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Guidance for Industry

IMPURITIES IN NEW VETERINARY MEDICINAL PRODUCTS (REVISED)
VICH GL11 (R)

REVISED FINAL GUIDANCE

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Additional copies of this final guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at http://www.fda.gov/cvm.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
November 21, 2007

1999D-2145

GDL4

VICH GL11 (QUALITY)
September 2007
Revised at Step 9

IMPURITIES IN NEW VETERINARY MEDICINAL PRODUCTS (REVISION)

Revised at Step 9
by the VICH Steering Committee in September 2007

This Guidance has been developed by the appropriate VICH Expert Working Group and is subject to consultation by the parties, in accordance with the VICH Process. At Step 9 of the Process the final draft will be recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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VICH GL- 11 (R)
IMPURITIES IN NEW VETERINARY MEDICINAL PRODUCTS

This guidance represents the Food and Drug Administration's (FDA's) current thinking on the subject matter. 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 the approach satisfies the requirements of the applicable statute(s) and regulation(s). 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

1.1 Objective of the guidance

This document provides guidance to registration applicants on the content and qualification of impurities in new veterinary medicinal products produced from chemically synthesized new veterinary drug substances not previously registered in a country, region, or member state. Alternative approaches may be used if such approaches satisfy the requirements of applicable statutes and regulations.

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.

1.2 Background

This guidance is complementary to the VICH GL10(R) guidance "Impurities in New Veterinary Drug Substances," which should be consulted for basic principles. The VICH GL18 guidance, "Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients" should also be consulted, if appropriate.

1.3 Scope of the guidance

This guidance addresses only those impurities in new veterinary medicinal products classified as degradation products of the new veterinary drug substance or reaction products of the new veterinary drug substance with an excipient and/or immediate container closure system (collectively referred to as "degradation products" in this guidance). Generally, impurities present in the new veterinary drug substance need not be monitored or specified in the new veterinary medicinal product unless they are also degradation products (see guidance VICH GL39 on specifications).

Impurities arising from excipients present in the new veterinary medicinal product or extracted or leached from the container closure system are not addressed in this guidance. This guidance also does not address new veterinary medicinal products used during the clinical research stages of development. The following types of products are not addressed in this guidance: biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin. Also excluded from this document are: (1) extraneous contaminants that should not occur in new veterinary medicinal products and are more appropriately addressed as good manufacturing practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

II. RATIONALE FOR THE REPORTING AND CONTROL OF DEGRADATION PRODUCTS

The registration applicant should summarize the degradation products observed during manufacture and/or stability studies of the new veterinary medicinal product. This summary should be based on sound scientific appraisal of potential degradation pathways in the new veterinary medicinal product and impurities arising from the interaction with excipients and/or the immediate container closure system. In addition, the registration applicant should summarize any laboratory studies conducted to detect degradation products in the new veterinary medicinal product. This summary should also 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 new veterinary 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 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 threshold of 1.0 % (Attachment 1). When identification of a degradation product is not feasible, 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 of 1.0 % 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 of 1.0 %. In certain circumstances, technical factors (e.g., manufacturing capability, a low new veterinary drug substance to excipient ratio, or the use of excipients that are crude products of animal or plant origin) can be considered as part of the justification for selection of alternative thresholds based upon manufacturing experience with the proposed commercial process.

III. ANALYTICAL PROCEDURES

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 guidances VICH GL1 and GL2 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 new veterinary drug substance, impurities arising from the synthesis of the new veterinary 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 (see attachment 1).

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 veterinary 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 new veterinary drug substance can be used to estimate the levels of degradation products. In cases where 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

Analytical results should be provided in the registration application for all relevant batches of the new veterinary medicinal 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 as opposed to in general terms such as "complies," "meets limit," etc. Any degradation product at a level greater than (>) the reporting threshold of 0.3 %(see Attachment 1), and total degradation products observed in the relevant batches of the new veterinary medicinal product, should be reported with the analytical procedures indicated. The results should be reported to one decimal place (e.g., 0.4%, 1.3%). Results should be rounded using conventional rules. 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 of 0.3% 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 veterinary medicinal 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 new veterinary drug substance used in the new veterinary medicinal product
- Storage conditions for stability studies

V. LISTING OF DEGRADATION PRODUCTS IN SPECIFICATIONS

The specification for a new veterinary medicinal 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 veterinary medicinal 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 veterinary medicinal 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 of 1.0% (Attachment 1). For degradation products known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the 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 of 1.0% (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 new veterinary drug substance (if applicable), its qualified level, its increase during stability studies, and the proposed shelf life and recommended storage conditions for the new veterinary medicinal 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 veterinary medicinal 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 veterinary medicinal 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 veterinary medicinal product is not adequately controlled and validated (see guidance VICH GL39 on specifications and decision tree #2 for establishing an acceptance criterion for a specified degradation product in a new veterinary medicinal product).

In summary, the new veterinary medicinal 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 of 1.0% (see Attachment 1)
- Total degradation products.

VI 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 registration 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 veterinary medicinal 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 veterinary medicinal 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 threshold of 1.0% given in Attachment 1 is exceeded and data are unavailable to qualify the proposed acceptance criterion of a degradation product, additional studies to obtain such data can be appropriate (see Attachment 2).

Higher or lower thresholds for qualification of degradation products can be appropriate for some individual new veterinary medicinal 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 veterinary medicinal products or therapeutic classes have previously been associated with adverse reactions in animals and/or humans. In these instances, a lower qualification threshold can be appropriate. Conversely, a higher qualification threshold can be appropriate for individual new veterinary medicinal products when the level of concern for safety is less than usual based on similar considerations (e.g., animal species, 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 2) 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 animal species, daily dose, and route and duration of new veterinary medicinal product administration. Such studies can be conducted on the new veterinary medicinal 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 address the clinical research stage of development, in the later stages of development, the thresholds in this guidance can be useful in evaluating new degradation products observed in new veterinary medicinal 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 2) if its level is greater than (>) the identification threshold of 1.0% given in Attachment 1. Similarly, qualification of the degradation product should be considered if its level is greater than (>) the qualification threshold of 1.0% given in Attachment 1.

Safety studies should provide a comparison of results of safety testing of the new veterinary medicinal product or new veterinary 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.

VII GLOSSARY

(The following definitions are presented for the purpose of this Revised Guidance.)

Degradation Product: An impurity resulting from a chemical change in the new veterinary drug substance brought about during manufacture and/or storage of the new veterinary medicinal 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 new veterinary drug substance or new veterinary medicinal product.

Development Studies: Studies conducted to scale-up, optimize, and validate the manufacturing process for a new veterinary medicinal 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 veterinary medicinal product that is not the new veterinary drug substance or an excipient in the new veterinary medicinal product.

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

New Veterinary Drug Substance: The designated therapeutic moiety that has not been previously registered in a region or member state in a veterinary medicinal product (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.

New Veterinary Medicinal Product: A pharmaceutical product type, for example, tablet, capsule, solution, cream, etc., containing a new or existing drug substance which has not previously been registered in a region or member state, and which contains a drug ingredient generally, but not necessarily, in association with excipients.

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 level(s) 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 veterinary medicinal 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).

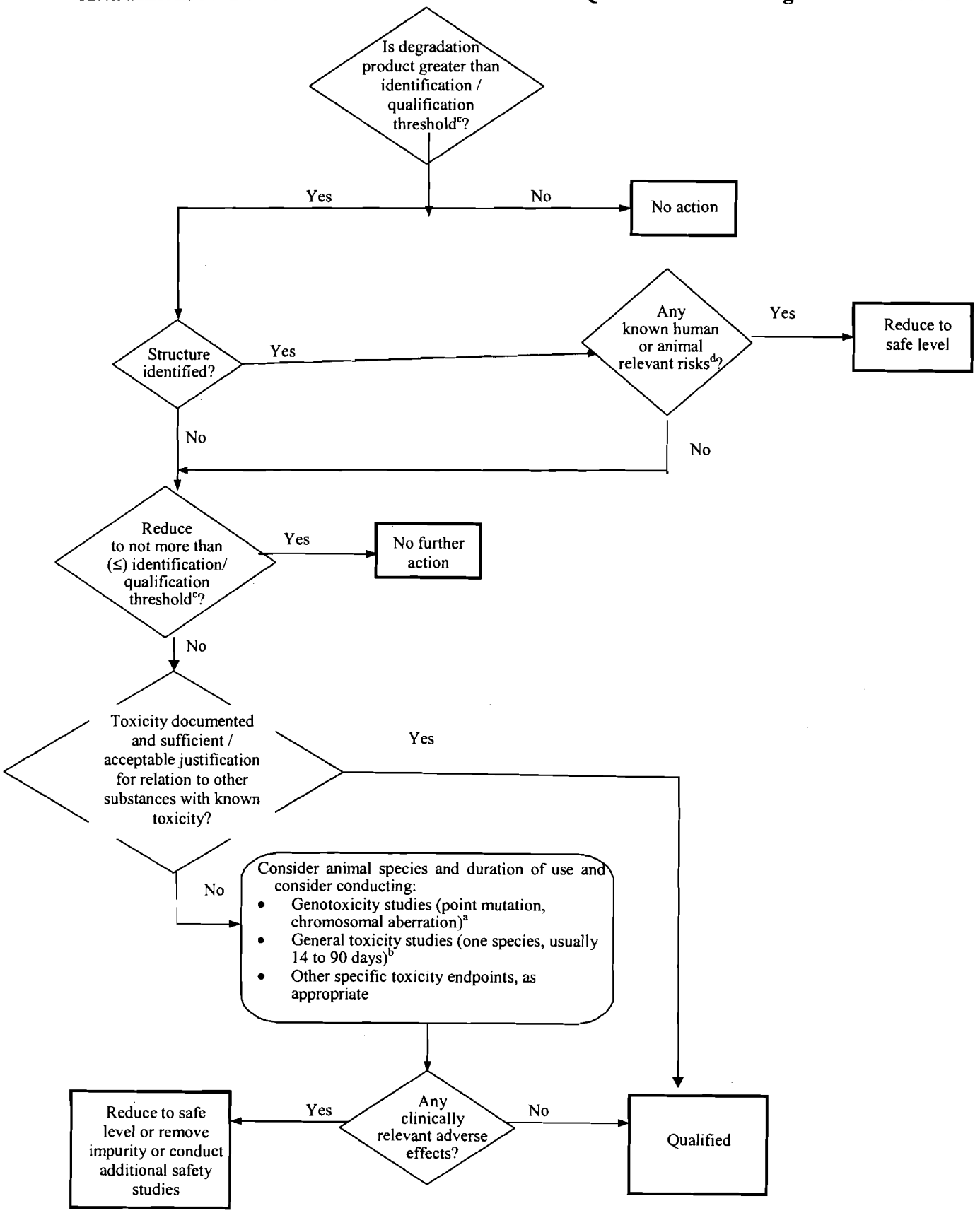
Unspecified Degradation Product: A degradation product that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new veterinary medicinal product specification.

Attachment 1: Thresholds for Degradation Products in New Veterinary Medicinal Products

Identification[1]	1.0%
Reporting[1]	0.3%
Qualification[1]	1.0%

1 Higher thresholds should be scientifically justified.

Attachment 2: Decision Tree for Identification and Qualification of a Degradation Product



Notes on Attachment 2

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 or animal exposure at the concentration present?