DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0448]

International Conference on Harmonisation; Draft Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guidance entitled ''Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.'' The draft guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use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 The draft guidance provides guidance on the selection of test procedures and the setting and justification of acceptance criteria for new chemical drug substances and new drug products produced from them. The draft guidance is intended to assist in the establishment of a single set of global specifications for new drug substances and new drug products.

DATES: Written comments by January 26, 1998.

ADDRESSES: Submit written comments on the draft guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the draft guidance are available from the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville,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

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: Eric B. Sheinin, Center for Drug Evaluation and Research (HFD–800), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–5918, or

Neil D. Goldman, Center for Biologic Evaluation and Research (HFM–416), Food and Drug Administration, 8800 Rockville Pike, Rockville, MD 20852, 301–827–0377.

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 July 1997, the ICH Steering Committee agreed that a draft guidance entitled ''Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances'' should be made available for public comment. The draft 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. A related document for biotechnology derived products is the subject of a separate Expert Working Group.

In accordance with Good Guidance Practices (62 FR 8961, February 27, 1997), this document is now being called a guidance, rather than a guideline.

The draft guidance provides guidance on the selection of test procedures and the setting and justification of acceptance criteria for new drug substances of synthetic chemical origin, and new drug products produced from them, that have not been registered previously in the United States, the European Union, or Japan. The draft guidance is intended to assist in the establishment of a single set of global specifications for new drug substances and new drug products.

This draft guidance represents the agency's current thinking on the selection of test procedures and the setting and justification of acceptance criteria for new chemical drug substances and 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, on or before January 26, 1998, submit to the Dockets Management Branch (address above) written comments on the draft guidance. 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 draft 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.htm''.

The text of the draft guidance follows:

Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances[1]

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1. Introduction

1.1 Specifications

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. ''Conformance to specifications'' means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development upon which specifications are based, adherence to good manufacturing practices (GMP's), and a validated manufacturing process, e.g., raw material testing, in-process testing, stability testing.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

1.2 Objective of the Guidance

This guidance is intended to assist, to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, that have not been registered previously in the United States, the European Union, or Japan.

1.3 Scope of the Guidance

The quality of drug substances and drug products is determined by their design, development, in-process controls, GMP controls, and process validation, and by specifications applied to them throughout development and manufacture. This guidance addresses specifications, i.e., those tests, procedures, and acceptance criteria used to assure the quality of the new drug substance and new drug product at release and during shelf life. Specifications are an important component of quality assurance, but are not its only component. All of the considerations listed above are necessary to ensure consistent production of drug substances and drug products of high quality.

This guidance addresses only the marketing approval of new drug products (including combination products); it does not address drug substances or drug products during the clinical research stages of drug development. Biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin are also not covered. A separate ICH guidance addresses specifications, tests, and procedures for biotechnological/biological products.

Guidance is provided with regard to acceptance criteria that should be established for all new drug substances and new drug products, i.e., universal acceptance criteria, and those that are considered specific to individual drug substances and/or dosage forms. This guidance reflects the current state of the art at the time it has been written, and should not be considered all-encompassing. New analytical technology, and modifications to existing technology, are continuously being developed. Such technologies should be used when justifiable.

Dosage forms addressed in this guidance include solid oral dosage forms, liquid oral dosage forms, and parenterals (small and large volume). This is not meant to be an all-inclusive list, or to limit the number of dosage forms to which this guidance applies. The dosage forms presented serve as models that may be applicable to other dosage forms that have not been discussed. The extended application of the concepts in this guidance to other dosage forms, e.g., inhalation dosage forms (powders, solutions, etc.), topical formulations (creams, ointments, gels), and transdermal systems, is encouraged.

2. General Concepts

The following concepts are important in the development and setting of harmonized specifications. They are not universally applicable, but each should be considered in particular circumstances. This guidance presents a brief definition of each concept and an indication of the circumstances under which it may be applicable. Generally, proposals to implement these concepts should be justified by the applicant and approved by the appropriate regulatory authority before being put into effect.

2.1 Periodic/Skip Testing: Periodic or skip testing is the performance of specified tests at release on preselected batches and/or at predetermined intervals, rather than on a batch-to-batch basis. This represents a less than full schedule of testing and should therefore be justified and presented to the regulatory authority prior to implementation. This concept may be applicable to, for example, dissolution (see section 2.4), residual solvents, and microbiological testing, e.g., for solid oral dosage forms. It is recognized that only limited data may be available at the time of submission of an application (see section 2.5). This concept may therefore sometimes be implemented postapproval in accordance with GMP.

2.2 Release Vs. Shelf-Life Acceptance Criteria: The concept of different acceptance criteria for release vs. shelf-life specifications applies to drug products only; it pertains to the establishment of more restrictive criteria for the release of a drug product than are applied to the shelf-life. Examples where this may be applicable include assay and impurity (degradation product) levels. In Japan and the United States, this concept may only be applicable to inhouse criteria, and not to the regulatory release criteria. In the European Union, there is a regulatory requirement for distinct specifications for release and for shelf-life.

2.3 In-Process Tests: In-process tests are tests that may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release. In-process tests that are used for the purpose of adjusting process parameters within an operating range, e.g., hardness and friability of tablet cores that will be coated, are not included in the specification. Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement (e.g., pH of a solution), may be acceptable to satisfy specification requirements when the test is included in the specification.

2.4 Design and Development Considerations: The experience and data accumulated during the development of a new drug substance or product should form the basis for the setting of specifications. It may be possible to propose excluding or replacing certain tests on this basis. Some examples are:

- Microbiological testing for drug substances and solid dosage forms that have been shown during development not to support microbial viability or growth.
- Extractables from product containers where it has been reproducibly shown that either no extractables are found in the drug product or the levels meet accepted standards for safety.
- Particle size testing may fall into this category, may be performed as an in-process test, or may be performed as a release test, depending on its relevance to product performance.
- Dissolution testing for immediate release solid oral drug products made from very water soluble drug substances may be replaced by disintegration testing, if these products have been demonstrated during development to have consistently rapid drug release characteristics. (See Decision trees #7(1) through #7(4)).

2.5 Limited Data Available at Filing: It is recognized that only a limited amount of data

may be available at the time of filing, which can influence the process of setting acceptance criteria. As a result, it may be necessary to propose revised acceptance criteria as additional experience is gained with the manufacture of a particular drug substance or drug product (example: acceptance limits for a specific impurity). The basis for the acceptance criteria at the time of filing will focus necessarily on safety and efficacy.

2.6 Parametric Release: Parametric release can be used as an operational alternative to routine release testing for the drug product. Sterility testing for terminally sterilized drug products is one example. In this case, the release of a batch is based on results from monitoring specific parameters, e.g., temperature and pressure, during the terminal sterilization phase(s) of drug product manufacturing. These parameters can generally be more accurately controlled and measured, so that they are more reliable in predicting sterility assurance than is end-product sterility testing. It is important to note that the sterilization process should be adequately validated before parametric release is proposed. When parametric release is performed, the attribute which is indirectly controlled (e.g., sterility), together with a reference to the associated test procedure, still should be included in the specifications.

2.7 Alternative Procedures: Alternative procedures are those that may be used to measure an attribute when such procedures control the quality of the drug substance or drug product to an extent that is comparable or superior to the official procedure. Example: For tablets that have been shown not to degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic. However, the chromatographic procedure should still be used to demonstrate compliance with the acceptance criteria during the shelf-life of the product.

2.8 Pharmacopoeial Tests and Acceptance Criteria: References to certain methods are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial methods should be utilized. Whereas differences in pharmacopoeial methods and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the methods and acceptance criteria defined are acceptable to regulatory authorities in all regions. This guidance is dependent on the successful completion of harmonization of pharmacopoeial methods for several attributes commonly considered in the specifications for new drug substances or new drug products.

The following attributes are essentially harmonized with respect to analytical method and acceptance criteria, except where noted, across the European Pharmacopoeia (Ph. Eur.), Japanese Pharmacopoeia (JP), and United States Pharmacopeia (USP):

Sterility
Residue on Ignition/Sulfated Ash
Bacterial Endotoxins
Color/Clarity
Particulate Matter
Dissolution (apparatus)
Disintegration (apparatus)

To signify the harmonized status of these general methods, the pharmacopoeias will include a statement in the text that indicates that the methods and acceptance criteria from all three pharmacopoeias are considered equivalent and are, therefore, interchangeable. An appropriate reference to the harmonized method and acceptance criteria is considered acceptable for a specification in all three regions. For example, sterility data generated using the JP method, as well as the JP method itself and its acceptance criteria, are considered acceptable for registration in all three regions. An appropriate reference may be expressed as JP/Ph. Eur./USP.

Harmonization of the following attributes will be completed prior to approval of a step 4 guidance:

Dissolution (media and acceptance criteria)
Disintegration (media and acceptance criteria)
Uniformity of Mass
Uniformity of Content
Extractable Volume
Preservative Effectiveness (scope of test and acceptance criteria)
Microbial Contamination

2.9 Evolving Technologies: New analytical technology and modifications to existing technology are continuously being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justifiable.

2.10 Impact of Drug Substance on Drug Product Specifications: In general, it should not be necessary to test the drug product for quality attributes uniquely associated with the drug substance. Example: It is normally not necessary to test the drug product for synthesis impurities that are controlled in the drug substance and are not degradation products. Refer to the ICH guidance ''Impurities in New Drug Products'' for detailed information.

2.11 Reference Standard: A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. The substance may be either the new drug substance or a known impurity. It has a quality appropriate to its use. For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and/or controlled, and purity should be measured by a quantitative procedure.

3. Guidelines

3.1 Specifications: Definition and Justification

3.1.1 Definition of Specifications

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use. ''Conformance to specifications'' means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

It is possible that, in addition to release tests, a specification may list in-process tests, periodic (skip) tests, and other tests which are not always conducted on a batch-by-batch basis. In such cases, the applicant should specify which tests are routinely conducted batch-by-batch, and which tests are not, with an indication and justification of the actual testing frequency. In this situation, the drug substance and/or drug product should meet the acceptance criteria if tested.

It should be noted that changes in the specification after approval of the application may need prior approval by the regulatory authority.

3.1.2 Justification of Specifications

When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included. The justification should refer to relevant development data, pharmacopoeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate. Additionally, a reasonable range of expected analytical and manufacturing variability should be considered. It is important to consider all of this information.

Approaches other than those set forth in this guidance may be applicable and acceptable. The applicant should justify alternative approaches. Such justification should be based on data derived from the new drug substance synthesis and/or the new drug product manufacturing process. This justification may consider theoretical tolerances for a given procedure or acceptance criterion, but the actual results obtained should form the primary basis for whatever approach is taken.

Test results from primary stability and scale-up/validation batches should be considered in setting and justifying specifications. If multiple manufacturing sites are planned, it may be valuable to consider data from these sites in establishing the initial tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug substance or drug product at any particular site. If data from a single representative manufacturing site are used in setting tests and acceptance criteria, product manufactured at all sites should still comply with these criteria.

Presentation of test results in graphic format may be helpful in justifying individual acceptance criteria, particularly for assay values and impurity levels. Data from development work should be included in such a presentation, along with stability data available for new drug substance or new drug product batches manufactured by the proposed commercial processes. Justification for exclusion of a test from the specification should be based on development data and on process validation data (where available).

When only limited data are available, the initially approved tests and acceptance criteria should be reviewed as more

information is collected, with a view towards possible modification. This could involve loosening, as well as tightening, acceptance criteria as appropriate.

3.2 Universal Tests/Criteria

Implementation of the recommendations in the following section should take into account the ICH guidances ''Text on Validation of Analytical Procedures'' and ''Validation of Analytical Procedures: Methodology.''

3.2.1 New Drug Substances

The following tests and acceptance criteria are considered generally applicable to all new drug substances.

(a) *Description*: A qualitative statement about the state (e.g., solid, liquid) and color of the new drug substance. If any of these characteristics change during storage, this change should be investigated and appropriate action taken.

(b) *Identification*: Identification testing should optimally be able to discriminate between compounds of closely related structure that are likely to be present. Identification tests should be specific for the new drug substance, e.g., infrared spectroscopy (IR). Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of tests into a single procedure, such as HPLC (high pressure/performance liquid chromatography)/UV (ultraviolet)-diode array, HPLC/MS (mass spectroscopy), or GC (gas chromatography)/MS may be acceptable. If the new drug substance is a salt, identification testing should be performed for the individual ions.

New drug substances which are optically active may also need specific identification testing. Please refer to section 3.3.1.(d) in this guidance for further discussion of this topic.

(c) *Assay*: A specific, stability-indicating procedure should be included to determine the content of the new drug substance. In many cases it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities.

In cases where use of a nonspecific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance, the combination of the assay and a suitable test for impurities can be used.

(d) *Impurities*: Organic and inorganic impurities and residual solvents are included in this category. Refer to the ICH guidances ''Impurities in New Drug Substances'' and ''Residual Solvents in Pharmaceuticals'' for detailed information.

Decision tree #1 addresses the extrapolation of meaningful limits on impurities from the body of data generated during development. At the time of filing, it is unlikely that sufficient data will be available to assess process consistency. Therefore, it is inappropriate to establish acceptance criteria that tightly encompass the batch data at the time of filing. (See section 2.5, limited data available at filing.)

3.2.2 New Drug Products

The following tests and acceptance criteria are considered generally applicable to all new drug products:

(a) *Description*: A qualitative description of the dosage form should be provided (e.g., size, shape, color). If any of these characteristics change during manufacture or storage, this change should be investigated and appropriate action taken. The acceptance criteria should include the final acceptable appearance. If color changes during storage, a quantitative procedure may be appropriate.

(b) *Identification*: Identification testing should establish the identity of the new drug substance(s) in the new drug product and should be able to discriminate between compounds of closely related structure which are likely to be present. Identity tests should be specific for the new drug substance, e.g., infrared spectroscopy. Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of tests into a single procedure, such as HPLC/UV-diode array, may be acceptable.

(c) *Assay*: A specific, stability-indicating assay to determine strength should be included for all new drug products. In many cases it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities. Results of content uniformity testing for new drug products can be used for quantitation of drug product strength, if the methods used for content uniformity are also appropriate as assays.

In cases where use of a nonspecific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance, the combination of the assay and a suitable test for impurities can be used.

(d) *Impurities*: Organic and inorganic impurities and residual solvents are included in this category. Refer to the ICH guidances ''Impurities in New Drug Products'' and ''Residual Solvents in Pharmaceuticals'' for detailed information.

Organic impurities arising from degradation of the new drug substance should be monitored in the new drug product. Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products. Process impurities from the new drug substance synthesis are normally controlled during drug substance testing, and therefore are not included in the total impurities limit. When it has been conclusively demonstrated via appropriate analytical methodology, with a significant body of data, that the drug substance does not degrade in the specific formulation, and under the specific storage conditions proposed in the new drug application, degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.

Decision tree #2 addresses the extrapolation of meaningful limits on degradation products from the body of data generated during development. At the time of filing, it is unlikely that sufficient data will be available to assess process consistency. Therefore, it is inappropriate to establish acceptance criteria that tightly encompass the batch data at the time of filing. (See section 2.5, limited data available at filing).

3.3 Specific Tests/Criteria

In addition to the universal tests listed above, the following tests may be considered on a case by case basis for drug substances and/or drug products. Individual tests/criteria should be included in the specification when the tests have an impact on the quality of the drug substance and drug product for batch control. Tests other than those listed below may be needed in particular situations or as new information becomes available.

3.3.1 New Drug Substances

(a) *Physicochemical properties*: These are properties such as pH of an aqueous solution, melting point/range, and refractive index. The procedures used for the measurement of these properties are usually unique and do not need much elaboration, e.g., capillary melting point, Abbé refractometry. The tests performed in this category should be determined by the physical nature of the new drug substance and by its intended use.

(b) *Particle size*: For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and/or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided.

Decision tree #3 provides additional guidance on when particle size testing should be considered.

(c) *Solid state forms*: Some new drug substances exist in different solid state forms (polymorphs or solvates) that differ in their physical properties. Differences in these forms could, in some cases, affect the quality or performance of the new drug products. In cases where differences exist that have been shown to affect drug product performance, bioavailability, or stability, then the appropriate solid state should be specified.

Physico-chemical measurements and techniques are commonly used to determine whether multiple forms exist. Examples of these procedures are: Melting point (including hot-stage microscopy), solid state IR, X-ray powder diffraction, thermal analysis procedures (like DSC (differential scanning calorimetry), TGA (thermogravimetric analysis) and DTA (differential thermal analysis)), Raman spectroscopy, scanning electron microscopy, and solid state NMR (nuclear magnetic resonance spetroscopy).

Decision trees #4(1) through #4(3) provide additional guidance on when, and how, solid state forms should be monitored and controlled.

Note: These decision trees should be followed sequentially. Trees #1 and #2 consider whether polymorphism is exhibited by the drug substance and whether the different polymorphic forms can affect performance of the drug product. Tree #3 should only be applied when polymorphism has been demonstrated for the drug substance

and has been shown to affect these properties. Tree #3 considers the potential for change in polymorphic forms in the drug product and whether such a change has any effect on product performance.

It is generally technically very difficult to measure polymorphic changes in drug products. A surrogate test (e.g., dissolution) can generally be used to monitor product performance, and polymorph content should only be used as a test and acceptance criterion of last resort.

The decision trees focus on polymorphism, but the same decision process can be applied to other solid state criteria, such as hydration and solvation, where appropriate.

(d) *Tests for new drug substances that are optically active*: Chiral impurities are excluded from ICH guidances on ''Impurities in New Drug Substances'' and ''Impurities in New Drug Products'' because of practical difficulties in quantifying them at the qualification and identification thresholds given in those guidances. However, chiral impurities in chiral new drug substances and the resulting new drug products should be treated according to principles established in those guidances.

Decision tree #5 summarizes when and if chiral identity tests, impurity tests, and assays may be needed for both new drug substances and new drug products, according to the following concepts:

Drug Substance: Impurities. For chiral drug substances that are developed as a single enantiomer, control of the other enantiomer should be considered in the same manner as for other impurities. However, technical limitations may preclude the same limits of determination or qualification being applied. If it is technically difficult to effect control in the drug substance itself, assurance of control could be given by appropriate testing of a starting material or intermediate, with suitable justification.

Assay. An enantioselective determination of the drug substance should be part of the specification. It is considered acceptable for this to be achieved either through use of a chiral assay procedure or by the combination of an achiral assay together with appropriate methods of controlling the enantiomeric impurity.

Identity. The identity test(s) should be capable of distinguishing a single enantiomer from its opposite enantiomer. Where a drug substance is a racemate, the identity method should be capable of verifying the racemic nature and distinguishing it from either enantiomer.

Drug Product: Degradation products. Control of the other enantiomer in a drug product is necessary if that enantiomer has been shown to be a degradation product.

Assay. Where development studies have demonstrated that the enantiomer is not a degradation product, an achiral assay may be sufficient. However, a chiral assay is preferred or, alternatively, the combination of an achiral assay plus a procedure to control the presence of the opposite enantiomer.

Identity. An identity test should be established that is capable of verifying the presence of the correct enantiomer or the racemate, as appropriate.

(e) *Water content*: This test is important in cases where the new drug substance is known to be hygroscopic or degraded by moisture or when the drug substance is known to be a stoichiometric hydrate. The acceptance criteria may be justified with data on the effects of hydration or moisture absorption. In some cases, a Loss on Drying procedure may be adequate; however, a detection procedure that is specific for water (e.g., Karl Fischer titration) is preferred.

(f) *Inorganic impurities*: The need for inclusion of tests and acceptance criteria for inorganic impurities should be studied during development and based on knowledge of the manufacturing process. Where justified, procedures and acceptance criteria for sulfated ash/residue on ignition should follow pharmacopoeial precedents; other inorganic impurities may be determined by other appropriate procedures, e.g., atomic absorption spectroscopy.

(g) *Microbial limits*: There may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa). These should be suitably determined using pharmacopoeial procedures. In special cases, sterility testing or endotoxin testing may be appropriate. For example, the drug substance is manufactured as sterile (sterility testing appropriate) or will be used to formulate an injectable drug product (endotoxin testing appropriate).

Decision tree #6 provides additional guidance on when microbial limits should be included.

3.3.2 New Drug Products

Additional tests and acceptance criteria generally should be included for particular new drug products. The following selection presents a representative sample of both the drug products and the types of tests and acceptance criteria which may be appropriate. The specific dosage forms addressed include solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Application of the concepts in this guidance to other dosage forms is encouraged. Note that issues related to optically active drug substances and to solid state considerations for drug products are discussed in section 3.3.1 of this guidance.

3.3.2.1 The following tests are applicable to tablets (coated and uncoated) and hard capsules. One or more of these tests may also be applicable to soft capsules and granules.

(a) *Dissolution/disintegration*: For rapidly dissolving products containing drugs that are highly soluble throughout the physiological pH range, disintegration testing may sometimes be sufficient. Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution. In such cases, dissolution testing may not always be necessary, or may be proposed as a skip test. It is expected that development information will be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing.

Single-point measurements are normally considered to be suitable for immediate release dosage forms. For modified release dosage forms, appropriate test conditions and sampling procedures should be established. For example, multiple-time-point sampling should be performed for extended release dosage forms, and two-stage testing (using different media in succession or in parallel, as appropriate) may be appropriate for delayed release dosage forms. In these cases it is important to consider the populations of individuals who will be taking the drug product (e.g., achlorhydric elderly) when designing the tests and acceptance criteria.

Where multiple-point acceptance criteria are necessary, in vitro/in vivo correlation may be used to establish these criteria when human bioavailability data are available for formulations exhibiting different release rates. Where such data are not available, and drug release cannot be shown to be independent of in vitro test conditions, then acceptance criteria should be established on the basis of available batch data. Normally, the permitted variability in release rate at any given time point should not exceed a total numerical difference of +/-10 percent of the labeled content of drug substance (i.e., a total variability of 20 percent: a requirement of 50 +/-10 percent thus means an acceptable range from 40 to 60 percent) unless a wider range is supported by a bioequivalency study.

Decision trees #7(1) through #7(4) provide additional guidance on the use of dissolution and disintegration testing.

(b) *Hardness/friability*: It is normally appropriate to perform hardness and/or friability testing as an in-process control (see section 2.3). Under these circumstances, it is normally not necessary to include these attributes in the specification. If the characteristics of hardness and friability have a critical impact on drug product quality (e.g., chewable tablets), acceptance criteria should be included in the specification.

(c) *Uniformity of dosage units*: This term includes both uniformity of content and uniformity of mass; a pharmacopoeial procedure should be used. If appropriate, these tests may be performed as in-process controls; the acceptance criteria should be included in the specification.

(d) *Water content*: A test for water content should be included when appropriate. The acceptance criteria may be justified with data on the effects of hydration or water absorption on the drug product. In some cases, a Loss on Drying procedure may be adequate; however, a detection procedure which is specific for water (e.g., Karl Fischer titration) is preferred.

(e) *Microbial limits*: Microbial limit testing is seen as an attribute of GMP, as well as of quality assurance. In general, it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination. It should be noted that, whereas this guidance does not directly address excipients elsewhere, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases.

Acceptance criteria should be set for the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture that is justified by data and experience. With acceptable scientific justification, it may be possible to propose no microbial limit testing for solid oral dosage forms.

Decision tree #8 provides additional guidance on the use of microbial limit testing.

3.3.2.2 *Oral liquids*: One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids.

(a) *Uniformity of dosage units*: This term includes both uniformity of content and uniformity of mass. Generally, acceptance criteria should be set for weight variation, fill volume, and/or uniformity of fill. Pharmacopoeial procedures should be used.

If appropriate, tests may be performed as in-process controls; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multiple-dose packages.

The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated based on the total measured weight or volume of drug divided by the total number of doses expected. If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. The dispensing equipment to be used is normally determined during development.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

(b) *pH*: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

(c) *Microbial limits*: Microbial limit testing is seen as an attribute of GMP, as well as of quality assurance. In general, it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination. It should be noted that, whereas this guidance does not directly address excipients elsewhere, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases. With acceptable scientific justification, it may be possible to propose no microbial limit testing for powders intended for reconstitution as oral liquids.

Acceptance criteria should be set for the total count of aerobic microorganisms, total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience.

Decision tree #8 provides additional guidance on the use of microbial limit testing.

(d) *Antimicrobial preservative content*: For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content may be appropriate. These criteria should be based on the levels necessary to maintain microbiological product quality throughout the shelf-life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Release testing for antimicrobial preservative content should normally be performed. Under certain circumstances, in-process testing may suffice in lieu of release testing. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scaleup, and throughout the shelf-life (e.g., in stability testing, see the ICH guidance ''Stability Testing of New Drug Substances and Products''), although chemical testing for preservative content is the attribute normally included in the specification.

(e) *Antioxidant preservative content*: Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary, and in-process testing may suffice in lieu of release testing. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

(f) *Extractables*: Generally, where development and stability data show no significant evidence of extractables, elimination of this test may be proposed. This should be reinvestigated if the container/closure system changes.

Where data demonstrate the need, tests and acceptance criteria for extractables from the container/closure system components (e.g., rubber stopper, cap liner, plastic bottle) are considered appropriate for oral solutions packaged in nonglass systems, or in glass containers with nonglass closures. The container/closure components should be listed, and data collected for these components as early in the development process as possible.

(g) *Alcohol content*: Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be specified. It may be assayed or calculated.

(h) *Dissolution*: In addition to the attributes recommended immediately above, it may be appropriate (e.g., insoluble drug substance) to include dissolution testing and acceptance criteria for oral suspensions and dry powder products for resuspension. The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures using either pharmacopoeial or non-pharmacopoeial apparatus and conditions should be validated.

Single-point measurements are normally considered suitable for immediate release dosage forms. Multiple-point sampling, at appropriate intervals, should be performed for modified release dosage forms. Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Dissolution testing may be performed as an in-process test, or as a release test, depending on its relevance to product performance. The discussion of dissolution for solid oral dosage forms (above), and of particle size distribution (immediately following), should also be considered here.

(i) *Particle size distribution*: Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure for these formulations.

Particle size distribution testing may be performed as an in-process test or as a release test, depending on its relevance to product performance. If these products have been demonstrated during development to have consistently rapid drug release characteristics, exclusion of a particle size distribution test from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and/or lower particle size limits should be well defined.

Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo, as well as the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

(j) *Redispersibility*: For oral suspensions which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate test. The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification.

(k) *Rheological properties*: For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity) in the specification. The test and acceptance criteria should be stated. Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification.

(l) *Specific gravity*: For oral suspensions or relatively viscous or nonaqueous solutions, acceptance criteria for specific gravity may be appropriate. Testing may be performed as an in-process control.

(m) *Reconstitution time*: Acceptance criteria for reconstitution time should be provided for dry powder products which require reconstitution. The choice of diluent should be justified. Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification.

(n) *Water content*: For oral products requiring reconstitution, a test and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient if the effect of absorbed moisture vs. water of hydration has been adequately characterized during the development of the product. In certain cases, a more specific procedure (e.g., Karl Fischer titration) may be preferable.

3.3.2.3 *Parenteral Drug Products*: The following tests may be applicable to parenteral drug products.

(a) *Uniformity of dosage units*: This term includes both uniformity of content and uniformity of mass; a pharmacopoeial procedure should be used. Generally, acceptance criteria should be set for weight variation, fill volume, or uniformity of fill.

If appropriate, these tests may be performed as in-process controls; the acceptance criteria should be included in the specification. This test may be applied to both single-dose and multiple-dose packages.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

(b) *pH*: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

(c) *Sterility*: All parenteral products should have a test procedure and acceptance criterion for evaluation of sterility. Where data generated during development and validation justify parametric release, this approach may be proposed for terminally sterilized drug products.

(d) *Endotoxins*: A test procedure and acceptance criterion for endotoxins, using a procedure such as the limulus amoebocyte lysate test, should be included in the specification.

(e) *Pyrogens*: Pyrogenicity testing may be proposed as an alternative to endotoxin testing where justified.

(f) *Particulate matter*: Parenteral products should have appropriate acceptance criteria for particulate matter. This will normally include limits for visible particulates (also designated ''foreign matter'') and/or clarity of solution, as well as for subvisible particulates.

(g) *Water content*: For nonaqueous parenterals, and for parenteral products for reconstitution, a test procedure and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient for parenteral products if the effect of absorbed moisture vs. water of hydration has been adequately characterized during development. In certain cases, a more specific procedure (e.g., Karl Fischer titration) may be preferred.

(h) *Antimicrobial preservative content*: For parenteral products needing an antimicrobial preservative, acceptance criteria for preservative content may be appropriate. These criteria should be based on the levels necessary to maintain microbiological product quality throughout the shelf-life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Release testing for antimicrobial preservative content should normally be performed. Under certain circumstances, in-process testing may suffice in lieu of release testing. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scaleup, and throughout the shelf-life (e.g., in stability testing, see the ICH guidance ''Stability Testing of New Drug Substances and Products''), although chemical testing for preservative content is the attribute normally included in the specification.

(i) *Antioxidant preservative content*: Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary and in-process testing may suffice in lieu of release testing. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

(j) *Extractables*: Control of extractables is considered significantly more important for parenteral products than for oral liquids. However, where development and stability data show no significant evidence of extractables, elimination of this test may be proposed. This should be reinvestigated if the container/closure system changes.

Where data demonstrate the need, acceptance criteria for extractables from the container/closure components are considered appropriate for parenteral products packaged in nonglass systems or in glass containers with elastomeric closures. This testing may be performed at release only, where justified by data obtained during development. The container/closure system components (e.g., rubber stopper) should be listed, and data collected for these components as early in the development process as possible.

(k) *Functionality testing of delivery systems*: Parenteral formulations packaged in prefilled syringes, autoinjector cartridges, or the equivalent, should have test procedures and acceptance criteria related to the functionality of the delivery system. These may include control of syringeability, pressure, and seal integrity (leakage), and/or parameters such as tip cap removal force, piston release force, piston travel force, and power injector function force. Data generated during product development may be sufficient to justify skip lot testing or elimination of some attributes from the specification.

(l) *Osmolality*: When the tonicity of a product is declared in its labeling, appropriate control of its osmolality should be performed. Data generated during development and validation may be sufficient to justify performance of this procedure as an in-process control, skip lot testing, or direct calculation of this attribute.

(m) *Particle size distribution*: Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for injectable suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Particle size distribution testing may be performed as an in-process test or as a release test, depending on its relevance to product performance. If the product has been demonstrated during development to have consistently rapid drug release characteristics, exclusion of particle size controls from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing when development studies demonstrate that particle size is the primary factor influencing dissolution; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and/or lower particle size limits should be well defined.

Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo and the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

(n) *Redispersibility*: For injectable suspensions which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate test. The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification.

(o) *Reconstitution time*: Acceptance criteria for reconstitution time should be provided for all parenteral products which require reconstitution. The choice of diluent should be justified. Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification.

4. Glossary

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Chiral: Not superposable with its mirror image, as applied to molecules, conformations, and macroscopic objects, such as crystals. The term has been extended to samples of substances whose molecules are chiral, even if the macroscopic assembly of such molecules is racemic.

Combination product: A drug product that contains more than one drug substance.

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, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product.

Enantiomers: Compounds with the same molecular formula as the drug substance, that differ in the spatial arrangement of atoms within the molecule and are nonsuperimposable mirror images.

Impurity: (1) Any component of the new drug substance that is not the chemical entity defined as the new drug substance. (2) Any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product.

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

New drug product: A pharmaceutical product type, for example, tablet, capsule, solution, cream, that 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.

New drug substance: The designated therapeutic moiety, that has not previously been 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.

Polymorphism: The occurrence of different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

Quality: The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity of the article.

Racemate: A composite (solid, liquid, gaseous, or in solution) of equimolar quantities of two enantiomeric species. It is devoid of optical activity.

Reagent: A substance, other than a starting material or solvent, that is used in the manufacture of a new drug substance.

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance or the manufacture of a new drug product.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. ''Conformance to specifications'' means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant.

Specific test: A test that is considered to be applicable to particular new drug substances or particular new drug products depending on their specific properties and/or intended use.

Specified impurity: An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to assure the quality of the new drug substance or new drug product.

Unidentified impurity: An impurity that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Universal test: A test that is considered to be potentially applicable to all new drug substances, or all new drug products (e.g., appearance, identification, assay, and impurity tests).

5. References

International Conference on Harmonisation, ''Impurities in New Drug Substances,'' 1995.

International Conference on Harmonisation, ''Impurities in New Drug Products,'' 1996.

International Conference on Harmonisation, ''Stability Testing of New Drug Substances and Products,'' 1994.

International Conference on Harmonisation, ''Text on Validation of Analytical Procedures,'' 1994.

International Conference on Harmonisation, ''Validation of Analytical Procedures: Methodology,'' 1996.

International Conference on Harmonisation, ''Residual Solvents in Pharmaceuticals,'' 1996.

6. Attachments: Decision Trees #1 through #8

For the decision trees referenced in this guidance, see the following pages.

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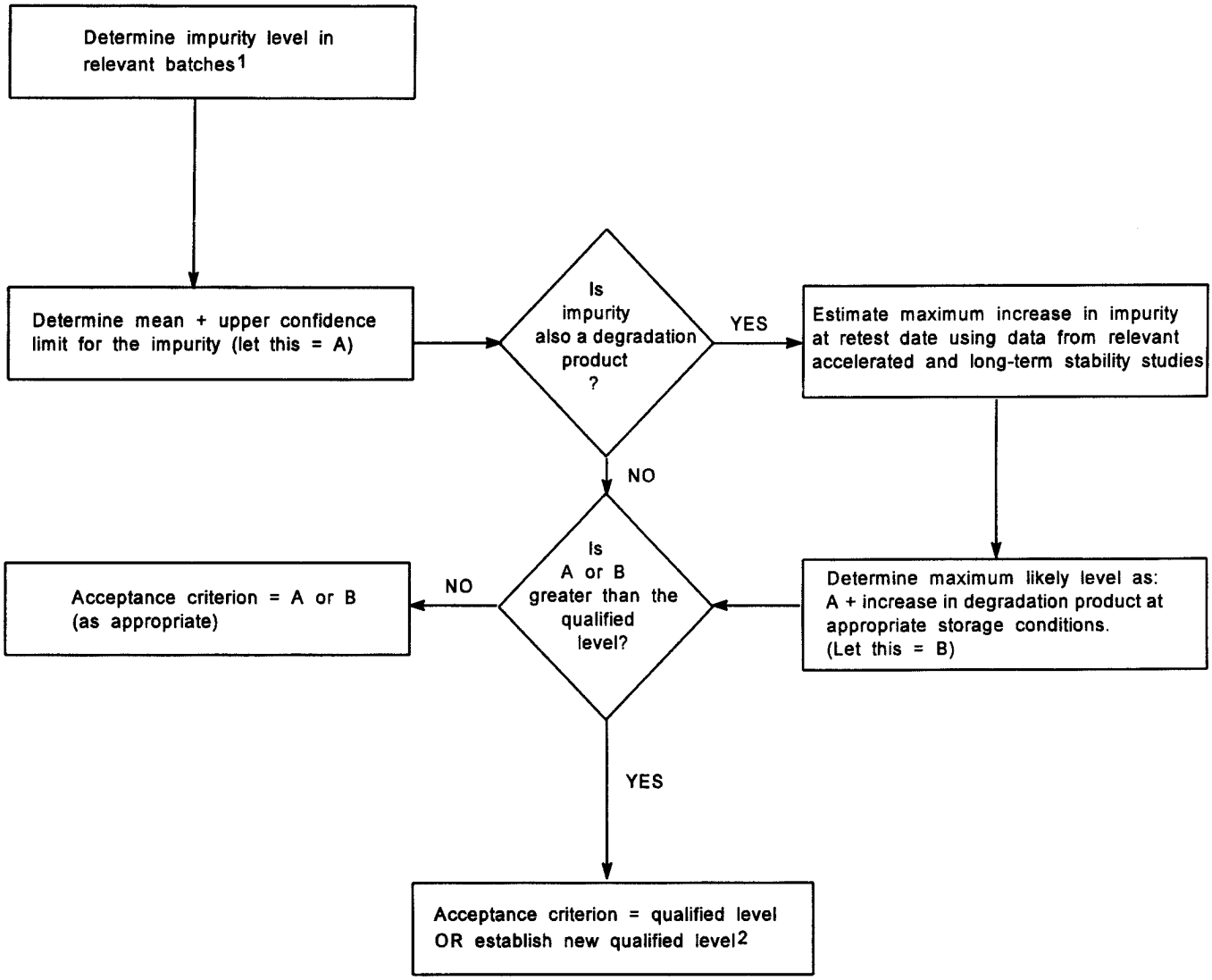
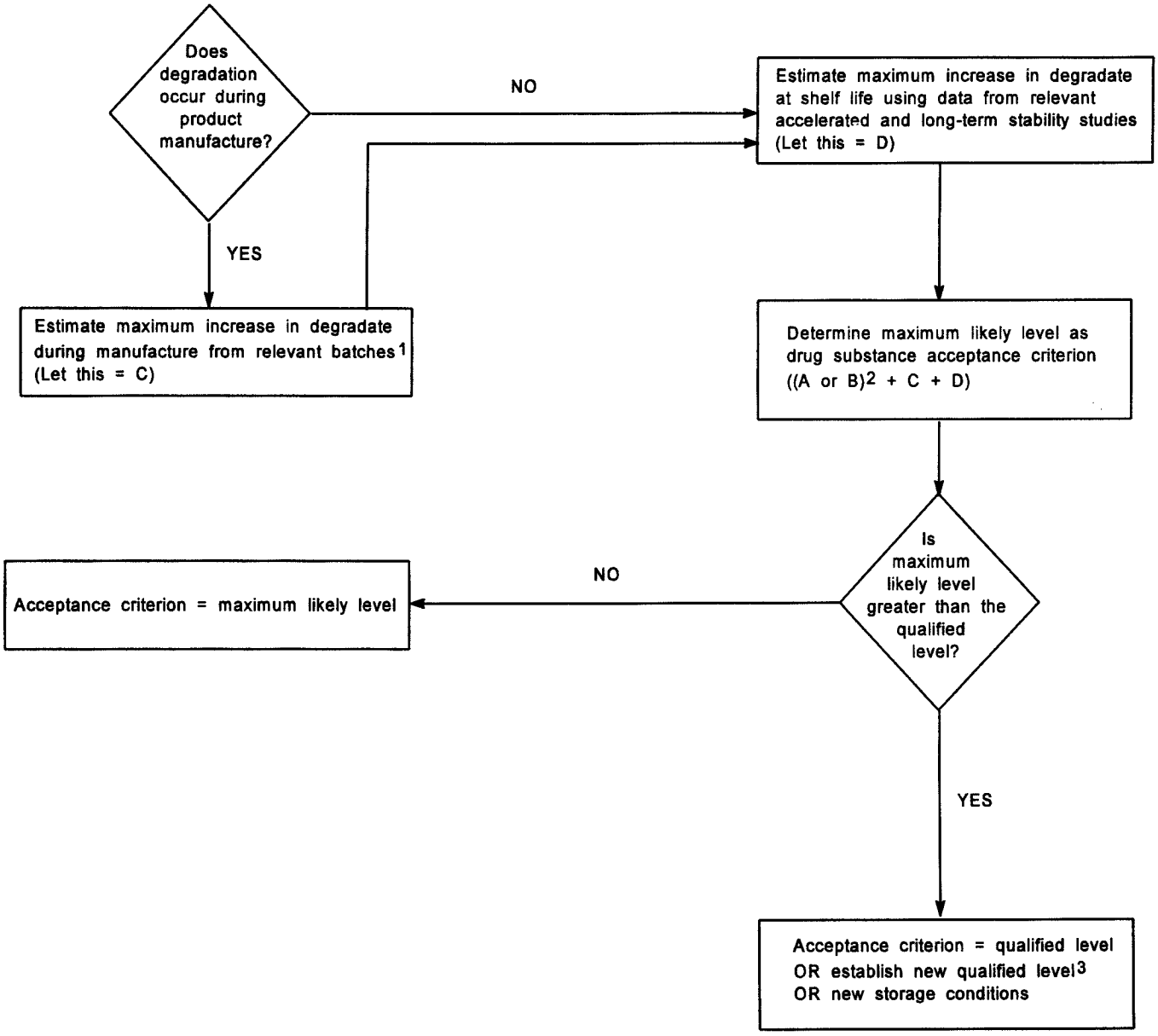
DECISION TREE #1: ESTABLISHING ACCEPTANCE CRITERIA FOR A SPECIFIED IMPURITY IN A NEW DRUG SUBSTANCE



1 Relevant batches are those from development, pilot and scale-up studies.
2 Refer to ICH Guidance on Impurities in New Drug Substances

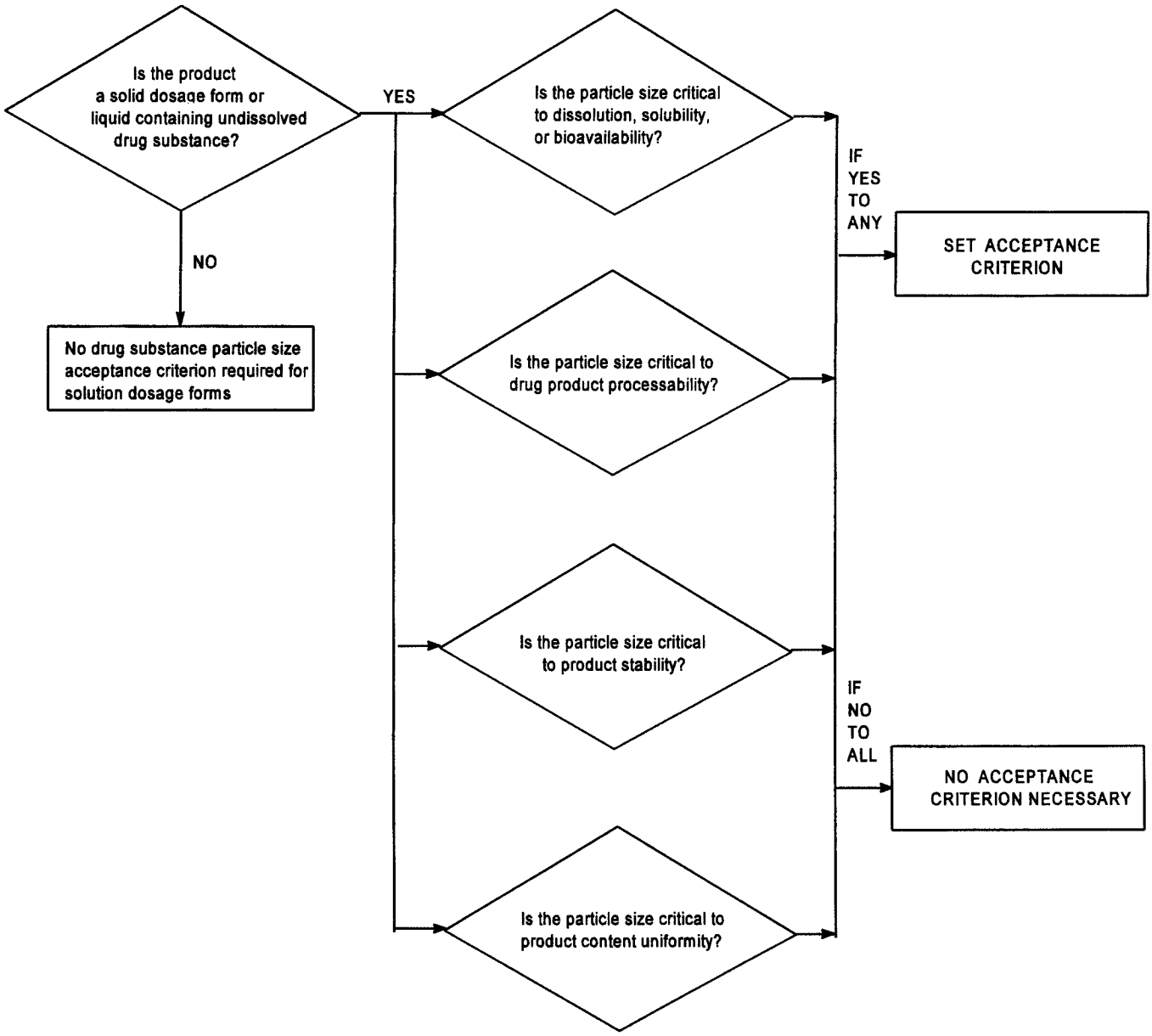
Definition: upper confidence limit = three times the standard deviation of batch analysis data

DECISION TREE #2: ESTABLISHING ACCEPTANCE CRITERIA
FOR A DEGRADATION PRODUCT IN A NEW DRUG PRODUCT



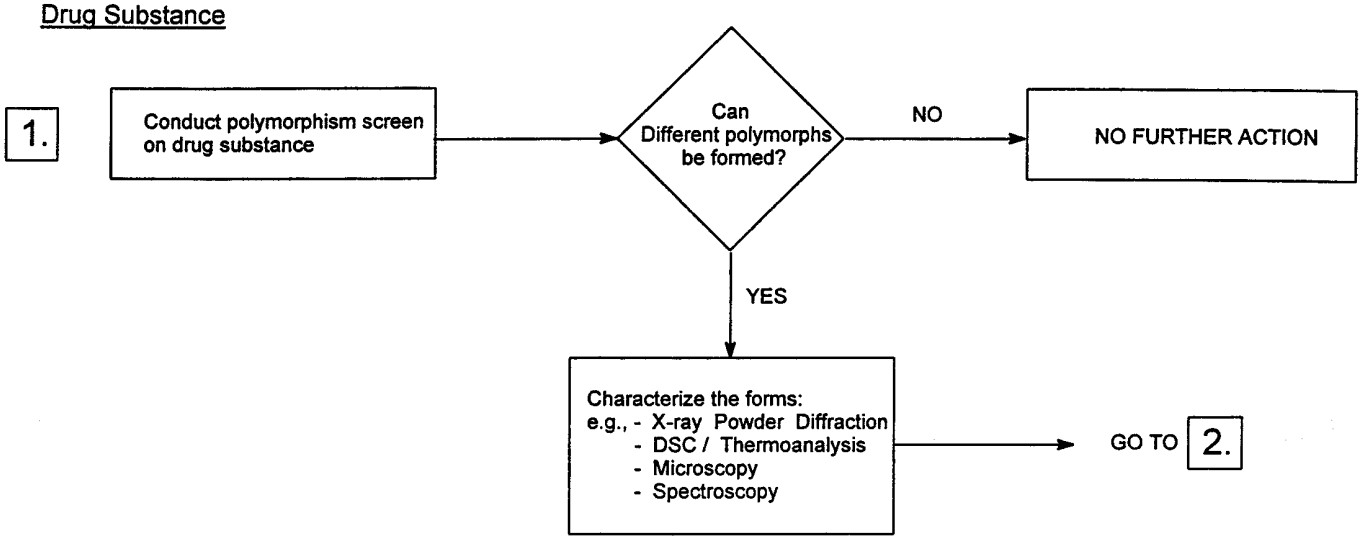
[1] Relevant batches are those from development, pilot and scale-up studies.
[2] Refer to Decision Tree 1
[3] Refer to ICH Guidance on Impurities in New Drug Substances

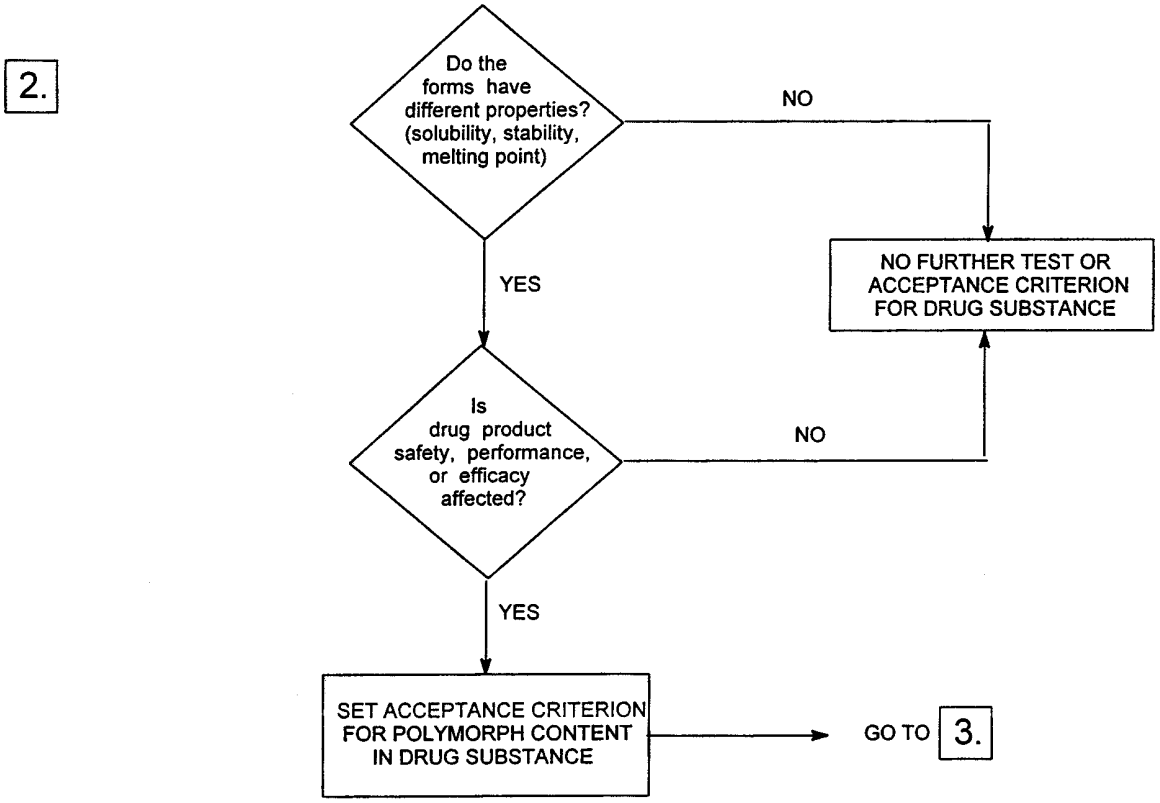
DECISION TREE #3: SETTING ACCEPTANCE CRITERIA
FOR
DRUG SUBSTANCE PARTICLE SIZE DISTRIBUTION



DECISION TREES #4: INVESTIGATING THE NEED TO SET ACCEPTANCE CRITERIA FOR POLYMORPHISM IN DRUG SUBSTANCES AND DRUG PRODUCTS

Drug Substance



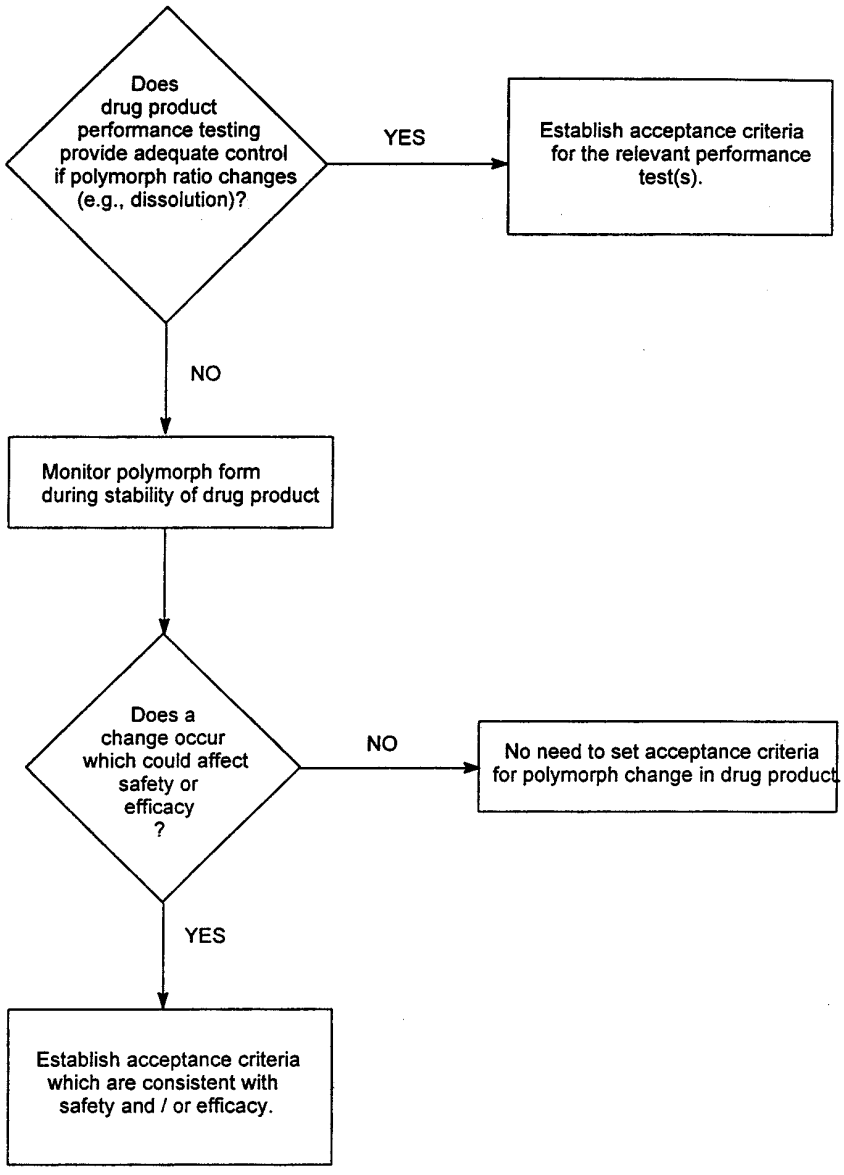


DECISION TREES #4: INVESTIGATING THE NEED TO SET ACCEPTANCE CRITERIA FOR POLYMORPHISM IN DRUG SUBSTANCES AND DRUG PRODUCTS

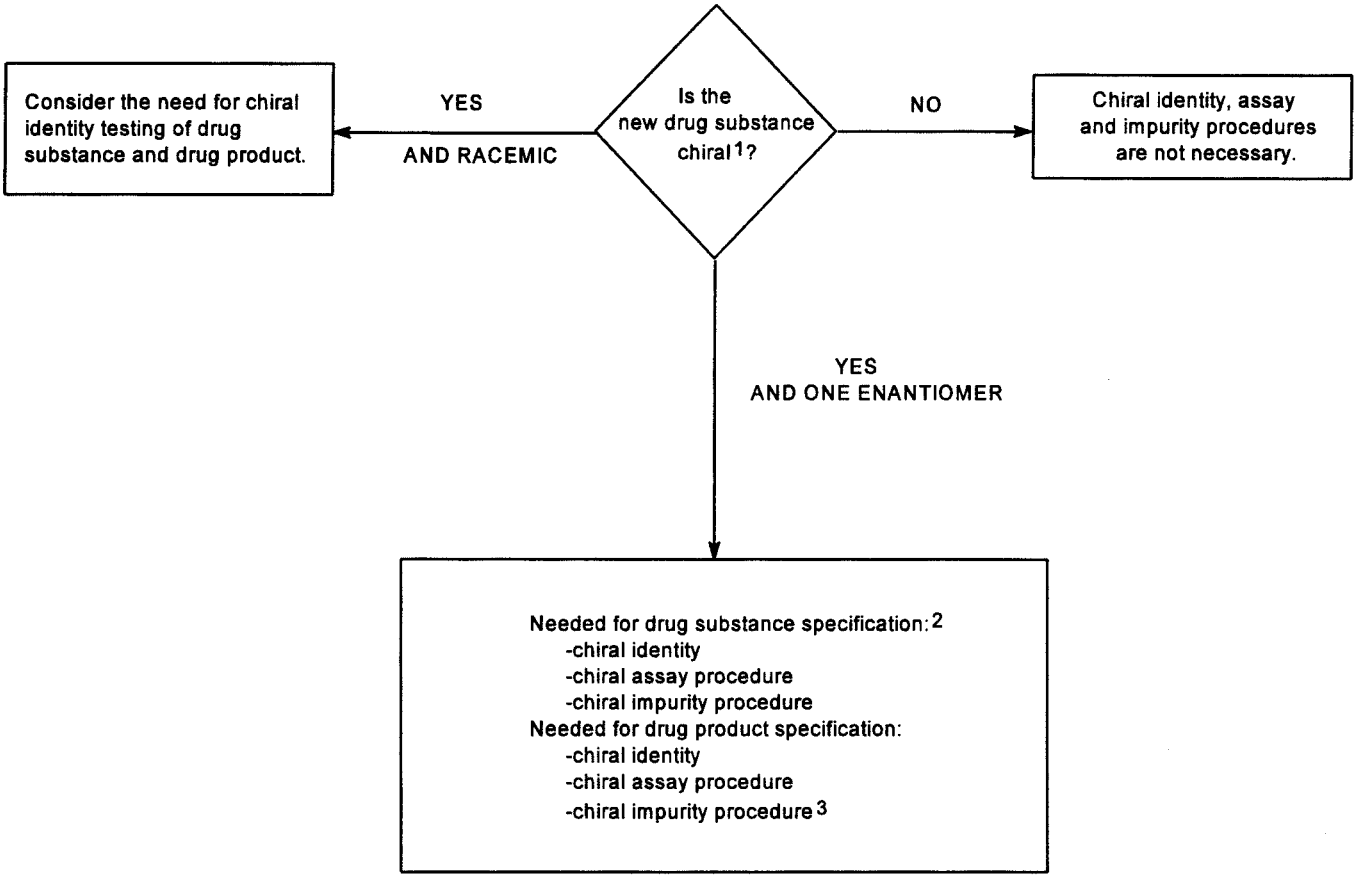
Drug Product - Solid Dosage Form or Liquid Containing Undissolved Drug Substance

N.B.: Undertake the following process only if technically possible to measure polymorph content in the drug product.

3.



DECISION TREE #5: ESTABLISHING IDENTITY, ASSAY AND CHIRAL IMPURITIES PROCEDURES IN A NEW DRUG PRODUCT CONTAINING A CHIRAL DRUG SUBSTANCE

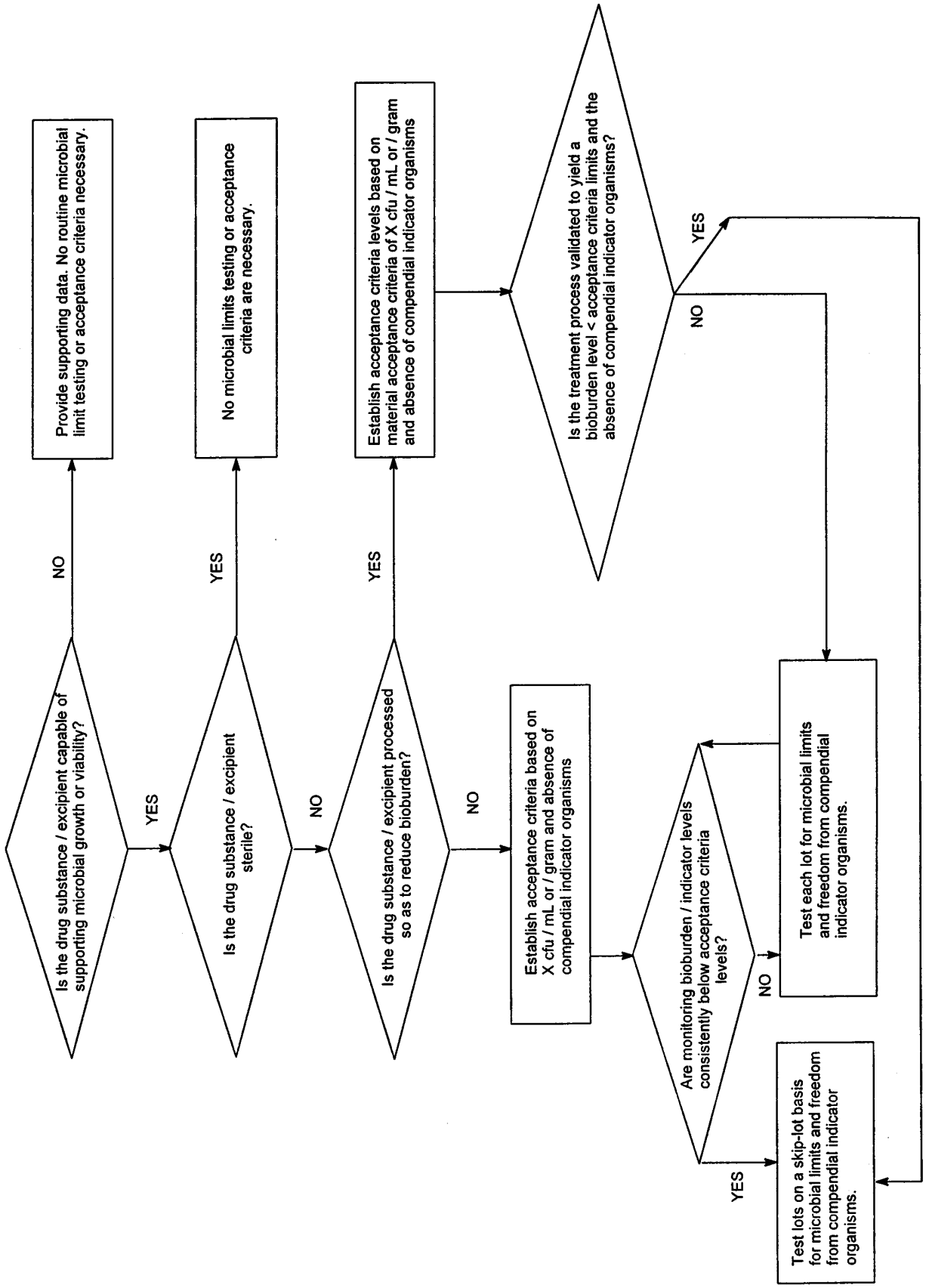


[1] Chiral substances of natural origin are not addressed in this Guidance.

[2] As with other impurities arising in and from raw materials used in drug substance synthesis, control of chiral quality could be established alternatively by applying limits to appropriate starting materials or intermediates when justified from development studies. This will be essentially the case when there are multiple chiral centers (e.g., three or more), or when measurement in drug substance at an appropriate sensitivity is technically impossible.

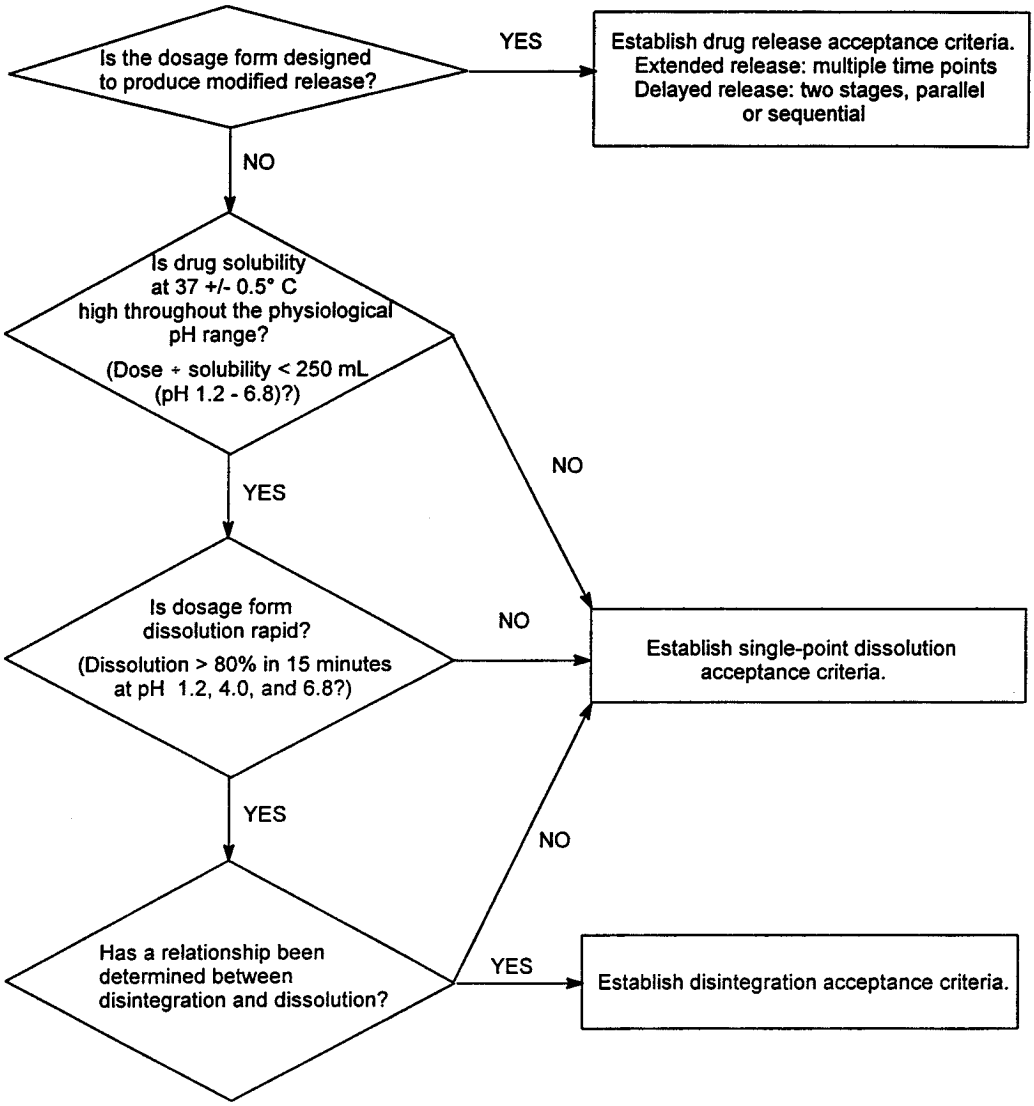
[3] A chiral assay may not be necessary if chiral impurity testing is done via a method which is equivalent to an assay procedure.

DECISION TREE #6: MICROBIOLOGICAL QUALITY ATTRIBUTES OF DRUG SUBSTANCE AND EXCIPIENTS



DECISION TREES #7: SETTING ACCEPTANCE CRITERIA FOR DRUG PRODUCT DISSOLUTION

1. What type of drug release acceptance criteria are appropriate?



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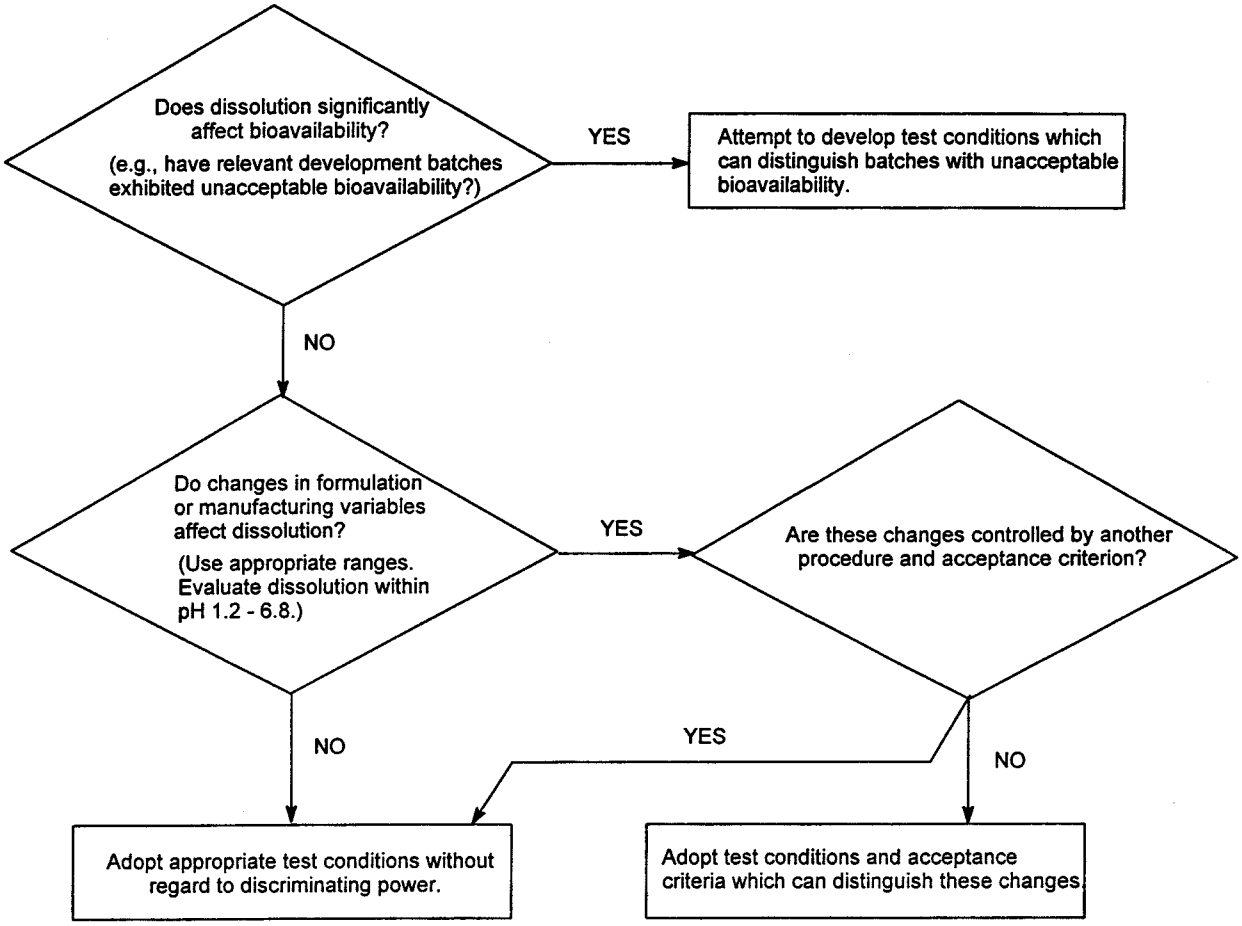
DECISION TREES #7: SETTING
ACCEPTANCE CRITERIA FOR
DRUG PRODUCT DISSOLUTION

2. What specific test conditions are appropriate? [immediate release]



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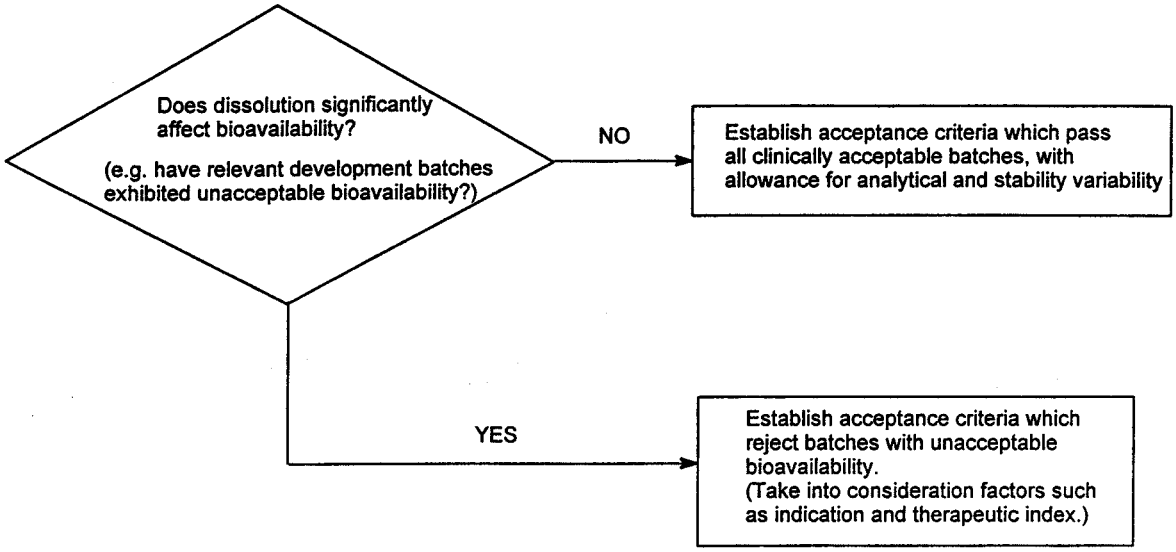
DECISION TREES #7: SETTING ACCEPTANCE CRITERIA FOR DRUG PRODUCT DISSOLUTION

3. What are appropriate acceptance criteria? [immediate release]



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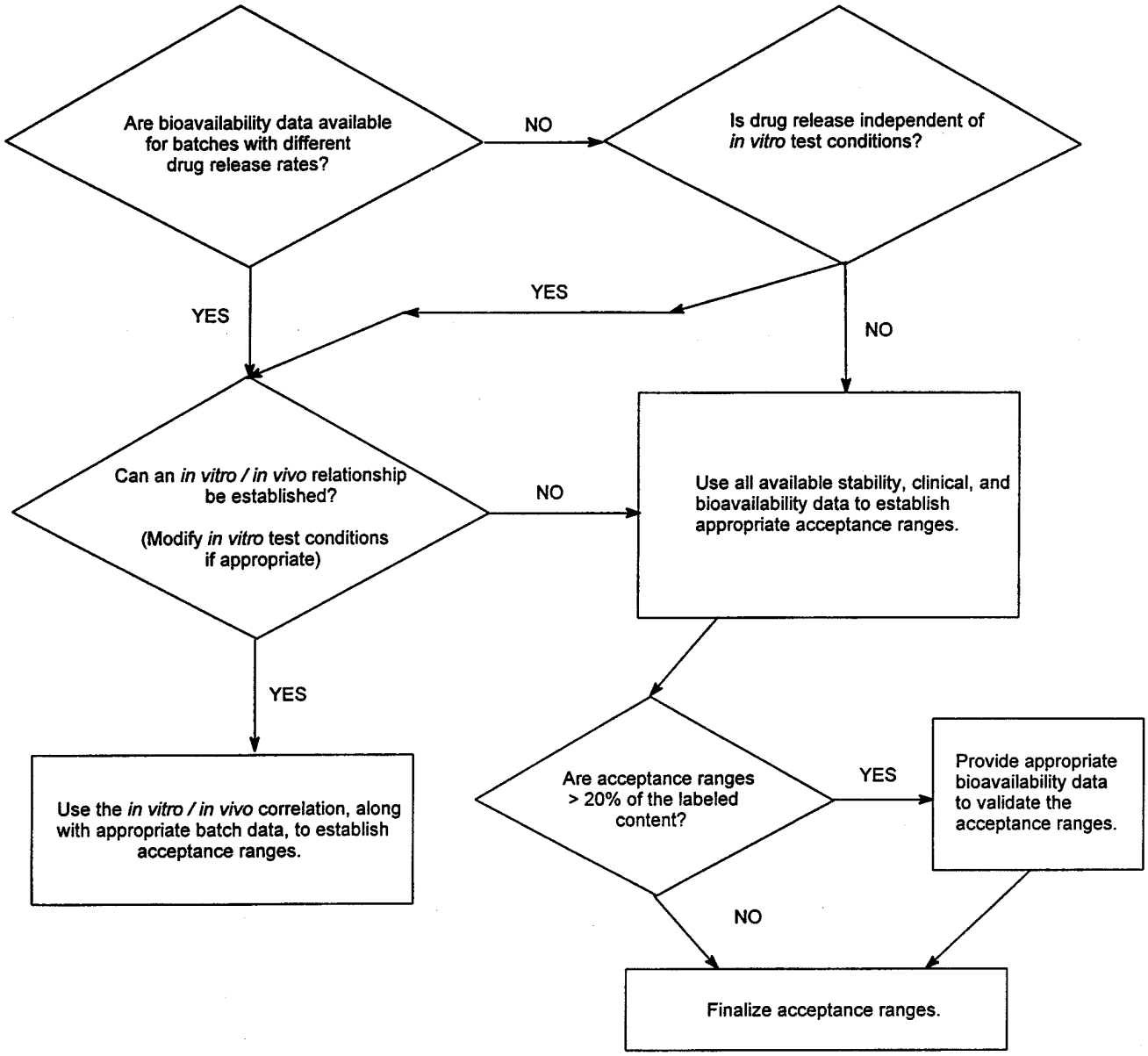
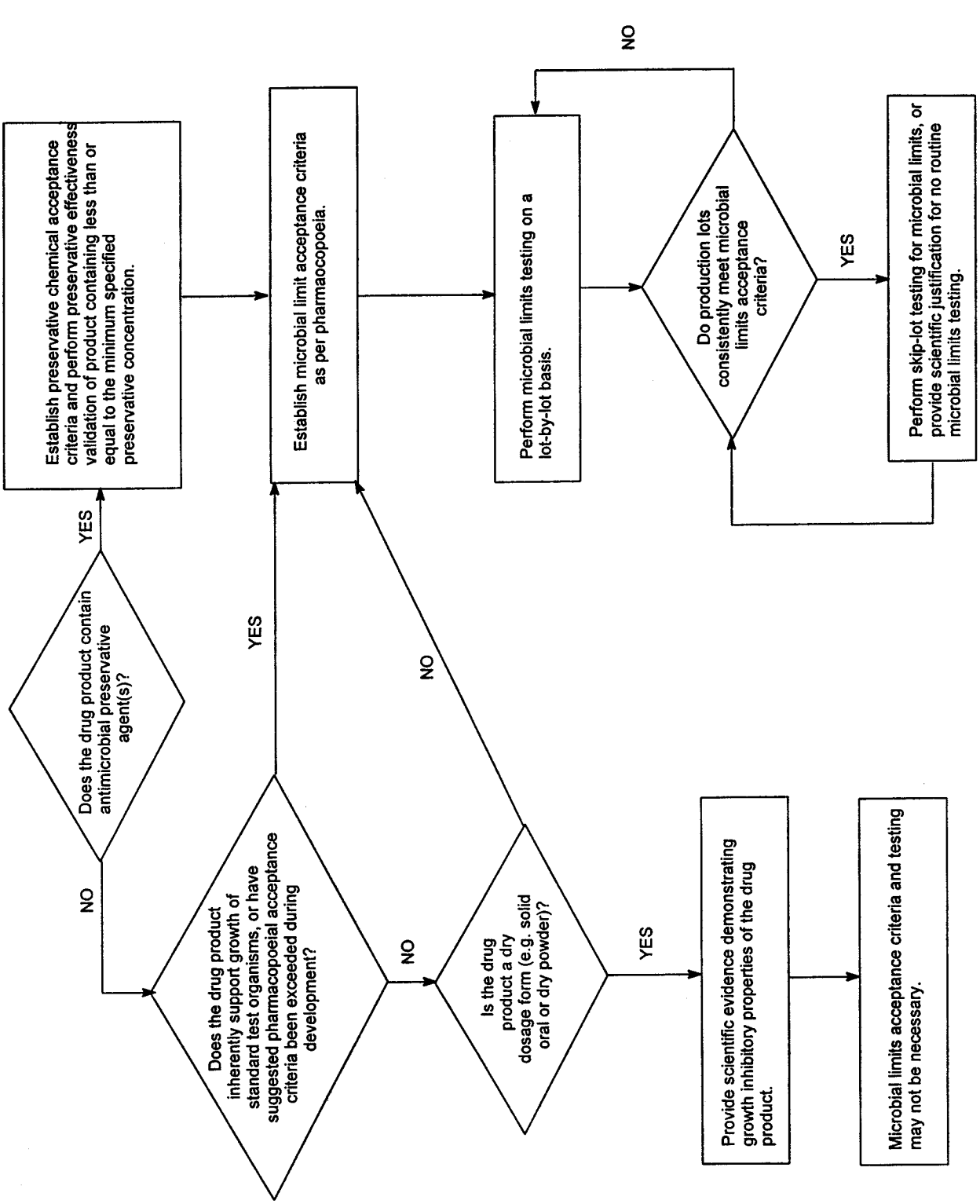
DECISION TREES #7: SETTING ACCEPTANCE CRITERIA FOR DRUG PRODUCT DISSOLUTION

4. What are appropriate acceptance ranges? [extended release]



DECISION TREE #8: MICROBIOLOGICAL QUALITY ATTRIBUTES OF NON-STERILE DRUG PRODUCTS



Dated: November 18, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–30916 Filed 11–24–97; 8:45 am]

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