DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96D–0009]

International Conference on Harmonisation; Guideline on Impurities in New Drug Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guideline entitled ''Impurities in New Drug Products.'' The guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline provides guidance for registration or marketing 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. The guideline is an annex to the ICH guideline entitled ''Impurities in New Drug Substances.''

DATES: Effective May 19, 1997. Submit written comments at any time.

ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the guideline are available from the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Albinus M. D'Sa, Center for Drug Evaluation and Research (HFD–170), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3741.

Regarding ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In the **Federal Register** of March 19, 1996 (61 FR 11268), FDA published a draft tripartite guideline entitled ''Impurities in New Drug Products.'' The notice gave interested persons an opportunity to submit comments by June 17, 1996.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies at the ICH meeting held on November 6, 1996.

In the **Federal Register** of January 4, 1996 (61 FR 372), the agency published a guideline entitled ''Impurities in New Drug Substances.'' The guideline provides guidance to applicants for drug marketing registration on the content and qualification of impurities in new drug substances produced by chemical synthesis and not previously registered in a country, region, or member state.

This guideline is an annex to that guideline and provides guidance for registration or marketing 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. The guideline addresses only those impurities in drug products classified as degradation products of the active ingredient or reaction products of the active ingredient with an excipient and/or immediate container/closure system. Impurities arising from excipients present in the drug product are not addressed in this guideline.

This guideline represents the agency's current thinking on impurities in new 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.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and, where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Interested persons may, at any time, submit written comments on the guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guideline is available on the Internet using the World Wide Web (WWW) (http://www.fda.gov/cder/guidance.htm).

The text of the guideline follows:

Impurities in New Drug Products

1. Introduction

1.1 Objective of the Guideline

This document provides guidance recommendations for registration or marketing applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances not previously registered or approved for marketing in a region or member State.

1.2 Background

This guideline is an annex to the Guideline on Impurities in New Drug Substances, which should be consulted for basic principles.

1.3 Scope of the Guideline

This guideline addresses only those impurities in drug products classified as degradation products of the active ingredient or reaction products of the active ingredient with an excipient and/or immediate container/closure system (collectively referred to in this guideline as degradation products). Impurities arising from excipients present in the drug product are not covered in this document. This guideline also does not address the regulation of drug products used during the clinical research stages of development. Biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin are not covered. Also excluded from this document are: Extraneous contaminants, which should not occur in drug products and are more appropriately addressed as good manufacturing practice issues, polymorphic form, a solid state property of the new drug substance, and enantiomeric impurities. Impurities present in the new drug substance need not be monitored in drug products unless they are also degradation products.

2. Guidelines

2.1 Analytical Procedures

The registration or marketing application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantitation of degradation products. Analytical methods should be validated to demonstrate that impurities unique to the new drug substance do not interfere with or are separated from specified and unspecified degradation products in the drug product.

Degradation product levels can be measured by a variety of techniques, including those which 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 may be used to estimate the levels of degradation products. In cases where the response factors are not close, this practice may still be used if a correction factor is applied or the degradation products are, in fact, being overestimated. Specifications 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 or marketing application. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed.

2.2 Rationale for the Reporting and Control of Impurities

The applicant should summarize those degradation products observed during stability studies of the drug product. This summary should be based on sound scientific appraisal of potential degradation pathways in the 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 drug product. This summary 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 which are not degradation products, e.g., process impurities from the drug substance and excipients and their related impurities. The impurity profile of the drug product batches representative of the proposed commercial process should be compared with the profiles of drug product batches used in development and any differences discussed.

Degradation products observed in stability studies conducted at recommended storage conditions should be identified when the identification thresholds given in ATTACHMENT I are equaled or exceeded (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 these guidelines such values would not be rounded to 0.1 percent). When identification of a degradation product is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the registration or marketing application.

Degradation products below the indicated levels generally would 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.

2.3 Reporting Impurity Content of Batches

Analytical results should be provided in tabular format for all relevant batches of new drug product used for clinical, safety, and stability testing, as well as batches which are representative of the proposed commercial process. Because the degradation test 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 identification threshold. The recommended target value for the reporting threshold (as a percentage of the drug substance) can be found in ATTACHMENT 1. A higher reporting threshold should only be proposed, with justification, if the target reporting threshold cannot be achieved.

In addition, where an analytical method 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 methods are used), from representative batches including long-term and accelerated stability conditions should be provided. The procedure should be capable of quantifying at least at the reporting threshold and the chromatograms should show the location of the observed degradation products and impurities from the new drug substance.

The following information should be provided:

- Batch identity, strength, and size
- Date of manufacture
- Site of manufacture
- Manufacturing process, where applicable
- Immediate container/closure
- Degradation product content, individual and total
- Use of batch
- Reference to analytical procedure(s) used
- Batch number of the drug substance used in the drug product
- Storage conditions

2.4 Specification Limits for Impurities

The specifications for a new drug product should include limits for degradation products expected to occur under recommended storage conditions. Stability studies, knowledge of degradation pathways, product development studies, and laboratory studies should be used to characterize the degradation profile. Specifications should be set taking into account the qualification of the degradation products, the stability data, the expected expiry period, and the recommended storage conditions for the new drug product, allowing sufficient latitude to deal with normal manufacturing, analytical, and stability profile variation. The specification for the drug product should include, where applicable, limits for:

- Each specified degradation product
- Any unspecified degradation product
- Total degradation products

Although some variation is expected, significant variation in batch-to-batch degradation profiles may indicate that the manufacturing process of the new drug product is not adequately controlled and validated. A rationale for the inclusion or exclusion of impurities in the specifications should be presented. This rationale should include a discussion of the impurity profiles observed in the safety and clinical studies, together with a consideration of the impurity profile of the product manufactured by the proposed commercial process.

2.5 Qualification of Impurities

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 level(s) specified. The applicant should provide a rationale for selecting degradation product limits based on safety considerations. The level of any degradation product present in a new drug product that has been adequately tested and found safe in safety and/or clinical studies is 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, would not need further qualification. It may be possible to justify a higher level of a degradation product than the level administered in safety studies. The justification 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 percentage change in the degradation product; and (3) other safety factors as appropriate.

If data are not available to qualify the proposed specification level of a degradation product, studies to obtain such data may be needed (see ATTACHMENT II) when the usual qualification thresholds given in ATTACHMENT I are equaled or exceeded. 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 clinical experience. For example, qualification may be especially important when there is evidence that such 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., patient population, drug class effects, and clinical considerations). 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 for alternative thresholds would be considered on a case-by-case basis.

The ''Decision Tree for Safety Studies'' (See Guideline on Impurities in New Drug Substances and ATTACHMENT II) describes considerations for the qualification of impurities when thresholds are equaled or exceeded. Alternatively, if data are available in the scientific literature, then such data may be submitted for consideration to qualify a degradation product. If neither is the case, additional safety testing should be considered. The studies desired to qualify a degradation product will depend on a number of factors, including the patient population, daily dose, route and duration of drug administration. 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 be considered acceptable.

2.6 New Impurities

During the course of drug development studies, the qualitative degradation profile of a new drug product may change, resulting in new degradation products that exceed the identification and/or qualification threshold. In this event, these new degradation products should be identified and/or qualified. 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 in ATTACHMENT I.

When a new degradation product equals or exceeds the threshold (for rounding, see section 2.2), the ''Decision Tree for Safety Studies'' should be consulted. Safety studies should provide a comparison of results of safety testing of the drug product or drug substance containing a representative level of the degradation product with previously qualified material, although studies using the isolated degradation products also may be considered acceptable (these studies may not always have clinical significance).

3. Glossary

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 (also called decomposition product).

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.

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

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.

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

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.

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.

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.

Reaction Product: Product arising from the reaction of a drug substance with an excipient in the drug product or immediate container/closure system.

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.

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

Toxic Impurity: An impurity having significant undesirable biological activity.

Unidentified Degradation Product: An impurity which is defined solely by qualitative analytical properties, e.g., chromatographic retention time.

Unspecified Degradation Product: A degradation product which is not recurring from batch to batch.

ATTACHMENT I

Thresholds for Reporting of Degradation Products in New Drug Products

Maximum daily dose[1]	Threshold[3]
≤ 1 g	0.1%
> 1 g	0.05%

Thresholds for Identification of Degradation Products in New Drug Products

Maximum daily dose[1]	Threshold[3]
< 1 mg	1.0% or 5 μg TDI[2] 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	0.1%

Thresholds for Qualification of Degradation Products in New Drug Products	
Maximum daily dose[1]	Threshold[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 2 mg TDI whichever is lower
> 2 g	0.1%

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

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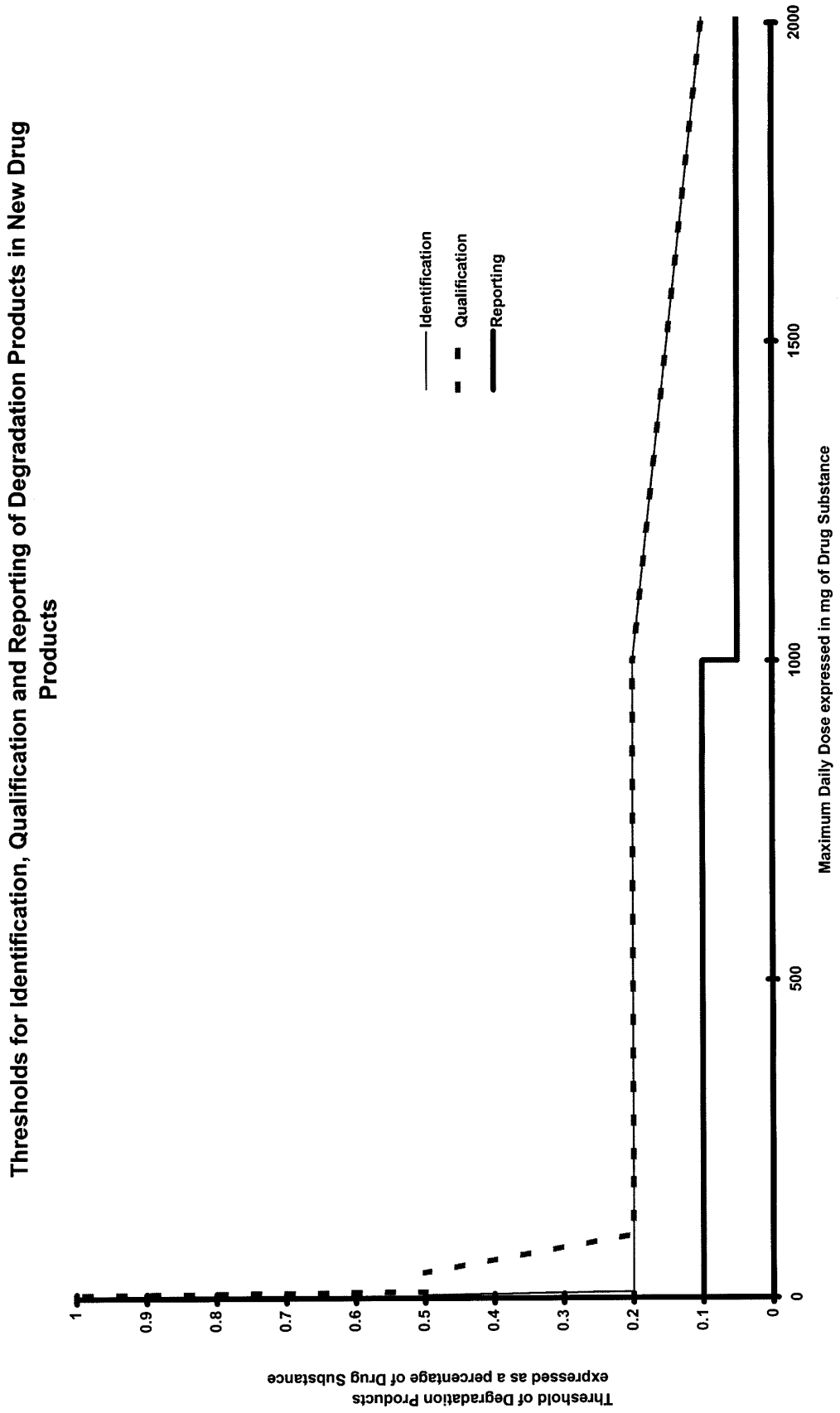
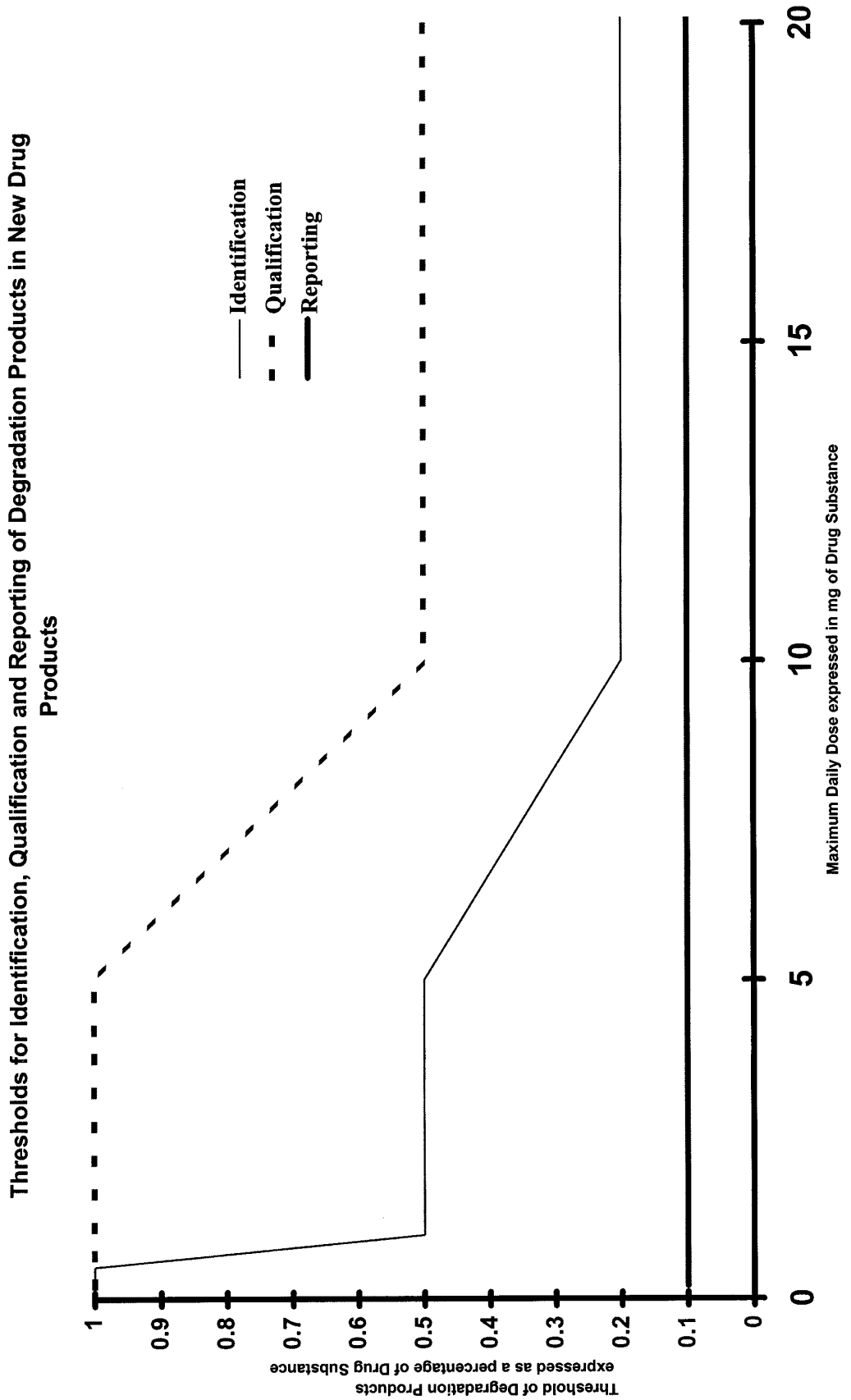
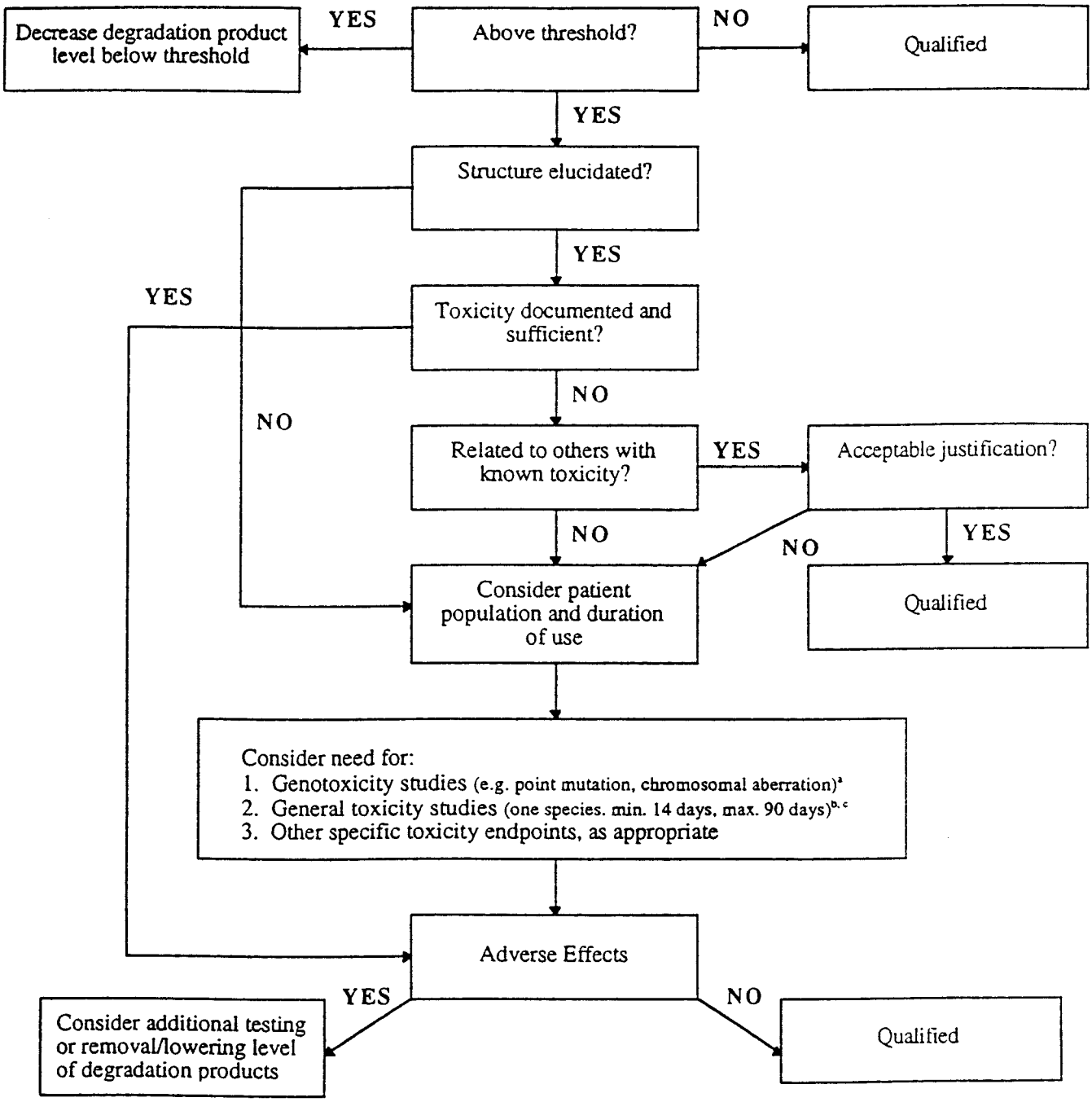

Thresholds for Identification, Qualification and Reporting of Degradation Products in New Drug Products
Identification
Qualification
Reporting
Threshold of Degradation Products expressed as a percentage of Drug Substance
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
500
1000
1500
2000
Maximum Daily Dose expressed in mg of Drug Substance


Thresholds for Identification, Qualification and Reporting of Degradation Products in New Drug Products
Identification
Qualification
Reporting
Threshold of Degradation Products expressed as a percentage of Drug Substance
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
Maximum Daily Dose expressed in mg of Drug Substance

ATTACHMENT II

DECISION TREE FOR SAFETY STUDIES



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[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 guidelines: ''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 days 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.

Dated: May 6, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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