Jefferson Street, Suite 400, Rockville, Maryland 20852, Telephone (301) 594–1847.

Agenda items for these meetings are subject to change as priorities dictate.

This notice is being published less than 15 days prior to the July 27–28 meetings due to the time constraints of reviews and funding cycles.

Dated: July 11, 2000.

John M. Eisenberg,

Director.

[FR Doc. 00–18146 Filed 7–18–00; 8:45 am]

BILLING CODE 4160–90–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

Reallotment of FY 1999 Funds for Low Income Home Energy Assistance Program (LIHEAP)

AGENCY: Office of Community Services, ACF, DHHS.

ACTION: Notice of determination concerning funds available for reallotment.

SUMMARY: Notice is hereby given that a preliminary determination has been made that fiscal year (FY) 1999 Low Income Home Energy Assistance Program (LIHEAP) funds are available for reallotment *to States, territories, and Tribes and tribal organizations receiving FY 2000 direct LIHEAP funding.* No subgrantees or other entities may apply for the funds, Section 2607(b)(1) of the Low Income Home Energy Assistance Act (the Act), Title XXVI of the Omnibus Budget Reconciliation Act of 1981 (42 U.S.C. 8621 *et seq.*), as amended, requires that if the Secretary of the Department of Health and Human Services determines that, as of September 1 of any fiscal year, an amount in excess of certain levels allotted to a grantee for any fiscal year will not be used by the grantee during the fiscal year, the Secretary must notify the grantee and publish a notice in the **Federal Register** that such funds may be realloted to LIHEAP grantees during the following fiscal year. If reallotted, the LIHEAP block grant allocation formula will be used to distribute the funds. (No funds may be reallotted to entities that are not direct LIHEAP grantees during FY 2000). It has been determined that $496,085.78 may be available for reallotment during FY 2000. This determination is based on revised reports from the State of Wyoming and the Pala Band of Mission Indians, which were submitted to the Office of Community Services as required by 45 CFR 96.82.

The statute allows grantees who have funds unobligated at the end of the fiscal year for which they are awarded to request that they be allowed to carry over up to 10 percent of their allotments to the next fiscal year. Funds in excess of this amount must be returned to DHHS and are subject to reallotment under section 2607(b)(1) of the Act. The amount described in this notice was reported as unobligated FY 1999 funds in excess of the amount that the State of Wyoming and the Pala Band of Mission Indians could carry over to FY 2000.

The State of Wyoming was notified by certified mail that $493,063.78 of its FY 1999 funds may be allotted. Additionally, the Pala Band of Mission Indians was notified by certified mail that $3,022 of its FY 1999 funds may be reallotted. In accordance with section 2607(b)(3), the Chief Executive Officers of the State of Wyoming and of the Pala Band of Mission Indians have 30 days from the date of the letter to submit comments to: Donald Sykes, Director, Office of Community Services, 370 L'Enfant Promenade, SW., Washington, DC 20447. The comment period expires August 18, 2000.

After considering any comments submitted, the Chief Executive Officers will be notified of the decision, and the decision also will be published in the **Federal Register**. If funds are reallotted, they will be allocated in accordance with section 2604 of the Act and must be treated by LIHEAP grantees receiving them as an amount appropriated for FY 2000. As FY 2000 funds, they will be subject to all requirements of the Act, including section 2607(b)(2), which requires that a grantee obligate at least 90% of its total block grant allocation for a fiscal year by the end of the fiscal year for which the funds are appropriated, that is, by September 30, 2000.

FOR FURTHER INFORMATION CONTACT: Janet Fox, Director, Division of Energy Assistance, Office of Community Services, 370 L'Enfant Promenade, SW., Washington, DC 20447; telephone (202) 401–9351.

Dated: June 30, 2000

Donald Sykes,

Director, Office of Community Services.

[FR Doc. 00–18141 Filed 7–18–00; 8:45 am]

BILLING CODE 4184–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96D–0009]

International Conference on Harmonisation; Draft Revised Guidance on Impurities in New Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft revised guidance entitled ''Q3B(R) Impurities in New Drug Products.'' The draft revised guidance, which updates a guidance on the same topic published in the **Federal Register** of May 19, 1997 (the 1997 guidance), was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft revised guidance clarifies the 1997 guidance, adds information, and provides consistency with more recently published ICH guidances. The draft revised guidance is intended to provide 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 draft revised guidance is a complement to the ICH guidance entitled ''Q3A Impurities in new Drug Substances,'' which is being revised also.

DATES: Submit written comments by September 18, 2000.

ADDRESSES: Submit written comments on the draft revised guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Copies of the draft revised guidance 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, 301–827–4573. Single copies of the draft revised guidance may be obtained by mail from the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, MD 20852, or by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800. Copies may be obtained from CBER's FAX

Information System at 1–888–CBER–FAX or 301–827–3844.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: Charles P. Hoiberg, Center for Drug Evaluation and Research (HFD–800), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–5169.

Regarding the 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 October 1999, the ICH Steering Committee agreed that a draft revised guidance entitled ''Q3B(R) Impurities in New Drug Products'' should be made available for public comment. The draft revised guidance is a revision of a guidance on the same topic published in the **Federal Register** of May 19, 1997 (62 FR 27454). The draft revised guidance is the product of the Quality Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Quality Expert Working Group.

In accordance with FDA's good guidance practices (62 FR 8961, February 27, 1997), this document is now being called a guidance, rather than a guideline.

In the **Federal Register** of January 4, 1996 (61 FR 372), the agency published an ICH guidance entitled ''Q3A Impurities in New Drug Substances.'' ICH Q3A, which is being revised also, 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 draft revised guidance is a complement to the ICH Q3A guidance 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 draft revised guidance 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 draft revised guidance.

The draft revised guidance includes revised text on threshold limits, revised text on degradation products, and new guidance on rounding. Additions to the glossary include definitions for the terms ''identification threshold,'' ''qualification threshold,'' ''reporting threshold,'' and ''rounding.'' The draft revised guidance was updated to include references to ICH guidances on analytical validation and specifications. Minor editorial changes were made to improve the clarity and consistency of the document.

This draft revised guidance 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.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the draft revised guidance by September 18, 2000. 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. A copy of the draft revised guidance 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 guidance is available on the Internet at http://www.fda.gov/cder/guidance/index.htm or http://www.fda.gov/cber/publications.htm.

The text of the draft revised guidance follows:

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

1. Introduction

1.1 Objective of the Guidance

This document provides guidance recommendations for registration or applications for marketing 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.

1.2 Background

This guidance is a complement to the ICH Q3A guidance on impurities in new drug substances, which should be consulted for basic principles.

1.3 Scope of the Guidance

This guidance addresses only those impurities in 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). Impurities arising from excipients present in the product are not covered by this guidance. This guidance also does not address the regulation of products used during the clinical research stages of development. Biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin are not covered. Also excluded from this guidance are: Extraneous contaminants that 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 or specified in drug products unless they are also degradation products (see ICH Q6A guidance for specifications).

[1] This draft revised guidance 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.

2. Guidance

2.1 Analytical Procedures

The application for a marketing authorization should include documented evidence that the analytical procedures have been validated and are 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 product (see ICH Q2A and Q2B guidances for analytical validation).

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 application for marketing authorization. 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 that are not degradation products, e.g., process impurities from the drug substance and excipients and their related impurities. The impurity profile of the batches representative of the proposed commercial process should be compared with the profiles of batches used in development, and any differences discussed.

Degradation products observed in stability studies conducted at recommended storage conditions should be identified when present at a level greater than (>) the identification thresholds given in Attachment 1. When identification of a degradation product is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application for marketing authorization.

Degradation products present at a level of not more than (≤) the 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 pharmacologic effects at levels lower than indicated. Conventional rounding rules should be applied, and the results presented with the same number of decimals as given in the limit.

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 that 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 product, the reporting level should be set below the identification threshold. The recommended target value for the reporting threshold (expressed as a percentage of the drug substance) is found in Attachment I. 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 Degradation Products

The specifications for a new drug product should include limits for degradation products expected to occur during manufacture 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. Specifications should be set taking into account the qualification of the degradation products, the stability data, the content arising from the drug substance specification, the expected expiry period, and the recommended storage conditions for the product, allowing sufficient latitude to deal with normal manufacturing, analytical, and stability profile variation. The specifications for the 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. All impurities at a level greater than (>) the reporting threshold should be summed and reported as Total Impurities. The summation should be performed on the unrounded individual values, and the total value should be rounded and reported as described in section 2.2.

2.5 Qualification of Degradation Products

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, do 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: The amount of degradation product administered in previous safety and/or clinical studies and found to be safe; the percentage change in the degradation product; and 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 2) when the usual qualification thresholds set out in Attachment 1 are exceeded. Higher or lower thresholds for qualification of degradation products may be appropriate for some individual 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 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 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). 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 threshold limits based upon manufacturing experience with the proposed commercial process. Proposals for alternative thresholds would be considered on a case-by-case basis.

The ''Decision Tree for Safety Studies'' (Attachment 2) describes considerations for the qualification of impurities when thresholds are 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, and route and duration of product administration. Such studies should normally be conducted on the product or substance containing the degradation products to be controlled, although studies using isolated degradation products are considered acceptable.

2.6 New Degradation Products

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 qualification of the level of the degradation product unless it is present at a level of not more than (≤) the threshold values as set out in Attachment 1.

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

3. Glossary

Degradation product: A molecule resulting from a chemical change in the substance 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.

Identification threshold: A limit above which (>) an impurity needs identification.

Identified degradation product: A degradation product 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 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 may be a complex, simple ester, or salt of a previously approved substance.

Potential degradation product: An impurity that, from theoretical considerations, may arise during or after manufacture or storage of the drug product. It may or may not actually appear in the substance or 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.

Qualification threshold: A limit above which (>) an impurity needs to be qualified.

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

Reporting threshold: A limit above which (>) an impurity needs to be reported.

Rounding: The process of reducing a result to the number of significant figures or number of decimal places as dictated by the appropriate limit. For example, a result greater than or equal to (≥) 0.05 and less than (<) 0.15 is rounded to 0.1.

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: An 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 ensure the safety and quality of the new drug product.

Toxic impurity: An impurity having significant undesirable biological activity.

Unidentified degradation product: A degradation product that is defined solely by qualitative analytical properties, e.g., chromatographic retention time.

Unspecified degradation product: A degradation product that is not included in the list of specified degradation products.

ATTACHMENT 1.

Thresholds for Reporting of Degradation Products in New Drug Products

Maximum Daily Dose [1]	Threshold [2]
≤ 1 gram (g)	0.1%
> 1 g	0.05%

Thresholds for Identification of Degradation Products in New Drug Products

Maximum Daily Dose [1]	Threshold [2]
< 1 milligram (mg)	1% or 5 micrograms (μg) TDI,[3] 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%

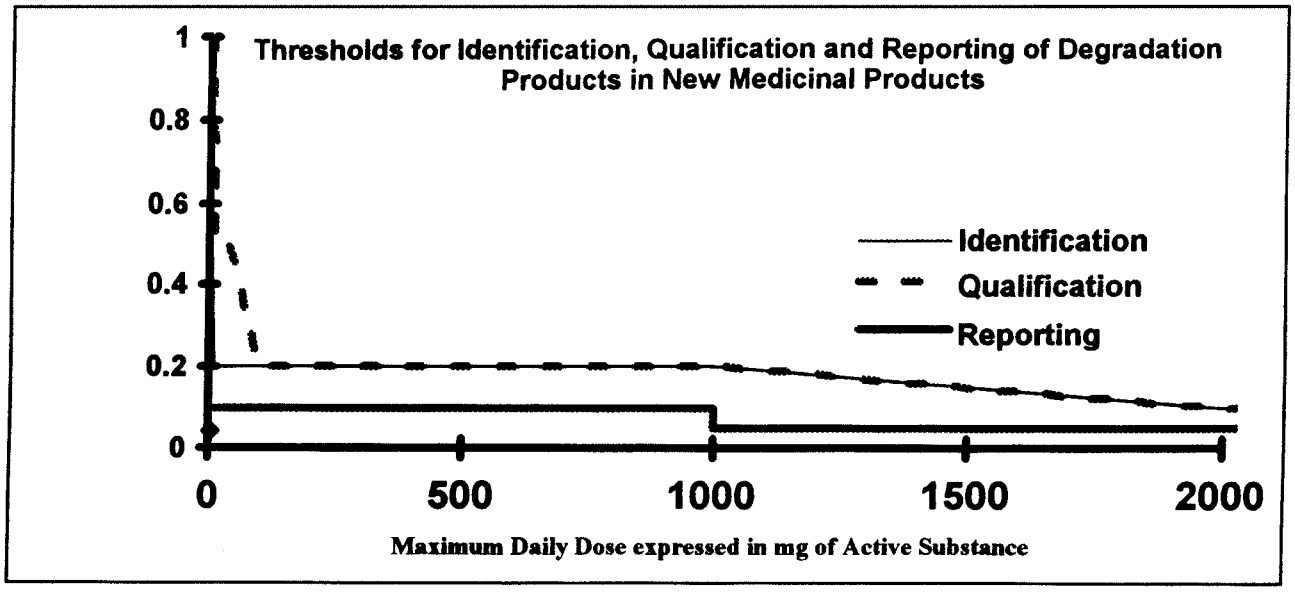
Thresholds for Qualification of Degradation Products in New Drug Products

Maximum Daily Dose [1]	Threshold [2]
< 10 mg	1% or 50 μg TDI, whichever is lower

Thresholds for Qualification of Degradation Products in New Drug Products	
Maximum Daily Dose [1]	Threshold [2]
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 substance administered per day.
[2] Threshold is based on percent of the substance. Higher reporting thresholds should be scientifically justified.
[3] Total daily intake.

BILLING CODE 4160–01–F



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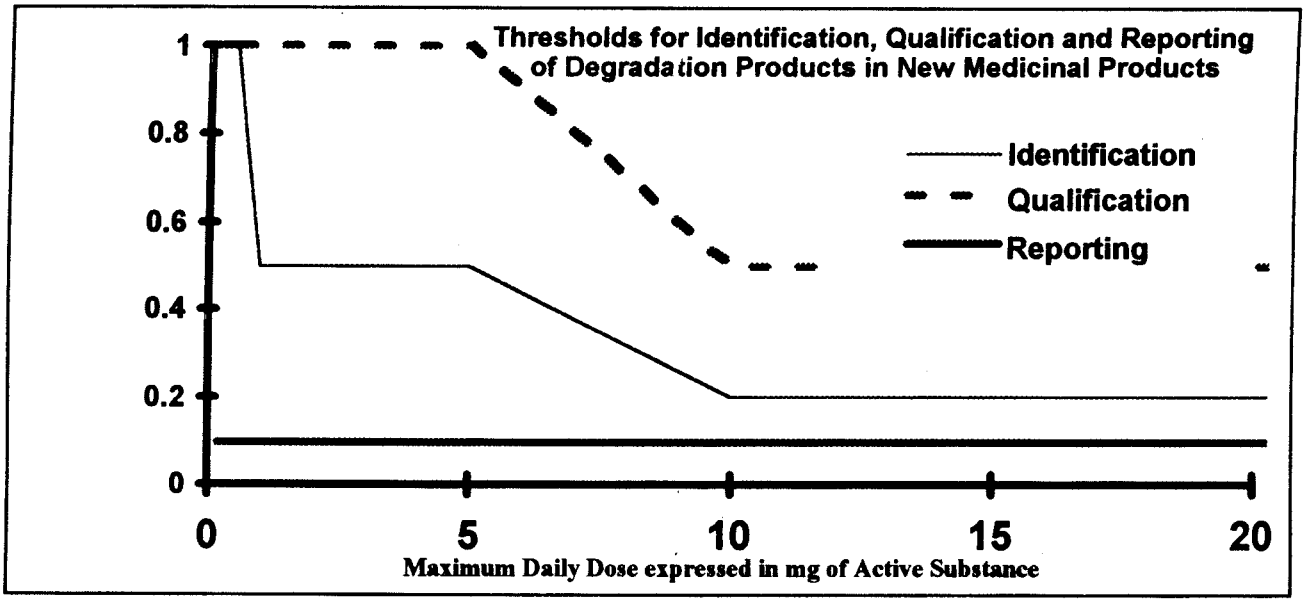
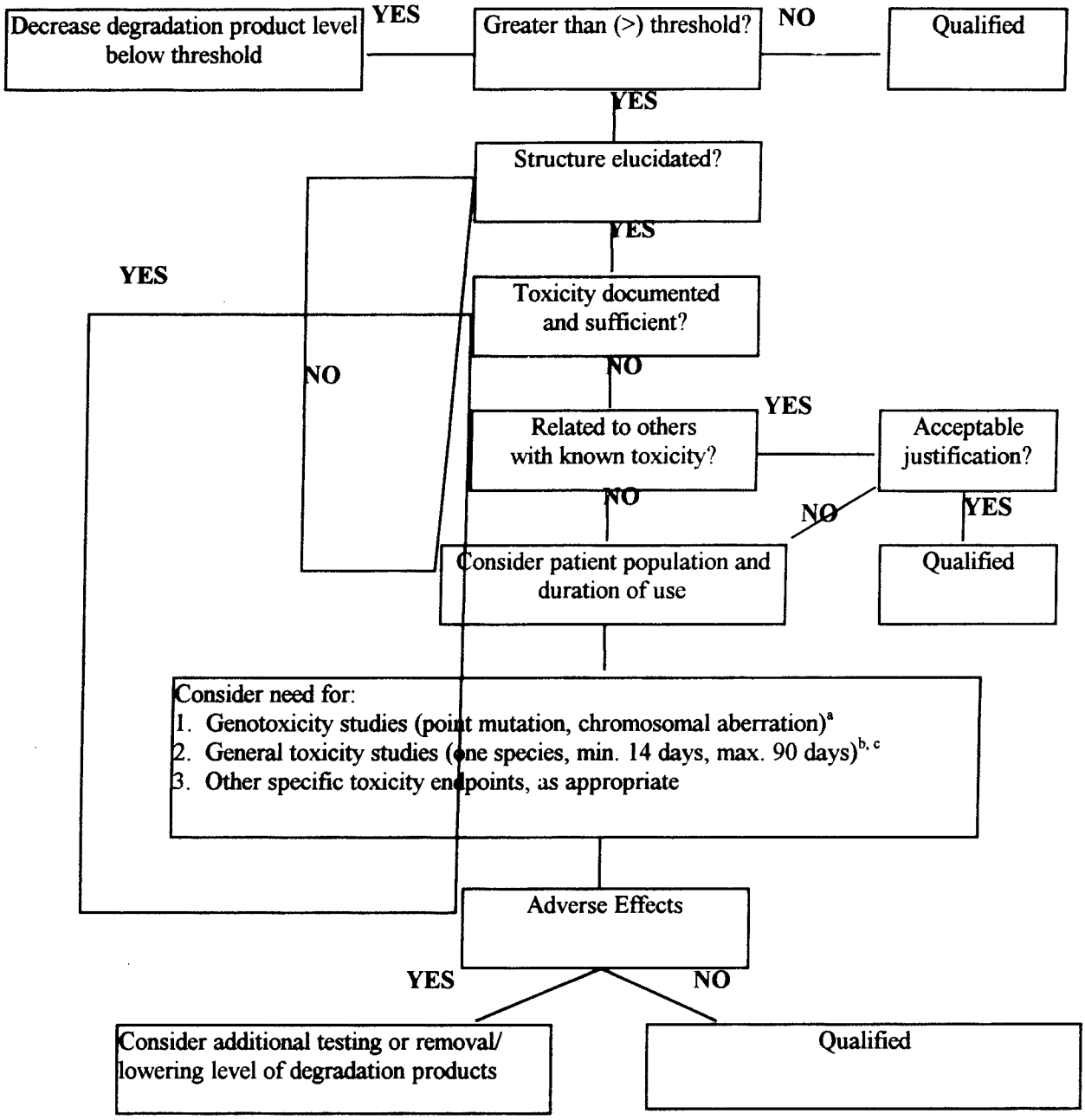


ATTACHMENT 2: DECISION TREE FOR SAFETY STUDIES



[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 recommended as an acceptable minimum screen, as discussed in the ICH guidances: ''S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals'' and ''S2B 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. If repeat-dose studies are desirable, a maximum duration of 90 days would be acceptable.

Dated: July 10, 2000.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 00–18150 Filed 7–18–00; 8:45 am]

BILLING CODE 4160–01–C