Draft - Not for Implementation

Guidance for Industry

ANDAs: Impurities in Drug Products

DRAFT GUIDANCE

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For questions on the content of the draft document, contact Devinder S. Gill (301) 827-5848.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1998
OGD #

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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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OGD #

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8/27/98

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Guidance for Industry[1]

ANDAs: Impurities in Drug Products

(Due to the complexity of this draft document, please identify specific comments by line number.)

I. INTRODUCTION

This guidance makes recommendations to applicants on identifying, qualifying, and reporting information on impurities in drug products in abbreviated new drug applications (ANDAs). The guidance discusses impurities in USP monograph and nonmonograph drug products produced from chemically synthesized drug substances. It addresses only those impurities classified as *degradation products* of the active ingredient or *reaction products* of the active ingredient with an excipient(s) and/or immediate container/closure system.

This guidance discusses two aspects of degradation products and other impurities in generic drug products:

1. Chemistry aspects, including classification and identification of impurities, generating reports, and analytical procedures

2. Safety aspects, including comparative studies and genotoxicity testing.

Specific guidance is provided on:

- qualifying degradation products found at the same or lower levels in a generic drug product than found in the related USP monograph, scientific literature, or the reference listed drug (RLD);

- qualifying degradation products found at higher levels in the generic drug product than found in the related USP monograph, scientific literature, or RLD;

- qualifying degradation products in generic drug products that are ***not*** found either in the related USP monograph, scientific literature, or in the RLD

[1]This guidance has been prepared under the direction of the Chemistry, Manufacturing, and Controls Coordination Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the review of impurities 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 statute, regulations, or both.

- levels, below which reporting, identification, and qualifications are not needed.

This guidance does not apply to biological or biotechnological products, oligonucleotides, peptides, radiopharmaceuticals, fermentation products and semisynthetic products derived therefrom, herbal products, or crude products of animal or plant origin. The recommendations in this guidance apply to new ANDA applications and also supplemental applications for (1) changes in the synthesis or process used to produce the drug substance, (2) qualitative changes in the formulation of the drug product, (3) changes in the manufacturing process of the drug product, or (4) changes in components of the container/closure system.

Once this guidance is finalized, it will be a companion document to the ICH guidance *Q3B Impurities in New Drug Products* (May 19, 1997). *Q3B* provides recommendations for (1) including information on specified degradation products (identified and unidentified degradation products in new drug products[2]) in certain new drug applications (NDAs) and (2) qualifying degradation products (the process of acquiring and evaluating data that establishes the biological safety of individual degradation products, or a given degradation profile, at the level(s) specified). Although generic drug products are not covered by *Q3B*, many of the recommendations in *Q3B* are applicable to generic drug products.

II. CLASSIFICATION OF IMPURITIES

This guidance addresses only the following classes of impurities, which are collectively referred to as degradation products.

- Degradation products of the active ingredient in the drug product
- Reaction products of the active ingredient with an excipient(s)
- Reaction products of the active ingredient with the immediate container/closure system

The degradation products are further subdivided into two classes:

- *Specified degradation products*: Identified or unidentified degradation products that are selected for inclusion in the drug product specification and are individually listed and limited to ensure the safety and quality of the drug product.

- *Unspecified degradation products*: Degradation products that do not appear in all

[2]*New drug products* are defined in *Q3B* as "products produced from chemically synthesized new drug substances." *New drug substances* are defined in the Glossary of this guidance.

batches or do not recur from batch to batch.

Process impurities arising from drug substance synthesis, which are present in the drug substance prior to formulation of the drug product, are covered in a separate guidance for industry.[3] Impurities present in the drug substance need not be monitored in the drug product unless they are also degradation products. Impurities arising from excipients present in the drug product are not covered in this document, but should be controlled while qualifying excipients. For recommendations regarding residual solvents present in the drug product, reference is made to the ICH guidance *Q3C Impurities: Residual Solvents* (December 1997). Also excluded from this document are (1) extraneous contaminants, which should not occur in drug products and are more appropriately addressed as good manufacturing practice issues; (2) polymorphic forms, solid state properties of the drug substance; and (3) enantiomeric impurities.

III. IDENTIFYING AND REPORTING IMPURITIES

The applicant should summarize those degradation products observed during stability studies of the drug product when reporting such information in ANDA submissions. The summary should be based on a sound scientific appraisal of potential degradation pathways of the drug substance in the drug product and of degradation products arising from the interaction of the drug substance with excipients and/or the immediate container/closure system. ANDA applicants can refer to scientific literature for degradation pathways. In addition, the applicant should summarize any laboratory studies conducted to detect and identify degradation products in the drug product.

A rationale should be provided for excluding from a report those impurities that are not degradation products (e.g., process impurities from the drug substance and excipients and their related impurities). To identify impurities attributed to excipients, comparative chromatograms using the same validated, stability indicating chromatographic method (e.g., high pressure liquid chromatography (HPLC)) should be provided for the drug product and the placebo product (i.e., drug product formulation without drug substance).

Degradation products observed in stability studies conducted at recommended storage conditions should be identified when the thresholds proposed in Attachment A, Table 1, are equaled or exceeded. Although it is a 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 degradation products. When identification of a degradation product is infeasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the drug product application.

[3] A guidance for industry on this topic, *ANDAs: Impurities in Drug Substances*, was published in draft for comment in June 1998.

Degradation products below the indicated levels generally do not need to be identified. However, identification should be attempted for those degradation products that are suspected to be unusually potent, producing toxic or significant pharmacologic effects at levels lower than indicated.

Identification of degradation products in a generic drug product can be accomplished by comparing the chromatographic profiles of a generic drug product with those of the RLD using the same validated, stability-indicating HPLC method for both drug products (i.e., comparative chromatographic studies). Degradation products that are present both in the generic drug product and the RLD can be identified by comparing the HPLC retention times of degradation products in a generic product with that of the RLD and by spiking the samples with a reference standard. If reference standards are unavailable, adequate structural characterization by spectroscopic and chromatographic methods should be provided to identify the degradation products. Degradation products that are not present in the RLD, but are present in the generic drug product, should be identified by thorough characterization using spectroscopic methods, such as IR, UV, NMR, MS, and X-ray crystal analysis.[4] Impurities (related substances) cited in *The United States Pharmacopeia (USP)* are excluded from structural characterization. The degradation profile of a generic drug product should be substantially similar to that of the RLD.

IV. ANALYTICAL PROCEDURES

ANDAs should include documentation that the analytical procedures are validated and suitable for the detection and quantitation of degradation products. Analytical procedures should be validated to demonstrate that the drug product components and impurities unique to the drug substance and excipients do not interfere with or are separated from the specified and unspecified degradation products in the drug product.

Degradation product levels can be measured using 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 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. Using the drug substance to estimate the levels of degradation products is considered acceptable when the response factors (e.g., extinction coefficients for UV detection) of the drug substance and degradation products are close. In cases where the response factors are not close, this practice may still be appropriate, provided a correction factor is applied or the degradation products are, in fact, being overestimated. Analytical procedures used to estimate identified or unidentified degradation products are often based on analytical assumptions

[4] Spectroscopic methods mentioned included IR (infrared), UV (ultraviolet), NMR (nuclear magnetic resonance), MS (mass spectrometry) and x-ray crystal analysis.

(e.g., equivalent detector response). These assumptions should be discussed in the drug product application.

V. REPORTING IMPURITY CONTENTS IN BATCHES

When reporting impurity contents in batches, analytical results should be provided in a tabular format for the stability batch(es). Because the degradation analytical testing procedure can be an important support tool for monitoring the manufacturing quality as well as for deciding the expiration dating period of the drug product, the reporting level should be set below the proposed identification threshold. The recommended target value for the reporting (as a percentage of the drug substance) can be found in Attachment A, Table 2. A higher reporting threshold should be proposed, and justified, only if the target reporting threshold cannot be achieved.

In addition, where an analytical procedure reveals the presence of impurities in addition to the degradation products (e.g., impurities arising from the synthesis of the drug substance), the origin of these impurities should be discussed. Chromatograms, or equivalent data (if other procedures are used), including available long-term and accelerated stability studies from a representative batch should be provided. The procedure should be able to quantify at least at the reporting level, and the chromatograms should show the location of the observed degradation products and impurities from the drug substance.

Information on the following should be provided in the report:

- Batch identity, strength, and size
- Manufacture date
- Manufacture site
- Manufacturing process, where applicable
- Immediate container/closure
- Degradation products, individual and total
- Reference to analytical procedure(s) used
- Batch number of the drug substance used in the drug product
- Storage conditions

VI. ACCEPTANCE CRITERIA FOR IMPURITIES

A *specification* is defined as a list of tests, reference to analytical procedures, and appropriate

acceptance criteria.[5] All ANDAs should include proposed acceptance criteria for degradation products expected to occur under recommended storage conditions. Stability studies, knowledge of degradation pathways, and laboratory studies should be used to characterize the degradation profile. The degradation profile provides a description of the degradation products observed in the drug product.

Acceptance criteria should be set taking into account the qualification of the degradation products, available long-term and accelerated stability data, the expected expiry period, and the recommended storage conditions for the drug product, allowing sufficient latitude to deal with normal manufacturing, analytical, and stability profile variation.

Acceptance criteria for degradation products in generic drug products can also be established and justified by comparing the generic product, under identical experimental conditions, with the RLD. USP monographs may have acceptance criteria for some degradation products (related compounds), for example, the captopril disulfide acceptance criteria in the Captopril Tablets monograph. The specifications for a drug product should include, where applicable, acceptance criteria for:

- each specified degradation product
- any unspecified degradation products
- total degradation products

Although some batch-to-batch variation is expected, significant variation in degradation profiles may indicate that either the manufacturing process of the drug product is inadequately controlled and validated or the analytical method is inadequately validated and is not stability indicating.

A rationale for the inclusion or exclusion of impurities in the specifications should be presented. The rationale should include a discussion of the impurity profile(s) observed in the bio/stability batch(es).

[5] *Acceptance criteria* include numerical limits, ranges, or other criteria for the tests described. See definition of term in Glossary.

VII. QUALIFYING IMPURITIES

Impurity *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) specified. The applicant should provide a rationale for selecting its degradation product acceptance criteria based on qualification thresholds, which determine the safety of the drug product.

A. Qualification Thresholds

When the usual qualification thresholds proposed in Attachment A, Table 3, are equaled or exceeded, degradation product levels should be qualified.

Higher or lower thresholds for qualification of degradation products may be appropriate for some individual drug products based on scientific rationale and level of concern, including drug class effects and historical safety data of the product. For example, qualification may be especially important when there is evidence that degradation products in certain drugs 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 drugs when the level of concern for safety is less than usual based on similar considerations (e.g., drug class effects, and history of the drug product). In unusual circumstances, technical factors (e.g., manufacturing capability, a low drug substance to excipient ratio, or the use of excipients that are also crude products of animal or plant origin) may be considered as part of the justification for selection of alternative thresholds. Proposals from applicants for alternative threshold levels will be considered by the FDA on a case-by-case basis.

B. Qualification Procedures

When the usual qualification thresholds proposed in Attachment A, Table 3, are equaled or exceeded, the feasibility of decreasing the degradation products to acceptable levels should be examined. In addition, degradation products that were also significant metabolites would not need further qualification. The study and knowledge of the degradation pathways could be used as a guide to control the degradation products to desirable levels. This could involve the use of purified active and inactive materials or changes in formulation and/or process as appropriate. Alternatively, the following procedures can be used for the qualification of degradation products in generic drug products.

1. USP and Literature References

If acceptance criteria are provided for a specified degradation product in the USP monograph for the drug product, that degradation product is qualified if its content does not exceed the specified limit. Also, the degradation products may be qualified from the peer-reviewed scientific literature if it is substantiated that this degradation product is an *ordinary impurity* (see USP <1086>) at the levels found. An English translation of referenced foreign language publications should be provided if being used to qualify the degradation products.

2. Comparative Chromatographic Studies

Degradation products present in a generic drug product can be qualified by comparing the chromatographic profiles of a generic drug product with those of the RLD using the same validated, stability-indicating chromatographic procedure for both drug products (i.e., comparative chromatographic studies). To obtain a meaningful comparison of the degradation profiles, it is important that any comparative stability studies be conducted on fresh batches of each product or, if possible, the dates of manufacture of the generic drug product batches should precede those of the corresponding RLD batches. The RLD samples are easily accessible and the applicant should not experience problems in developing validated analytical procedures for comparative studies as the generic drug product and the RLD formulations are generally similar. In addition, analytical procedures for the RLD may be requested from the Agency under the Freedom of Information Act (FOIA).

A degradation product present in the generic drug product would be considered qualified if the amount of identified degradation product in the generic drug product is no more than two times the amount of the corresponding degradation product in the RLD. The two-fold amount is justified for two reasons: (1) the RLD acceptance criteria for degradation products generally are set higher than what is observed in the RLD and (2) the safety studies to qualify the RLD generally are carried out at significantly higher levels than the acceptance criteria. However, the allowed degradation product levels should be no higher than the RLD levels for unidentified and toxic degradation products, or for certain dosage forms where sensitivity concerns are predominant.

3. QSAR Studies

When a degradation product in the generic drug product is either qualitatively different (new impurity) or present at more than two times the amount found in the RLD and literature references are unavailable to qualify the degradation product,

QSAR studies[6] can be used for qualification purposes. These studies provide 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 using an appropriate database and modules.

4. Genotoxicity Studies

In vitro genotoxicity tests can be considered as a last resort to qualify those degradation products that cannot be qualified by the above procedures. These tests are designed to detect compounds that induce genetic damage directly or indirectly by various mechanisms. Such studies should normally be conducted on the drug product or drug substance containing the degradation products to be controlled, although studies using isolated degradation products may work. Additional toxicity studies (in vivo toxicity studies) cannot be used for the generic drug products (section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act)).

C. Decision Tree

Attachment B, the Decision Tree for the Qualification of Degradation Products, gives a synopsis of considerations for qualifying degradation products when the proposed qualification thresholds are equaled or exceeded. Levels L1 through L4 do not include toxicity testing. Only in Level 5, where concern regarding possible toxicity is indicated, is in vitro toxicity testing recommended. Level L6 would be for those rare instances when a degradation product cannot be qualified using the recommended procedures in Level 1-5. In such cases, an NDA should be submitted in lieu of an ANDA. Additional clarification regarding the levels in the decision tree is provided below:

- *First Level (L1):* Is the degradation product in question above the threshold? Figures 1, 2, and Table 3 (Attachment A) provide proposed qualification thresholds. This level is identical to the corresponding level in the *Q3B.*

- *Second Level (L2):* This refers to structural identification or characterization either by spectroscopic procedures or using reference standards. However, in those rare cases where it is impossible to identify the degradation product by structure, the efforts made should be satisfactorily documented.

- *Third Level (L3a)*: It provides for the qualification of degradation products if the USP has a specification for an individual degradation product or the degradation

[6] Quantitative Structure Activity Relationship studies.

product is a significant metabolite. Reference to relevant scientific literature is also appropriate.

Third Level (L3b): A comparison of the degradation profile (identified degradation products) of the generic drug product with the RLD could be used for the qualification of degradation products. The degradation product is considered qualified if the amount of identified degradation product in the generic drug product is no more than two times the amount for the corresponding one in the RLD. The allowed degradation product levels should be no higher than the RLD levels for unidentified and toxic degradation products, or for certain dosage forms where sensitivity concerns are predominant.

Third Level (L3c): This level provides qualification standards if the degradation product is new or is observed at a higher level than two times the corresponding level in the RLD. If these degradation products are substantiated to be innocuous from the scientific literature, they are regarded as qualified. Alternatively, they may be qualified by lowering the impurity levels below the ICH threshold or as indicated in L3b or by following the next level in the decision tree.

- *Fourth Level (L4)*: Is the degradation product related to others with known toxicity? As one approach, the use of a QSAR database may help in identifying whether an degradation product is related to others of known toxicity. Modules currently recommended include the Rodent Carcinogenicity, Developmental Toxicity Potential; Ames Mutagenicity (five strains); and Skin Sensitization for topicals. If no potential for concern is indicated by QSAR evaluation, the degradation product is considered qualified. 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, it is recommended that the manufacturer lower the degradation product level as indicated in L3c or qualify the degradation product at the L5 Level.

- Fifth Level (L5): This level will evaluate the toxicity of a degradation product ***via*** a battery of in vitro genotoxicity tests (see Attachment C, footnote a). If the toxicity issues are confirmed by these tests, the applicant may consider reducing the degradation products to a level below the ICH threshold or go to the next level (L6) in the Decision Tree.

- Sixth Level (L6): This option involves in vivo testing. An application containing in vivo toxicity data would not be deemed acceptable by the OGD under Section 505(j) of the Act.

VIII. NEW IMPURITIES

During the course of generic drug development studies, the qualitative degradation profile of a drug product may change, resulting in new degradation products that exceed the identification and/or qualification threshold. These new degradation products should be identified and qualified. Such changes call for consideration of the need for qualification of the level of impurity unless it is below the threshold values as noted in Attachment A. The Decision Tree for the Qualification of Degradation Products in Drug Products (Attachment B) should be consulted for qualification studies.

ATTACHMENT A

Proposed Thresholds for Identifying, Qualifying and Reporting Degradation Products in Drug Products

Table 1
Thresholds for Identifying Degradation Products

Maximum Daily Dose[1]	Threshold [2]
< 1 mg.....	1.0 percent or 5 µg TDI [3] whichever is lower
1 mg - 10 mg.....	0.5 percent or 20 µg TDI whichever is lower
> 10 mg - 2 g.....	0.2 percent or 2 mg TDI whichever is lower
> 2 g.....	0.1 percent

[1] The amount of drug substance administered per day
[2] Threshold is based on percent of the drug substance
[3] Total Daily Intake

Table 2
Thresholds for Reporting of Degradation Products

Maximum Daily Dose[1]	Threshold[2]
≤ 1 g.....	0.1 percent
> 1 g.....	0.05 percent

[1] The amount of drug substance administered per day
[2] Threshold is based on percent of the drug substance

Table 3
Proposed Thresholds for Qualification of Degradation Products

Maximum Daily Dose[1]	**Threshold**[2]
< 10 mg.....	1.0 percent or 50 µg TDI[3] whichever is lower
10 mg - 100 mg.....	0.5 percent or 200 µg TDI whichever is lower
>100 mg - 2 g.....	0.2 percent or 2 mg TDI whichever is lower
>2 g.....	0.1 percent

[1] The amount of drug substance administered per day
[2] Threshold is based on percent of the drug substance
[3] Total Daily Intake

Figure1. Thresholds for Identification, Qualification and Reporting of Degradation Products in Drug Products

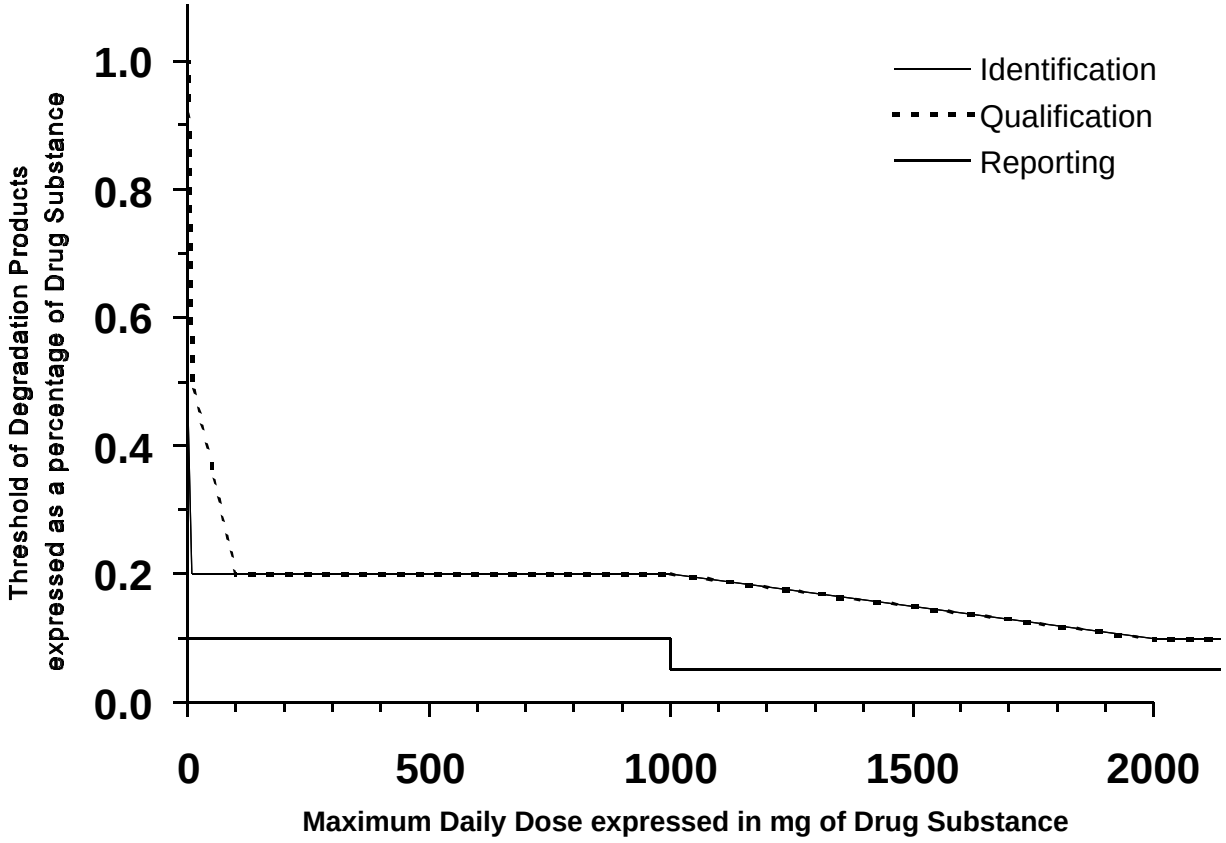

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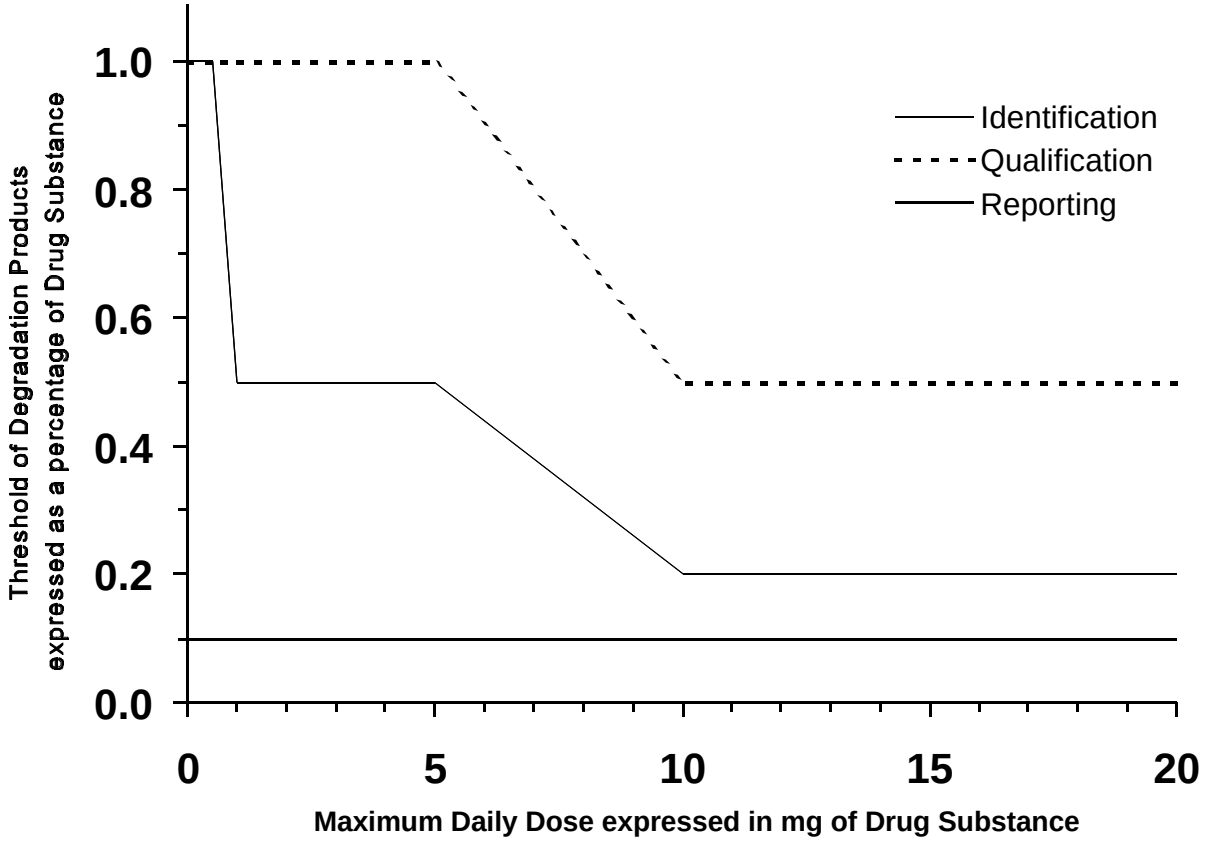
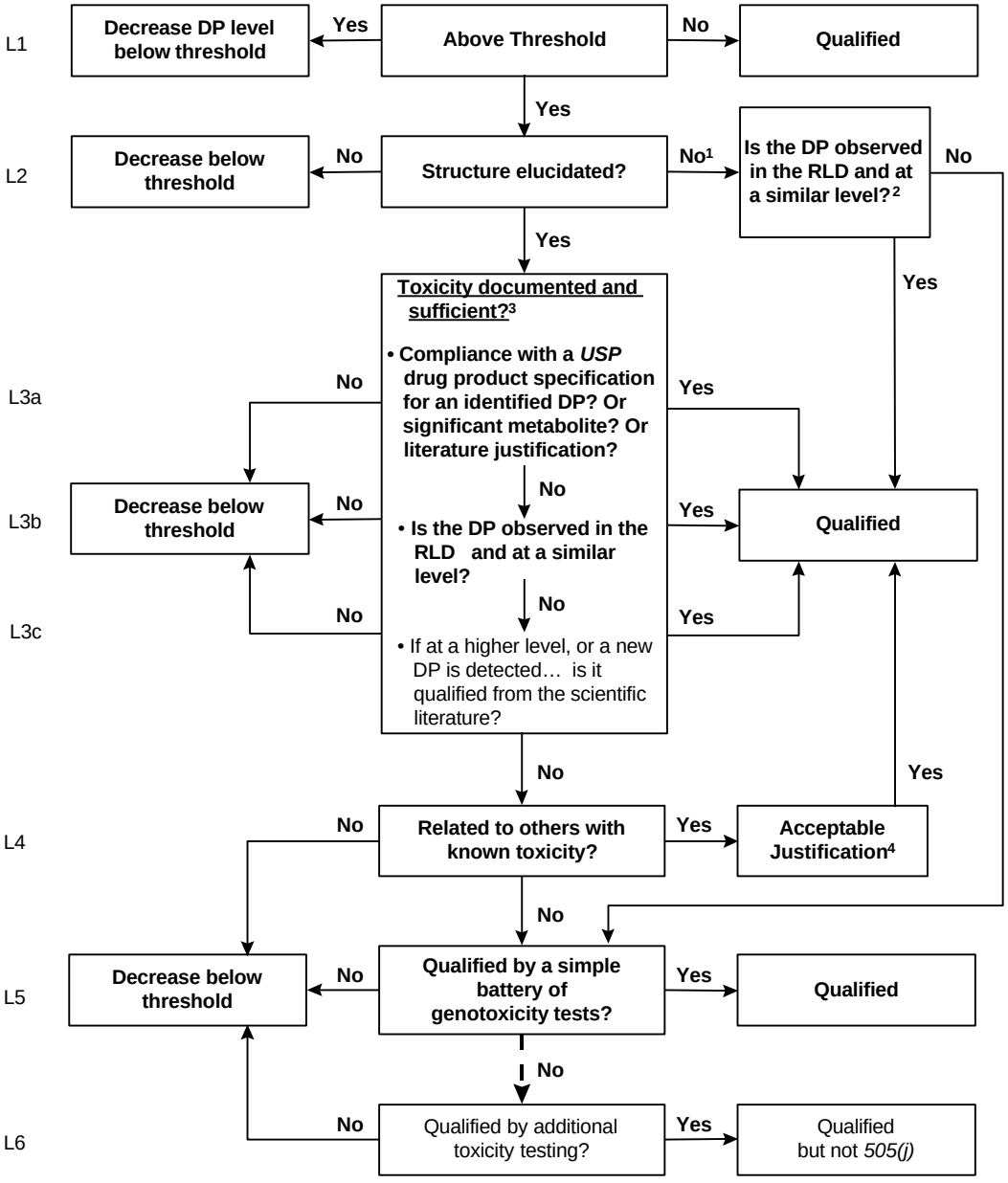
Figure 2. Thresholds for Identification, Qualification and Reporting of Degradation Products in Drug Products



ATTACHMENT B

Decision Tree for the Qualification of Degradation Products (DPs)

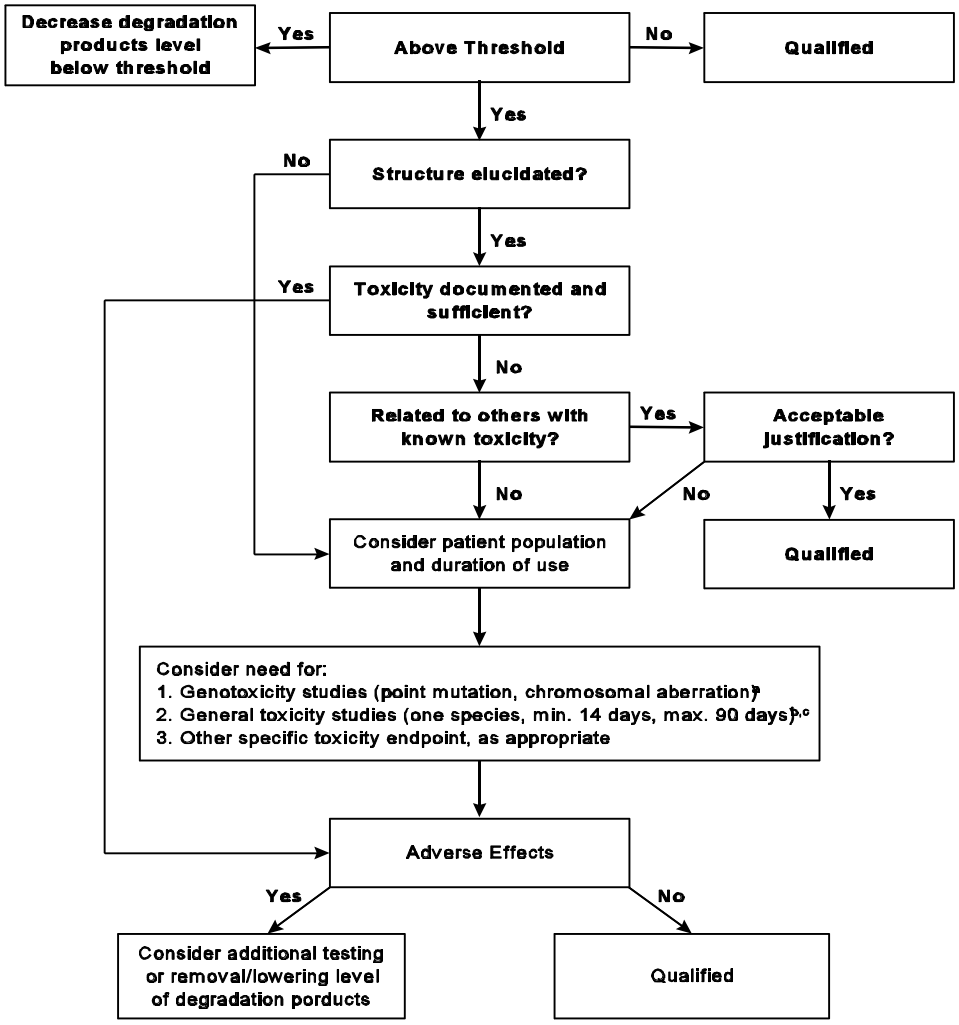
(Generic Products)



[1] Best effort; not possible; [2] RT, peak heights/areas spectral similarity; [3] Generic Drug Pathway; [4] e.g., qualified by QSAR

ATTACHMENT C

ICH Decision Tree for Safety Studies



[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 seen as an acceptable minimum screen, as discussed in the ICH Guidances "Genotoxicity: Specific Aspects of Regulatory Tests" and "Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals."

[b] 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 would be acceptable.

[C] On a case-by-case basis, single-dose studies may be acceptable, especially for single-dose drugs, and when such studies are conducted using an isolated impurity. If repeat-dose studies are desirable, a maximum duration of 90 days would be acceptable.

GLOSSARY

Acceptance Criteria: Numerical limits, or other suitable measures for acceptance of the results of analytical procedures (ICH guidance *Q6A*).

Degradation Product: A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of, e.g., light, temperature, pH, or water, or by reaction with an excipient and/or the immediate container/closure system (ICH guidance *Q3B*). It is also called a decomposition product.

Degradation Profile: A description of the degradation products observed in the drug substance or drug product (ICH guidance *Q3B*).

Development Studies: Studies conducted to scale-up, optimize, and validate the manufacturing process for a drug product (ICH guidance *Q3B*).

Drug Product: A finished dosage form, for example, a tablet or capsule that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 214.3).

Drug Substance: The active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body (21 CFR 314.3).

Genotoxicity Tests: In vitro tests designed to detect compounds which induce genetic damage directly or indirectly by various mechanisms. Compounds which are positive in tests that detect such kinds of damage have the potential to be human carcinogens and/or mutagens (i.e., may induce cancer and/or inheritable defects (ICH guidance *S2B*).

Identified Impurity: An impurity for which a structural characterization has been achieved (ICH guidance *Q3B*).

Impurity: Any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product (ICH guidance *Q3B*) .

New Drug Substance: The designated therapeutic moiety which has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester or salt of a previously approved drug substance (ICH guidance *Q3A*).

Potential Degradation Product: An impurity which, from theoretical considerations, may arise during or after manufacture or storage of the drug product. It may or may not actually appear in the drug substance or drug product (ICH guidance *Q3B*).

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 (ICH guidance *Q3B*).

Quantitative Structure Activity Relationship (QSAR): 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.

Safety Information: The body of information that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified (ICH guidance *Q3B*).

Specification: A list of tests, reference to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described (ICH guidance *Q6A*).

Specified Degradation Product: Identified or unidentified degradation product that is selected for inclusion in the drug product specifications and is individually listed and limited in order to assure the safety and quality of the drug product (ICH guidance *Q3B*).

Toxic Impurity: An impurity having significant undesirable biological activity (ICH guidance *Q3B*).

Unidentified Degradation Product: A degradation product which is defined solely by qualitative analytical properties, e.g., chromatographic retention time (ICH guidance *Q3B*).

Unspecified Degradation Product: A degradation product which is not recurring from batch to batch (ICH guidance *Q3B*).

REFERENCES

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