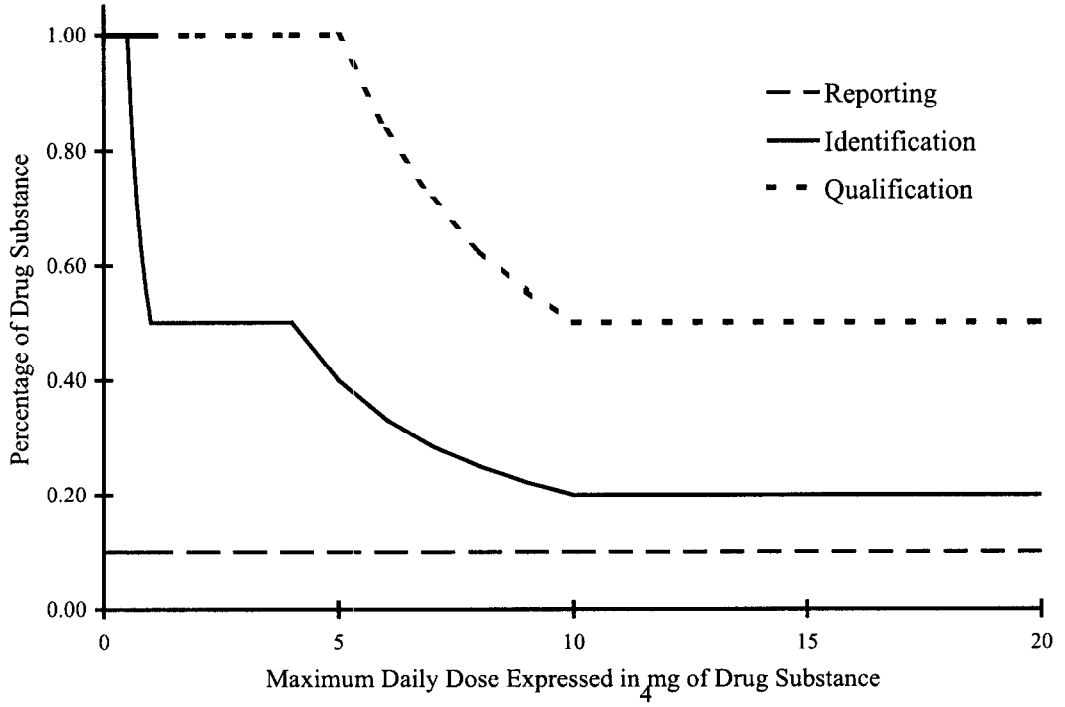
[1] The amount of drug substance administered per day
[2] Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.
[3] Higher thresholds should be scientifically justified.

Illustration of Thresholds for Reporting, Identification, and Qualification of Degradation Products in New Drug Products as a Function of Maximum Daily Dose

(Note: Actual threshold values should be taken from the preceding table in this attachment.)



Expanded Scale:



ATTACHMENT 2
ILLUSTRATION OF REPORTING DEGRADATION PRODUCT RESULTS FOR IDENTIFICATION AND QUALIFICATION IN AN APPLICATION

50 mg Maximum Daily Dose

'Raw' Result (%)	Reported Result (%) (Reporting Threshold = 0.1%)	Total Daily Intake (TDI) of the Degradation Product (rounded result in µg)	Action	
			Identification Threshold 0.2%	Qualification Threshold 200 µg TDI (equivalent to 0.4%)
0.04	Not reported	20	None	None
0.2143	0.2	100	None	None
0.349	0.3[1]	150	Yes	None[1]
0.550	0.6[1]	300	Yes	Yes[1]

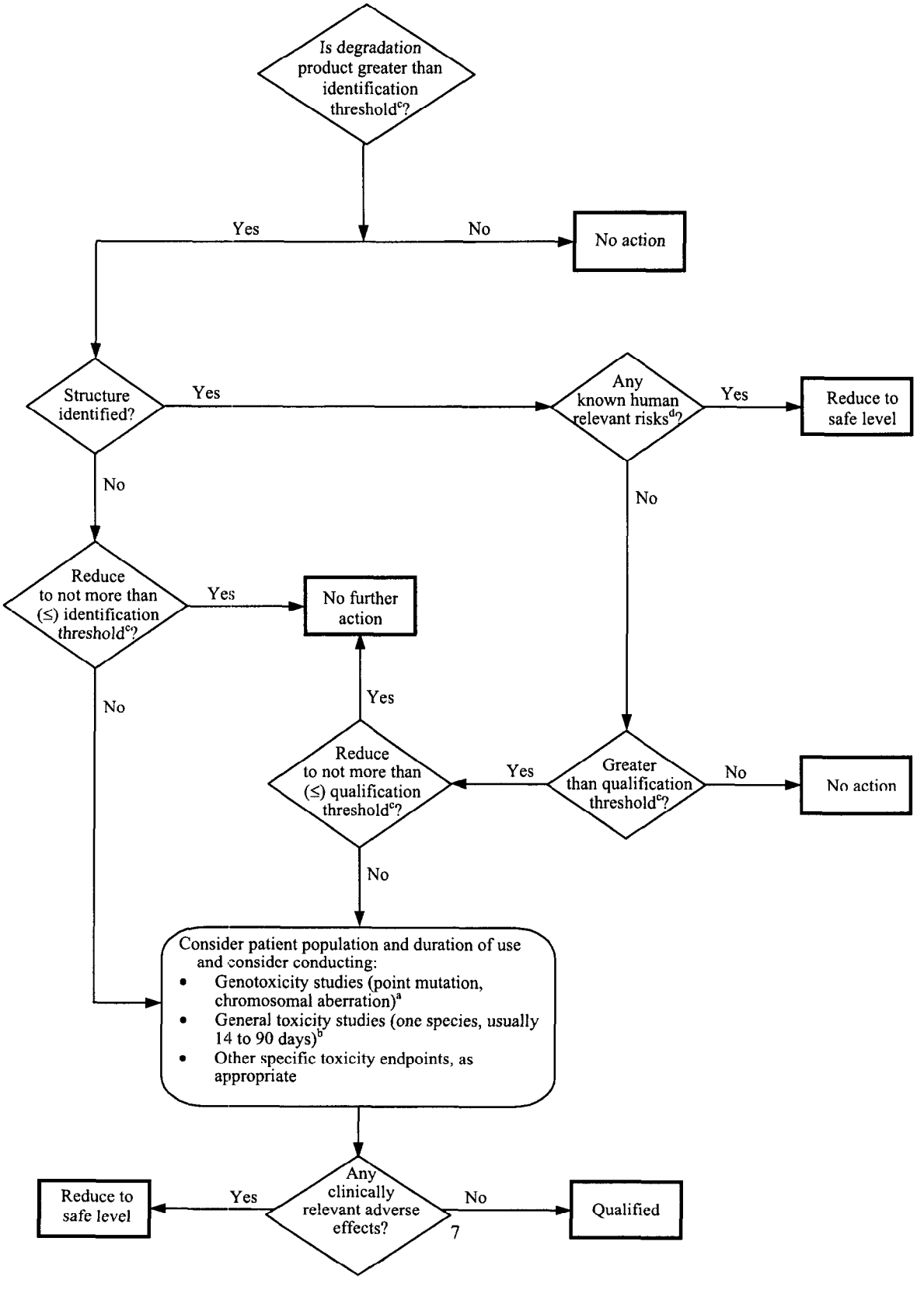
1.9 gram Maximum Daily Dose

'Raw' Result (%)	Reported Result (%) (Reporting Threshold = 0.05%)	Total Daily Intake (TDI) of the Degradation Product (rounded result in mg)	Action	
			Identification Threshold 2 mg TDI (equivalent to 0.11%)	Qualification Threshold 3 mg TDI (equivalent to 0.16%)
0.049	Not reported	1	None	None
0.079	0.08	2	None	None
0.183	0.18[1]	3	Yes	None[1,2]
0.192	0.19[1]	4	Yes	Yes[1]

[1] After identification, if the response factor is determined to differ significantly from the original assumptions, it can be appropriate to re-measure the actual amount of the degradation product present and re-evaluate against the qualification threshold (see Attachment 1).

[2] Although the reported result of 0.18% exceeds the calculated threshold value of 0.16%, in this case the action is acceptable since the TDI (when rounded) does not exceed 3 mg.

ATTACHMENT 3
DECISION TREE FOR IDENTIFICATION AND QUALIFICATION OF A DEGRADATION PRODUCT



Notes to 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 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.

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

[d] For example, do known safety data for this degradation product or its structural class preclude human exposure at the concentration present?