evaluating the quality and reliability of information and data for use in developing the VADS system contents; (3) apply the principles of pharmacology in constructing therapeutic regimens for use when approved antimicrobial products are not effective as labeled; (4) design a relational database allowing a user to efficiently search the VADS system for label and extralabel regimens based on therapeutic applications, and to then review regulatory and food safety information applicable to these regimens; and (5) subject the VADS system content to review prior to release and then constantly upgrade the content on the basis of new information and review by users.

II. Eligible Applicants

Assistance may only be provided to Iowa State University because of the following:

1. Iowa State University is the only organization that submitted an unsolicited application for the purpose stated above.

2. The project proposed by the applicant is unique and innovative in that pharmacokinetic, pharmacodynamic, clinical trial, and pathogen susceptibility information will be interpreted by clinical pharmacologists and reviewed by other experts in the appropriate fields prior to inclusion in the system. Users may either use the information as provided or examine the transparent development process used in constructing the system. In addition, by compiling available information to support prudent antimicrobial use, the VADS system will emphasize what information is not available, thereby aiding researchers in targeting research goals.

3. The team assembled to carry out the proposed work is uniquely qualified to achieve the goals of this application. Their combined experience encompasses practice in academic, general, and specialized production medicine settings as well as demonstrated competence in the application of clinical pharmacology and informatics in veterinary medicine. Support for the research team and the VADS system project has already been expressed in the form of start up funding provided by veterinary and producer organizations.

III. Funding

We anticipate that approximately $250,000 may be made available in fiscal year (FY) 2001 to support this project. If funded the award will begin sometime in FY 2001 and will be made for a 12-month budget period within a project period of up to 5 years. Funding estimates may change. Continuation awards within an approved project period will be made on the basis of satisfactory progress as evidenced by required reports and the availability of funds.

Dated: December 22, 2000.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 00–33372 Filed 12–28–01; 8:45 am]

BILLING CODE: 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0448]

International Conference on Harmonisation; Guidance on Q6A 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 guidance entitled "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances." The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance describes or provides recommendations concerning 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 guidance is intended to assist in the establishment of a single set of global specifications for new drug substances and new drug products.

DATES: Submit written comments by March 29, 2001.

ADDRESSES: Submit written comments on the guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Copies of the 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–003), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2847, or Neil D. Goldman, Center for Biologics Evaluation and Research (HFM–20), Food and Drug Administration, 1401 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 the **Federal Register** of November 25, 1997 (62 FR 62890), FDA published a draft tripartite guidance entitled "Q6A Specifications: Test Procedures and

Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances." The notice gave interested persons an opportunity to submit comments by January 26, 1998.

After consideration of the comments received and revisions to the guidance, a final draft of the guidance was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies on October 6, 1999.

In accordance with FDA's good guidance practices regulation (65 FR 56468, September 19, 2000), this document has been designated a guidance, rather than a guideline.

The guidance provides recommendations 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. This guidance is intended to assist in the establishment of a single set of global specifications for new drug substances and new drug products.

This guidance represents the agency's current thinking on the selection of tests 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 statutes and regulations.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the guidance at any time. 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 guidance and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guidance is available on the Internet at http://www.fda.gov/cder/guidance/index.htm or at http://www.fda.gov/cber/publications.htm.

The text of the guidance follows:

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

Table of Contents

1. Introduction
   1.1 Objective of the Guidance
   1.2 Background
   1.3 Scope of the Guidance
2. General Concepts
   2.1 Periodic or Skip Testing
   2.2 Release vs. Shelf-Life Acceptance Criteria
   2.3 In-Process Tests
   2.4 Design and Development Considerations
   2.5 Limited Data Available at Filing
   2.6 Parametric Release
   2.7 Alternative Procedures
   2.8 Pharmacopeial Tests and Acceptance Criteria
   2.9 Evolving Technologies
   2.10 Impact of Drug Substance on Drug Product Specifications
   2.11 Reference Standard
3. Guidance
   3.1 Specifications: Definition and Justification
   3.1.1 Definition of Specifications
   3.1.2 Justification of Specifications
   3.2 Universal Tests/Criteria
   3.2.1 New Drug Substances
   3.2.2 New Drug Products
   3.3 Specific Tests/Criteria
   3.3.1 New Drug Substances
   3.3.2 New Drug Products
4. Glossary
5. References
6. Attachments: Decision Trees #1 Through #8

1. Introduction

1.1 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.

1.2 Background

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 critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

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, and adherence to good manufacturing practices (GMP's), e.g., suitable facilities, a validated manufacturing process, validated test procedures, raw materials 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.

1.3 Scope of the Guidance

The quality of drug substances and drug products is determined by their design, development, in-process controls, GMP controls, process validation, and by specifications applied to them throughout development and manufacture. This guidance addresses specifications, i.e., those tests, procedures, and acceptance criteria that play a major role in assuring 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 factors listed above are considered 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) and, where applicable, new drug substances; it does not address drug substances or drug products during the clinical research stages of drug development. This guidance may be applicable to synthetic and semisynthetic antibiotics and synthetic peptides of low molecular weight; however, it is not sufficient to

[1] This guidance represents the Food and Drug Administration's current thinking on this topic. 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 statutes and regulations.

adequately describe specifications of higher molecular weight peptides and polypeptides, and biotechnological/biological products. The ICH guidance on "Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" addresses guidance specifications, tests, and procedures for biotechnological/biological products. Radiopharmaceuticals, products of fermentation, oligonucleotides, herbal products, and crude products of animal or plant origin are similarly not covered.

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 should not be considered all encompassing. New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when justified.

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., to inhalation dosage forms (powders, solutions, etc.), to topical formulations (creams, ointments, gels), and to 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 or 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-by-batch basis, with the understanding that those batches not being tested still meet all acceptance criteria established for that product. This represents a less than full schedule of testing and should therefore be justified and presented to and approved by the regulatory authority prior to implementation. This concept may be applicable to, for example, residual solvents and microbiological testing 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 should therefore generally be implemented postapproval. When tested, any failure to meet acceptance criteria established for the periodic test should be handled by proper notification of the appropriate regulatory authority(ies). If these data demonstrate a need to restore routine testing, then batch-by-batch release testing should be reinstated.

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 in-house criteria, and not to the regulatory release criteria. Thus, in these regions, the regulatory acceptance criteria are the same from release throughout shelf life; however, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criteria throughout its shelf life. In the European Union there is a regulatory requirement for distinct specifications for release and for shelf life where different.

2.3 In-Process Tests

In-process tests, as presented in this guidance, 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 that are conducted prior to release.

In-process tests that are only used for the purpose of adjusting process parameters within an operating range, e.g., hardness and friability of tablet cores that will be coated and individual tablet weights, 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 (hydrogen-ion concentration) of a solution) may be sufficient to satisfy specification requirements when the test is included in the specification. However, this approach should be validated to show that test results or product performance characteristics do not change from the in-process stage to finished product.

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 (see Decision Trees #6 and #8).
- 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 highly 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(2)).

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 should necessarily focus on safety and efficacy.

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.

2.6 Parametric Release

Parametric release can be used as an operational alternative to routine release testing for the drug product in certain cases, when approved by the regulatory authority. Sterility testing for terminally sterilized drug products is one example. In this case, the release of each batch is based on satisfactory results from monitoring specific parameters, e.g., temperature, pressure, and time during the terminal sterilization phase(s) of drug product manufacturing. These parameters can generally be more accurately controlled and measured, so they are more reliable in predicting sterility assurance than is end-product sterility testing. Appropriate laboratory tests (e.g., chemical or physical indicator) may be included in the parametric release program. It is important to note that the sterilization process should be adequately validated before parametric release is proposed, and maintenance of a validated state should be demonstrated by revalidation at established intervals. When parametric release is performed, the attribute that 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 Pharmacopeial Tests and Acceptance Criteria

References to certain procedures are found in pharmacopeias in each region. Wherever they are appropriate, pharmacopeial procedures should be used. Whereas differences in pharmacopeial procedures and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the procedures and acceptance criteria defined are acceptable to regulatory authorities in all regions.

The full utility of this guidance is dependent on the successful completion of harmonization of pharmacopeial procedures for several attributes commonly considered in the specification for new drug substances or new drug products. The Pharmacopoeial Discussion Group (PDG) of the European Pharmacopeia, the Japanese Pharmacopoeia (JP), and the United States Pharmacopeia has expressed a commitment to achieving harmonization of the procedures in a timely fashion.

Where harmonization has been achieved, an appropriate reference to the harmonized procedure and acceptance criteria is considered acceptable for a specification in all three regions. For example, after harmonization, sterility data generated using the JP procedure, as well as the JP procedure itself and its acceptance criteria, will be considered acceptable for registration in all three regions. To signify the harmonized status of these procedures, the pharmacopeias have agreed to include a statement in their respective texts that indicates that the procedures and acceptance criteria from all three pharmacopeias are considered equivalent and are, therefore, interchangeable.

Since the overall value of this guidance is linked to the extent of harmonization of the analytical procedures and acceptance criteria of the pharmacopeias, it is agreed by the members of the Q6A expert working group that none of the three pharmacopeias should change a harmonized monograph unilaterally. According to the PDG procedure for the revision of harmonized monographs and chapters, "no pharmacopoeia shall revise unilaterally any monograph or chapter after sign-off or after publication."

2.9 Evolving Technologies

New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justified.

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 considered 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 on "Q3B 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. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing. 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. Guidance

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 critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

It is possible that, in addition to release tests, a specification may list in-process tests as defined in section 2.3, periodic or skip tests, and other tests that 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, pharmacopeial 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 stability and scaleup/validation batches, with emphasis on the primary stability 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 proposing exclusion of a test from the specification should be based on development data and on process validation data (where appropriate).

3.2 Universal Tests/Criteria

Implementation of the recommendations in the following section should take into account the ICH guidances "Q2A Text on Validation of Analytical Procedures" and "Q2B 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 a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles or a combination of tests into a single procedure, such as HPLC (high-pressure liquid chromatography)/UV (ultraviolet) diode array, HPLC/MS (mass spectroscopy), or GC (gas chromatography)/MS is generally acceptable. If the new drug substance is a salt, identification testing should be specific for the individual ions. An identification test that is specific for the salt itself should suffice.

New drug substances that are optically active may also need specific identification testing or performance of a chiral assay. 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 should be used.

(d) *Impurities:* Organic and inorganic impurities and residual solvents are included in this category. Refer to the ICH guidances on "Q3A Impurities in New Drug Substances" and "Q3C Impurities: Residual Solvents" 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 considered inappropriate to establish acceptance criteria that tightly encompass the batch data at the time of filing (see section 2.5).

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, and 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 that are likely to be present. Identity tests should be specific for the new drug substance, e.g., infrared spectroscopy. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles, or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally acceptable.

(c) *Assay:* A specific, stability-indicating assay to determine strength (content) 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 for release, the combination of the assay and a suitable test for impurities can be used. A specific procedure should be used when there is evidence of excipient interference with the nonspecific assay.

(d) *Impurities:* Organic and inorganic impurities (degradation products) and residual solvents are included in this category. Refer to the ICH guidances on "Q3B Impurities in New Drug Products" and "Q3C Impurities: Residual Solvents" for detailed information.

Organic impurities arising from degradation of the new drug substance

and impurities that arise during the manufacturing process for the drug product 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. However, when a synthesis impurity is also a degradation product, its level should be monitored and included in the total degradation product limit. When it has been conclusively demonstrated via appropriate analytical methodology 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 considered inappropriate to establish acceptance criteria that tightly encompass the batch data at the time of filing (see section 2.5).

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, Abbe 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) *Polymorphic forms:* Some new drug substances exist in different crystalline forms that differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. 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.

Physicochemical 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, optical microscopy, and solid state NMR (nuclear magnetic resonance) spectroscopy.

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

Note: These decision trees should be followed sequentially. Trees #4(1) and #4(2) consider whether polymorphism is exhibited by the drug substance, and whether the different polymorphic forms can affect performance of the drug product. Tree #4(3) should only be applied when polymorphism has been demonstrated for the drug substance, and shown to affect these properties. Tree #4(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) (see Decision Tree #4(3)) can generally be used to monitor product performance, and polymorph content should only be used as a test and acceptance criterion of last resort.

(d) *Tests for chiral new drug substances:* Where a new drug substance is predominantly one enantiomer, the opposite enantiomer is excluded from the qualification and identification thresholds given in the ICH guidances on "Q3A Impurities in New Drug Substances" and "Q3B Impurities in New Drug Products" because of practical difficulties in quantifying it at those levels. However, that impurity in the chiral new drug substance and the resulting new drug product(s) should otherwise be treated according to the 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 quantification or qualification from being applied. Assurance of control also 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. For a drug substance developed as a single enantiomer, the identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture. For a racemic drug substance, there are generally two situations where a stereospecific identity test is appropriate for release/acceptance testing: (1) Where there is a significant possibility that the enantiomer might be substituted for the racemate, or (2) when there is evidence that preferential crystallization may lead to unintentional production of a nonracemic mixture.

Drug Product: Degradation products. Control of the other enantiomer in a drug product is considered necessary unless racemization has been shown to be insignificant during manufacture of the dosage form and on storage.

Assay. An achiral assay may be sufficient where racemization has been shown to be insignificant during manufacture of the dosage form and on storage. Otherwise a chiral assay should be used. Alternatively, the combination of an achiral assay plus a validated

procedure to control the presence of the opposite enantiomer may be used.

Identity. A stereospecific identity test is not generally needed in the drug product release specification. When racemization is insignificant during manufacture of the dosage form and on storage, stereospecific identity testing is more appropriately addressed as part of the drug substance specification. When racemization in the dosage form is a concern, chiral assay or enantiomeric impurity testing of the drug product will serve to verify identity.

(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 considered 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 (e.g., catalysts) should be studied during development and based on knowledge of the manufacturing process. Procedures and acceptance criteria for sulfated ash/residue on ignition should follow pharmacopeial 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 pharmacopeial procedures. The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. For example, sterility testing may be appropriate for drug substances manufactured as sterile, and endotoxin testing may be appropriate for drug substances used to formulate an injectable drug product.

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 that 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:* The specification for solid oral dosage forms normally includes a test to measure release of drug substance from the drug product. 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. In some cases (see section 3.3.2.1(b) Disintegration) dissolution testing may be replaced by disintegration testing (see Decision Tree #7(1)).

For immediate-release drug products where changes in dissolution rate have been demonstrated to significantly affect bioavailability, it is desirable to develop test conditions that can distinguish batches with unacceptable bioavailability. If changes in formulation or process variables significantly affect dissolution, and such changes are not controlled by another aspect of the specification, it may also be appropriate to adopt dissolution test conditions that can distinguish these changes (see Decision Tree #7(2)).

Where dissolution significantly affects bioavailability, the acceptance criteria should be set to reject batches with unacceptable bioavailability. Otherwise, test conditions and acceptance criteria should be established that pass clinically acceptable batches (see Decision Tree #7(2)).

For extended-release drug products, in vitro/in vivo correlation may be used to establish acceptance 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 mean 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 percent to 60 percent), unless a wider range is supported by a bioequivalency study (see Decision Tree #7(3)).

(b) *Disintegration:* For rapidly dissolving (dissolution >80 percent in 15 minutes at pH 1.2, 4.0, and 6.8) products containing drugs that are highly soluble throughout the physiological range (dose/solubility volume ≤ 250 milliliters (mL) from pH 1.2 to 6.8), disintegration may be substituted for dissolution. Disintegration testing is considered 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 be necessary. 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 versus disintegration testing (see Decision Tree #7(1)).

(c) *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.

(d) *Uniformity of dosage units:* This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopeial procedure should be used. In general, the specification should include one or the other, but not both. If appropriate, these tests may be performed in-process; the acceptance criteria should be included in the specification. When weight variation is applied to new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug

development that the homogeneity of the product is adequate.

(e) *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 considered adequate; however, a detection procedure that is specific for water (e.g., Karl Fischer titration) is preferred.

(f) *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 or proliferation. It should be noted that, whereas this guidance does not directly address excipients, 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, where permissible (see Decision Tree #6 for microbial testing of excipients).

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 aeruginosa). These should be determined by suitable procedures, using pharmacopeial procedures, and at a sampling frequency or time point in manufacture that is justified by data and experience. The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. With acceptable scientific justification, it should be possible to propose no microbial limit testing for solid oral dosage forms.

Decision Tree #8 provides additional guidance on the use of microbial limits 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 the mass of the dosage form and the content of the active drug substance in the dosage form; a pharmacopeial procedure should be used. In general, the specification should include one or the other, but not both. When weight variation is applied to new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.

If appropriate, tests may be performed in-process; 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 or proliferation. It should be noted that, whereas this guidance does not directly address excipients, 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, where permissible. 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 aeruginosa). These should be determined by suitable procedures, using pharmacopeial procedures, and at a sampling frequency or time point in manufacture that is justified by data and experience.

Decision Tree #8 provides additional guidance on the use of microbial limits testing.

(d) *Antimicrobial preservative content:* For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopeial antimicrobial preservative effectiveness test.

Testing for antimicrobial preservative content should normally be performed at release. 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 "Q1A 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 where permitted. 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 evidence that extractables from the container/closure systems are consistently below levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted. This should be reinvestigated if the container/closure system or formulation 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, etc.) 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. Dissolution testing should be performed at release. This test may be performed as an in-process test when justified by product development data. The testing apparatus, media, and conditions should be pharmacopeial, if possible, or otherwise justified. Dissolution procedures using either a pharmacopeial or nonpharmacopeial 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.

(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 should be performed at release. It may be performed as an in-process test when justified by product development data. 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 that settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate procedure.

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 periodic or skip testing, or elimination of this attribute from the specification may be proposed.

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

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

(m) *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 versus 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 the mass of the dosage form and the content of the active drug substance in the dosage form; a pharmacopeial procedure should be used. In general, the specification should be one or the other, but not both, and is applicable to powders for reconstitution. When weight variation is applied to new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.

If appropriate (see section 2.3), these tests may be performed in-process; 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 (see section 2.6).

(d) *Endotoxins/Pyrogens:* A test procedure and acceptance criterion for endotoxins, using a procedure such as the limulus amoebocyte lysate test, should be included in the specification. Pyrogenicity testing may be proposed as an alternative to endotoxin testing where justified.

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

(f) *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 versus water of hydration has been adequately characterized during development. In certain cases a more specific procedure (e.g., Karl Fischer titration) may be preferred.

(g) *Antimicrobial preservative content:* For parenteral products

needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopeial antimicrobial preservative effectiveness test.

Testing for antimicrobial preservative content should normally be performed at release. Under certain circumstances, in-process testing may suffice in lieu of release testing, where permitted. 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 "Q1A Stability Testing of New Drug Substances and Products"), although chemical testing for preservative content is the attribute normally included in the specification.

(h) *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.

(i) *Extractables:* Control of extractables from container/closure systems is considered significantly more important for parenteral products than for oral liquids. However, where development and stability data show evidence that extractables are consistently below the levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted. This should be reinvestigated if the container/closure system or formulation 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, etc.) should be listed, and data collected for these components as early in the development process as possible.

(j) *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. Under certain circumstances these tests may be performed in-process. Data generated during product development may be sufficient to justify skip lot testing or elimination of some or all attributes from the specification.

(k) *Osmolarity:* When the tonicity of a product is declared in its labeling, appropriate control of its osmolarity 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.

(l) *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 should be performed at release. It may be performed as an in-process test when justified by product development data. 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.

(m) *Redispersibility:* For injectable suspensions that settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate procedure. 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 may be proposed.

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

4. Glossary (the following definitions are presented for the purpose of this guidance)

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

Chiral: Not superimposable 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 light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product.

Delayed release: Release of a drug (or drugs) at a time other than immediately following oral administration.

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

Extended release: Products that are formulated to make the drug available over an extended period after administration.

Highly water soluble drugs: Drugs with a dose/solubility volume of less than or equal to 250 mL over a pH range of 1.2 to 6.8. (Example: Compound A has as its lowest solubility at 37±0.5 °C, 1.0 milligram (mg)/milliliter (mL) at pH 6.8, and is available in 100 mg, 200 mg, and 400 mg strengths. This drug would be considered a low solubility drug, as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL = 400 mL)).

Immediate release: Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

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.

In-process tests: 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 that are conducted prior to release.

Modified release: Dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms, such as a solution or an immediate-release dosage form. Modified-release solid oral dosage forms include both delayed- and extended-release drug products.

New drug product: A pharmaceutical product type, e.g., tablet, capsule, solution, cream, etc., that has not previously been registered in a region or Member State, and that 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.

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

Rapidly dissolving products: An immediate release solid oral drug product is considered rapidly dissolving when not less than 80 percent of the label amount of the drug substance dissolves within 15 minutes in each of the following media: (1) pH 1.2, (2) pH 4.0, and (3) pH 6.8.

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 critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

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 to ensure 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 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, "Q3A Impurities in New Drug Substances," 1996.

International Conference on Harmonisation, "Q3B Impurities in New Drug Products," 1997.

International Conference on Harmonisation, "Q1A Stability Testing of New Drug Substances and Products," 1994.

International Conference on Harmonisation, "Q2A Text on Validation of Analytical Procedures," 1995.

International Conference on Harmonisation, "Q2B Validation of Analytical Procedures: Methodology," 1996.

International Conference on Harmonisation, "Q3C Impurities: Residual Solvents," 1997.

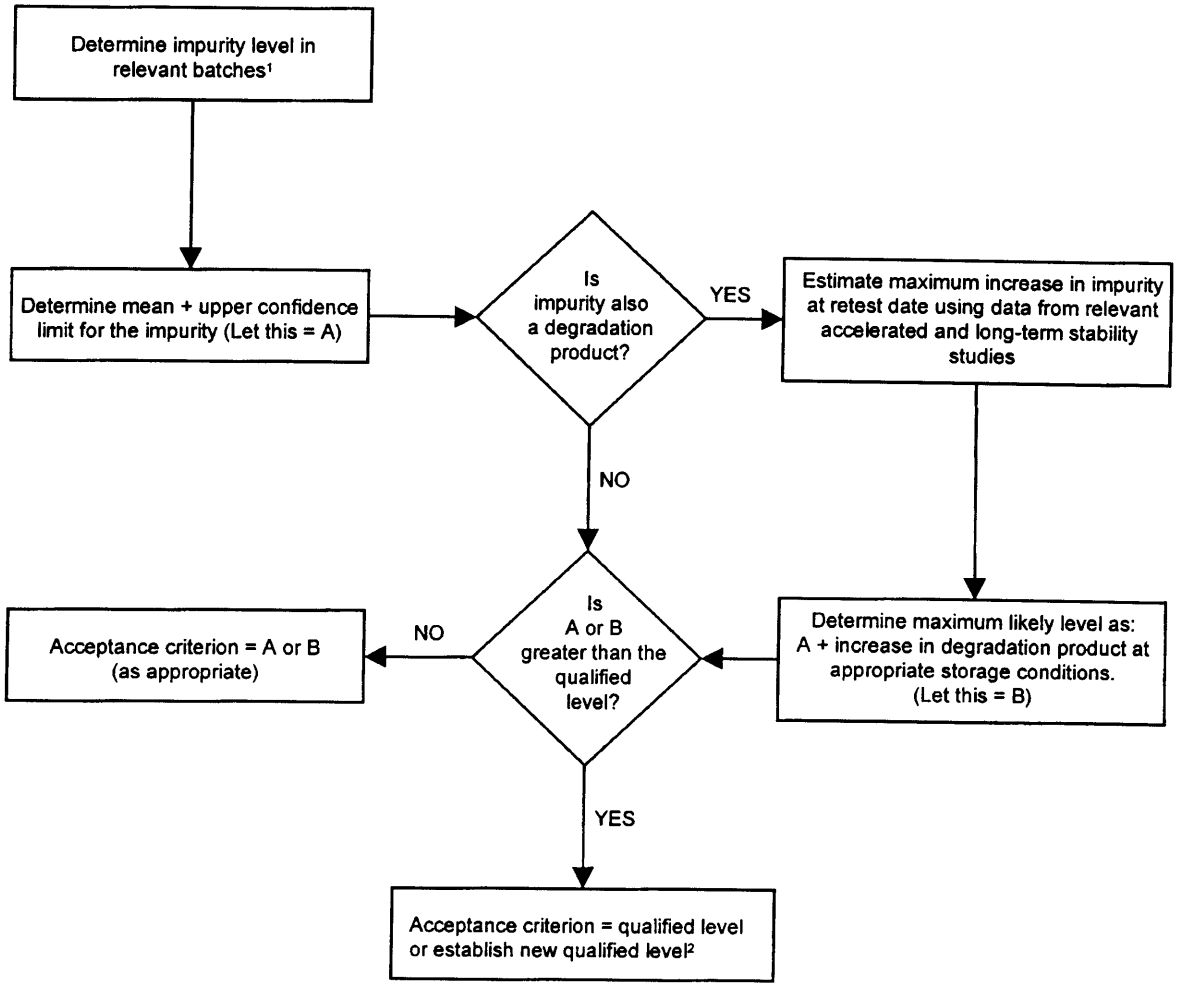
International Conference on Harmonisation, "Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products," 1999.

6. Attachments: Decision Trees #1 through #8

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

BILLING CODE 4160-01-F

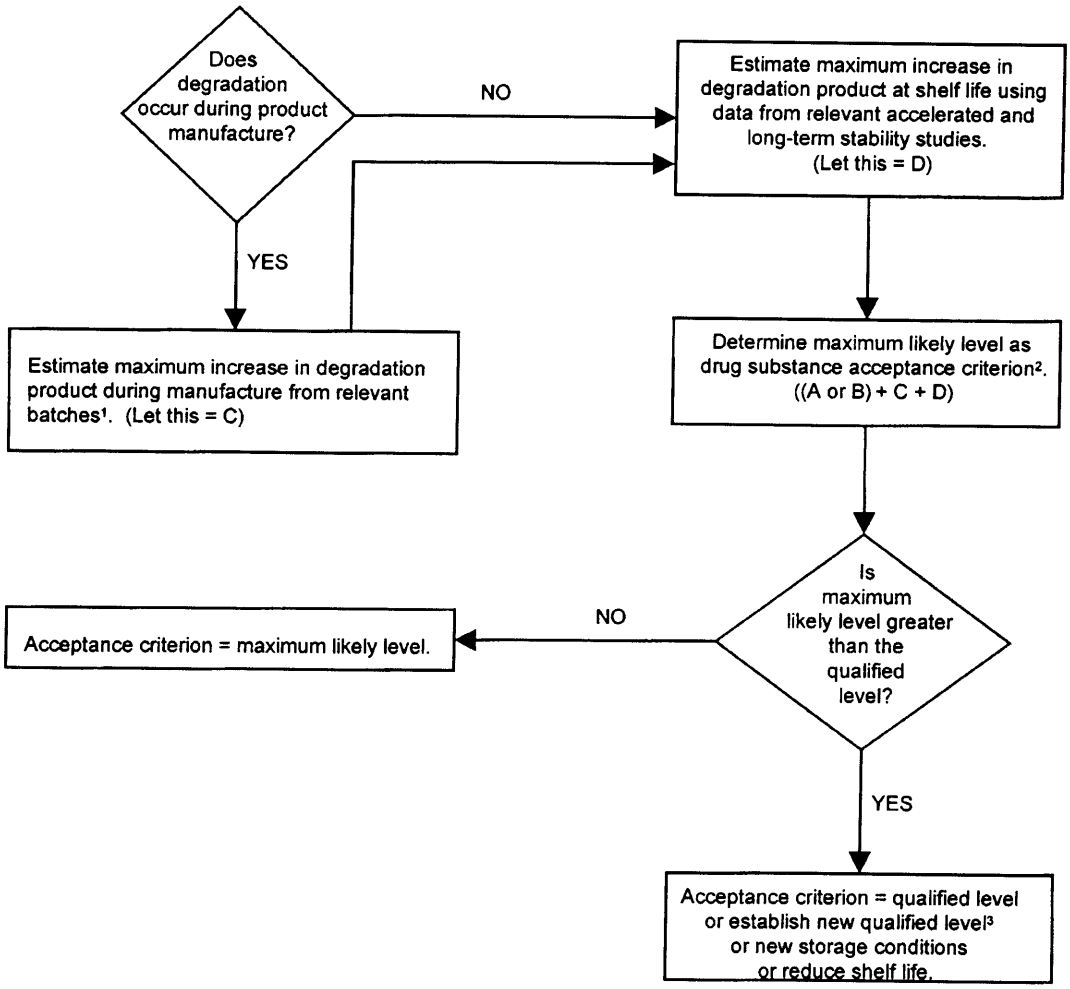
DECISION TREE #1: ESTABLISHING AN ACCEPTANCE CRITERION FOR A SPECIFIED IMPURITY IN A NEW DRUG SUBSTANCE



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

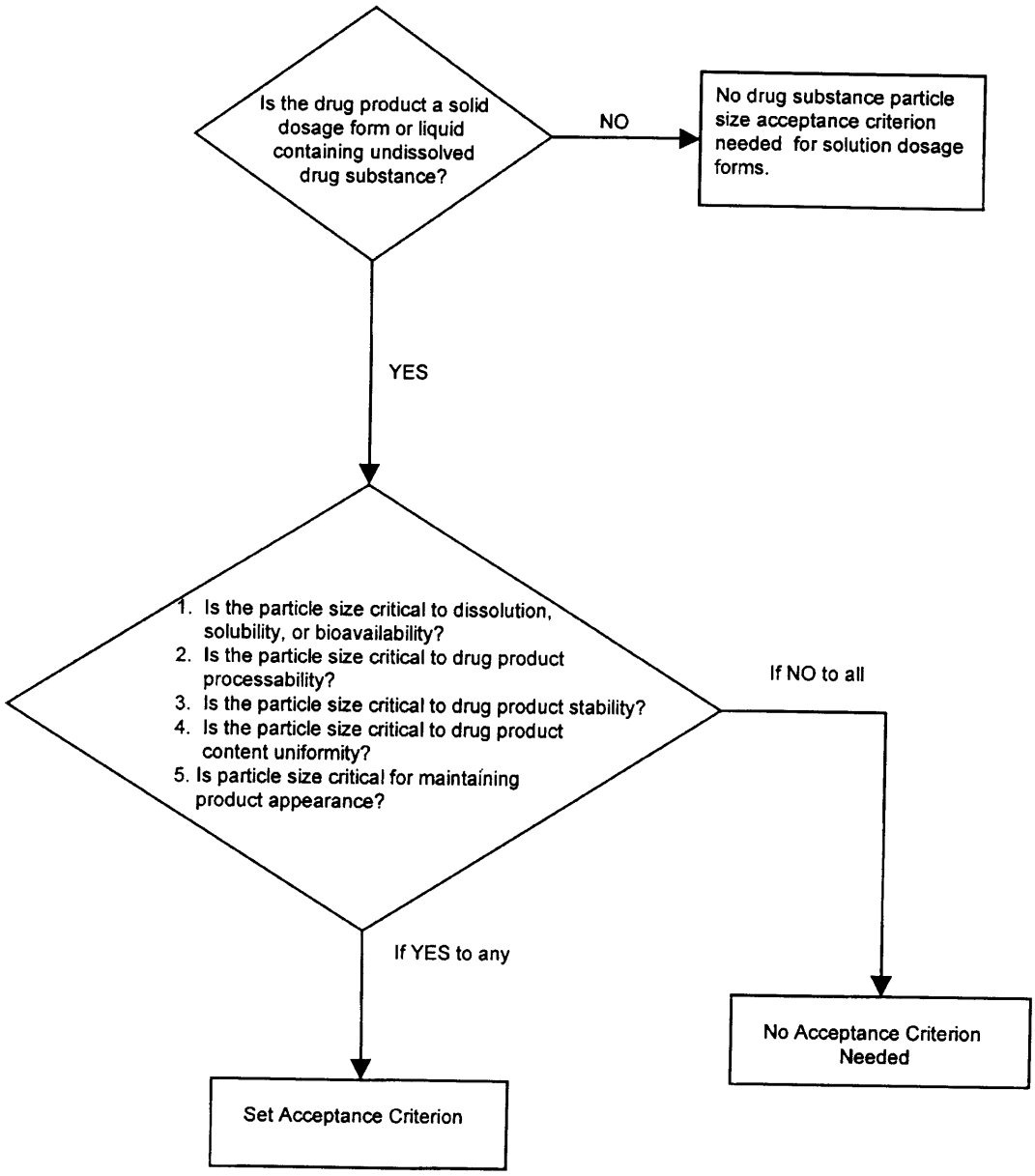
Definition: upper confidence limit = three times the standard deviation of batch analysis data

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

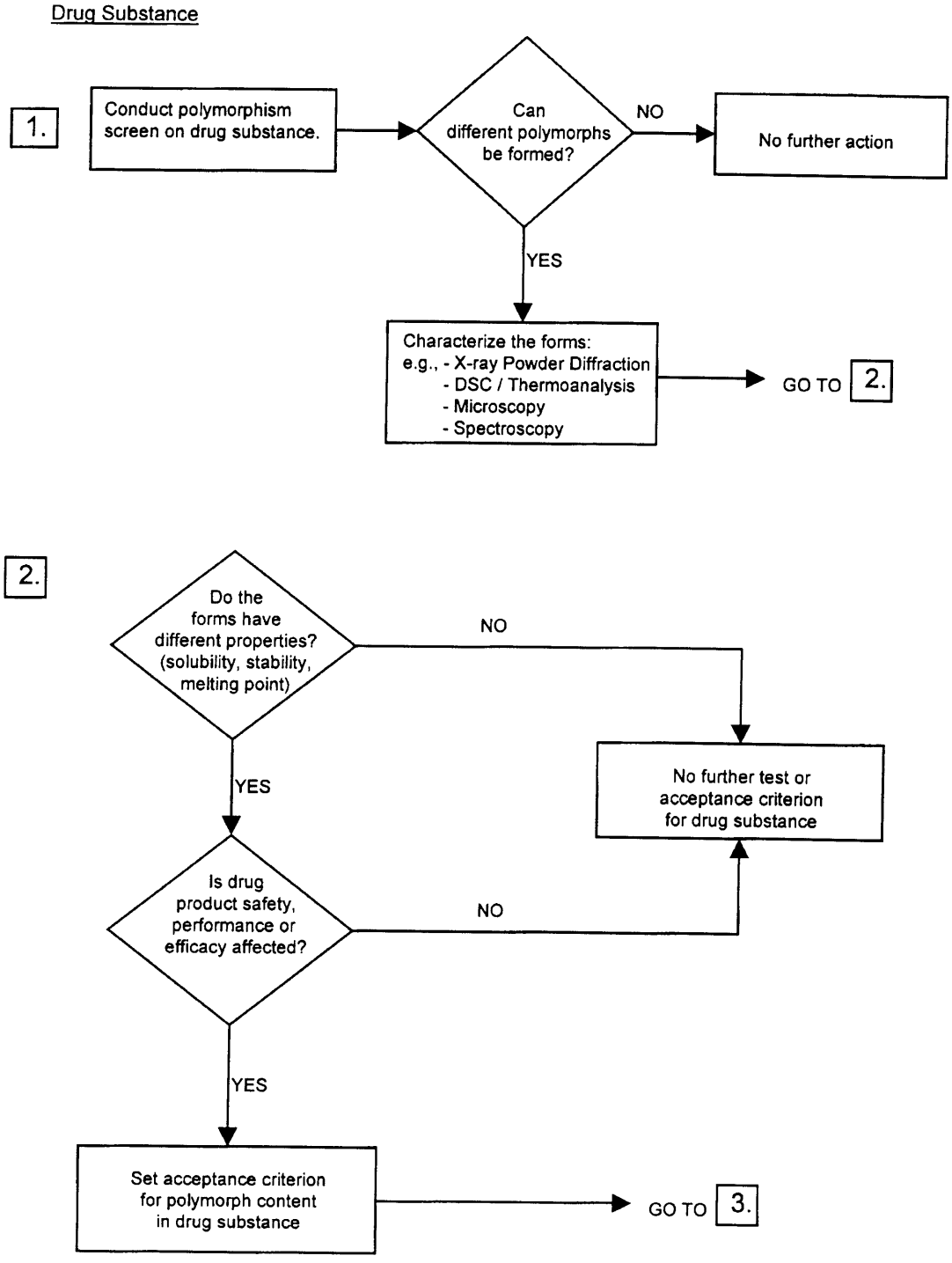


[1] Relevant batches are those from development, pilot and scale-up studies.
[2] Refer to Decision Tree 1 for information regarding A and B.
[3] Refer to ICH Guideline on Impurities in New Drug Products.

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



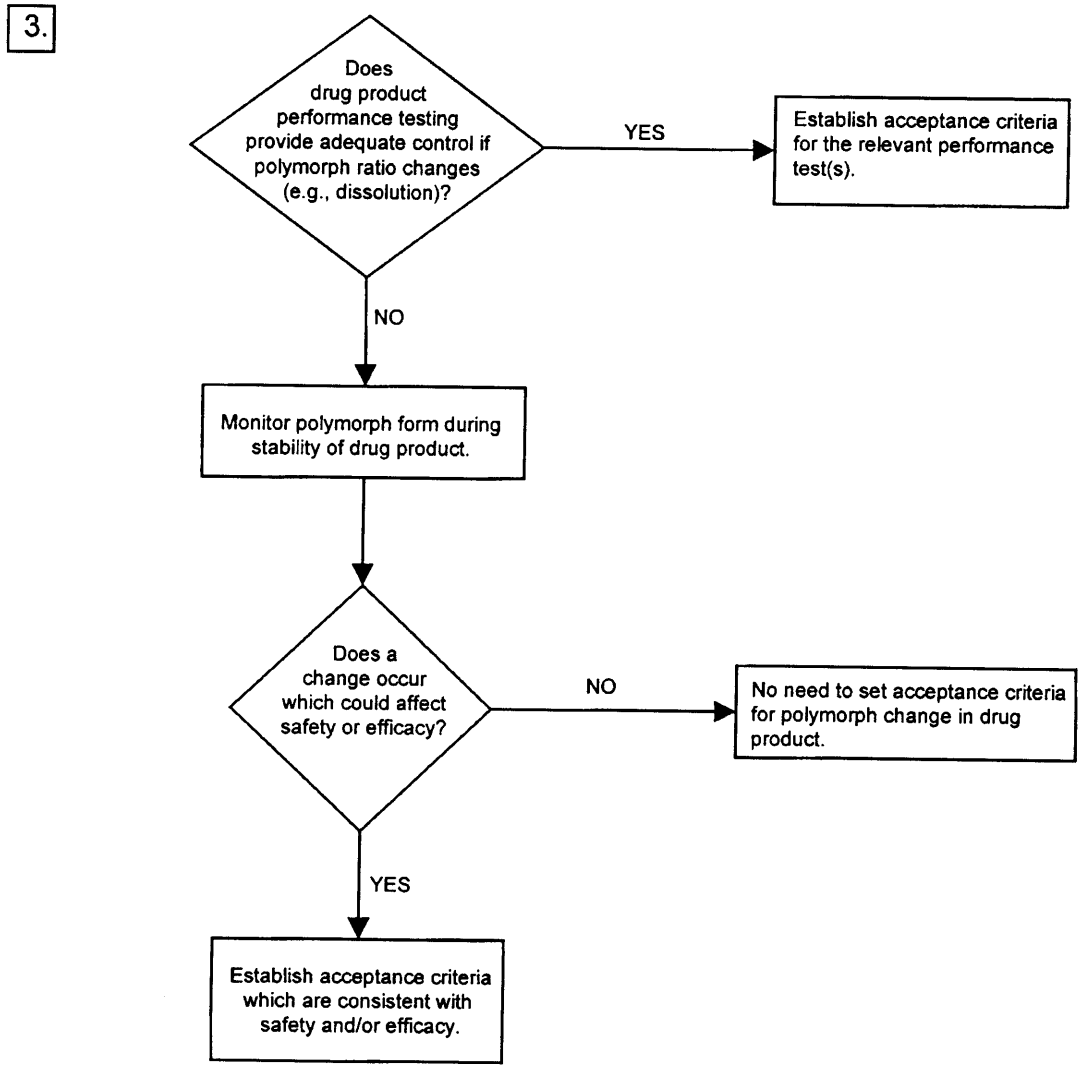
DECISION TREE #4: INVESTIGATING THE NEED TO SET ACCEPTANCE CRITERIA FOR POLYMORPHISM IN DRUG SUBSTANCES AND DRUG PRODUCTS



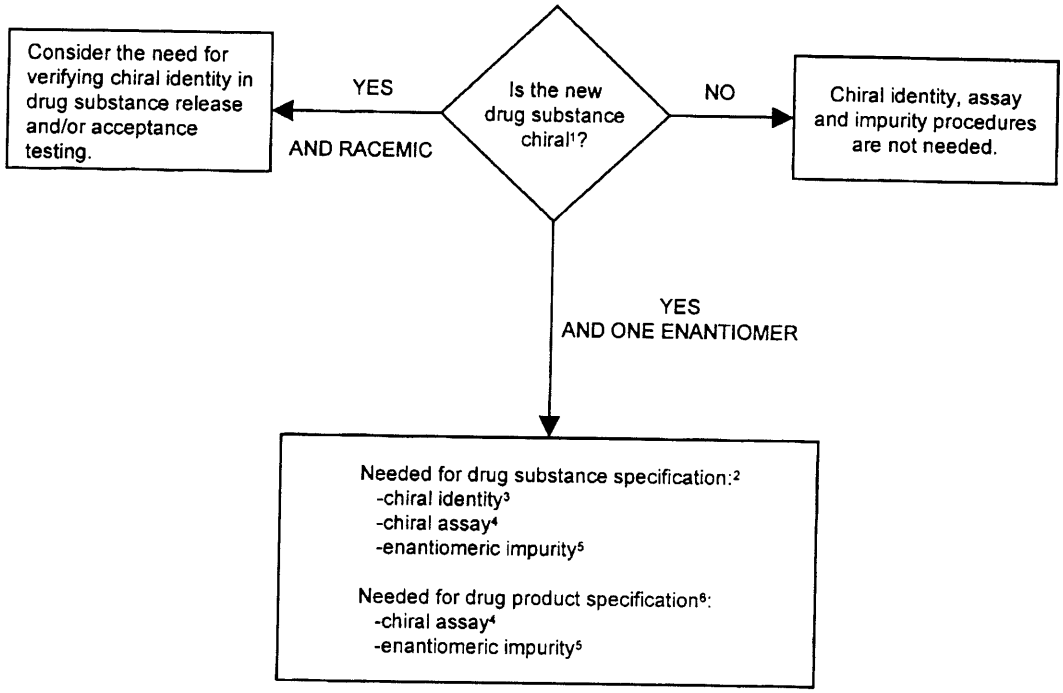
DECISION TREE #4: INVESTIGATING THE NEED TO SET ACCEPTANCE CRITERIA FOR POLYMORPHISM IN DRUG SUBSTANCES AND DRUG PRODUCTS

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

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



DECISION TREE #5: ESTABLISHING IDENTITY, ASSAY AND ENANTIOMERIC IMPURITY PROCEDURES FOR CHIRAL NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS CONTAINING CHIRAL DRUG SUBSTANCES



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

[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 developmental studies. This essentially will be the case when there are multiple chiral centers (e.g., three or more), or when control at a step prior to production of the final drug substance is desirable.

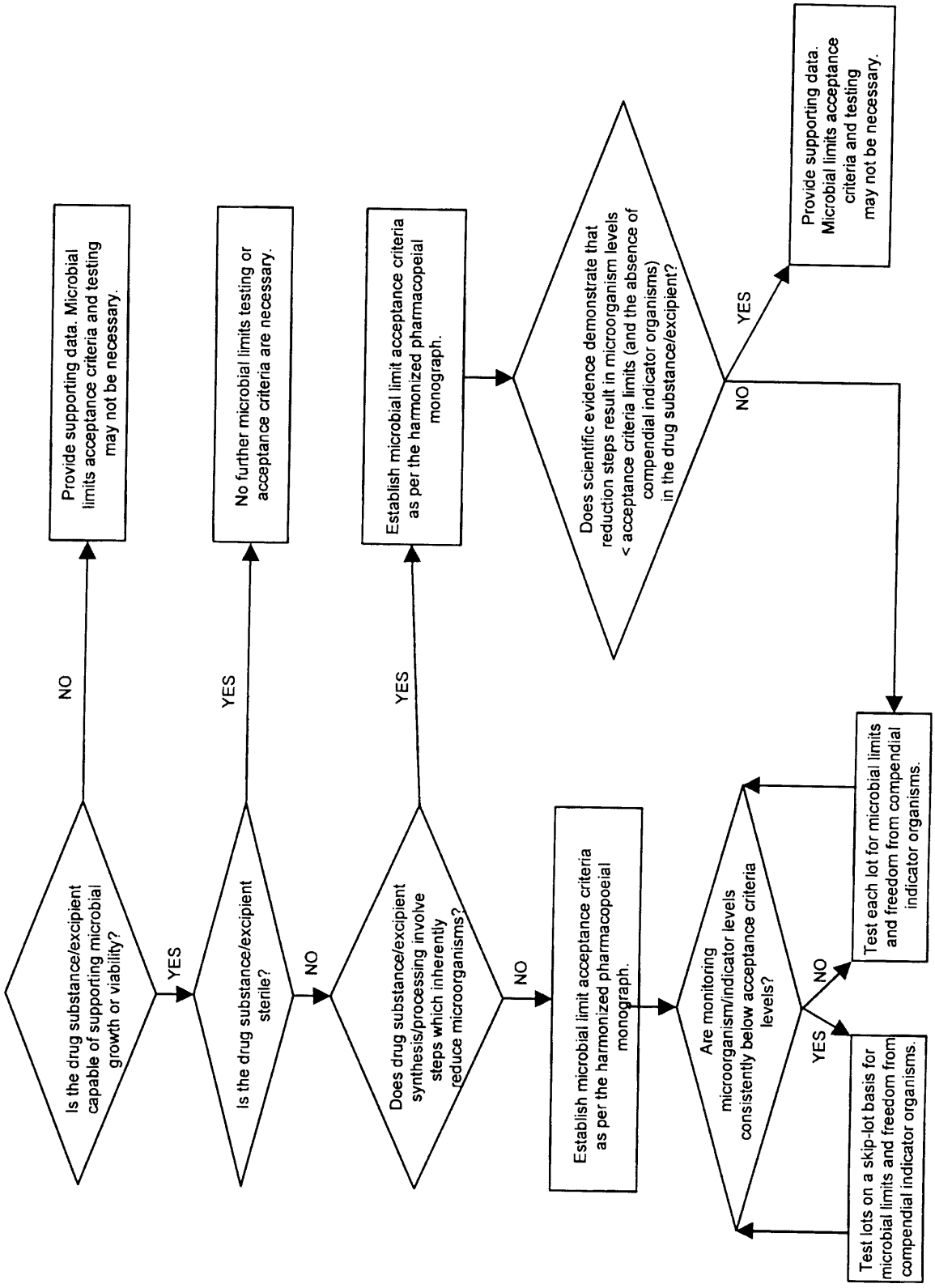
[3] A chiral assay or an enantiomeric impurity procedure may be acceptable in lieu of a chiral identity procedure.

[4] An achiral assay combined with a method for controlling the opposite enantiomer is considered acceptable in lieu of a chiral assay.

[5] The level of the opposite enantiomer of the drug substance may be derived from chiral assay data or from a separate procedure.

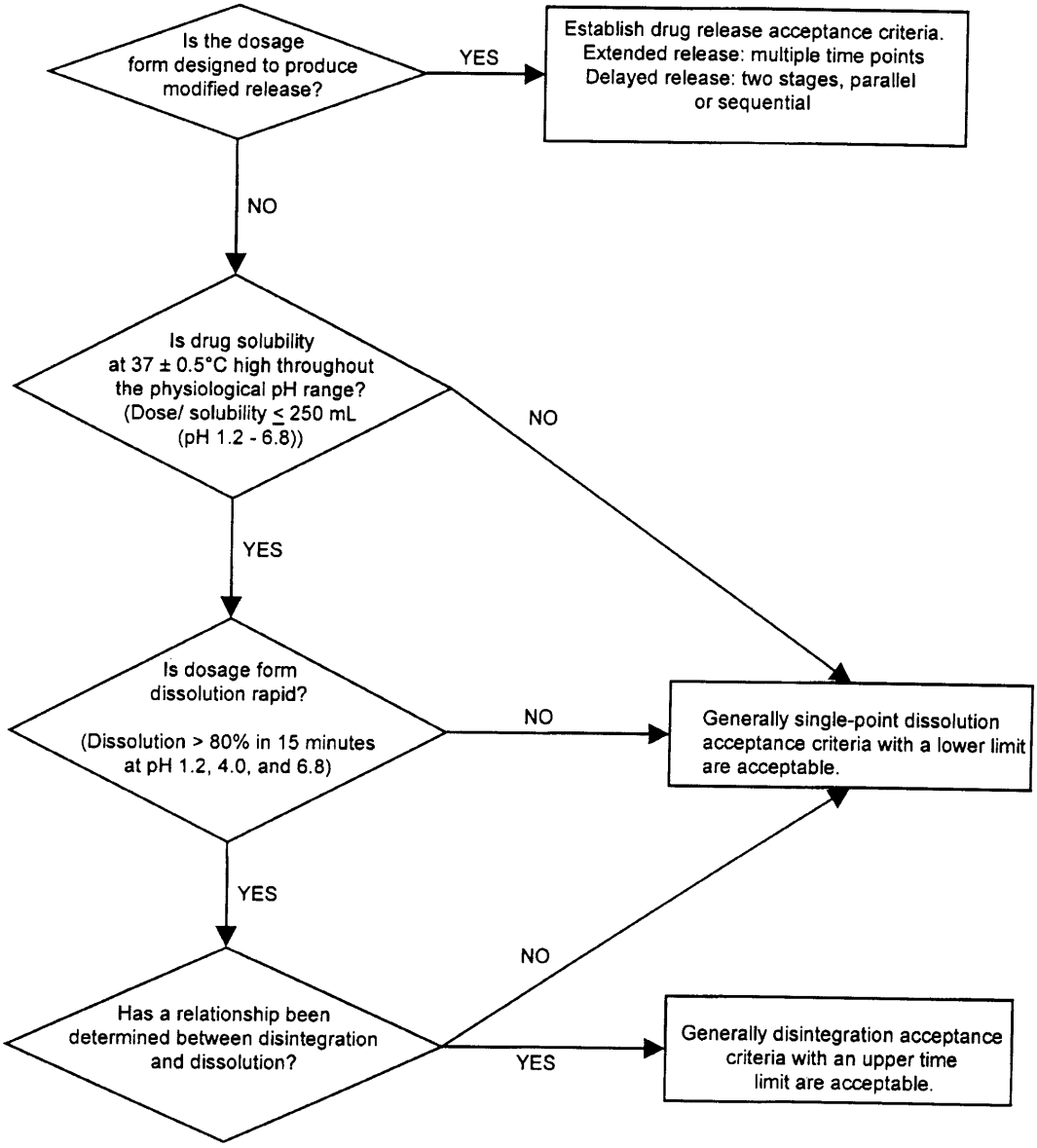
[6] Stereospecific testing of drug product may not be necessary if racemization has been demonstrated to be insignificant during drug product manufacture and during storage of the finished dosage form.

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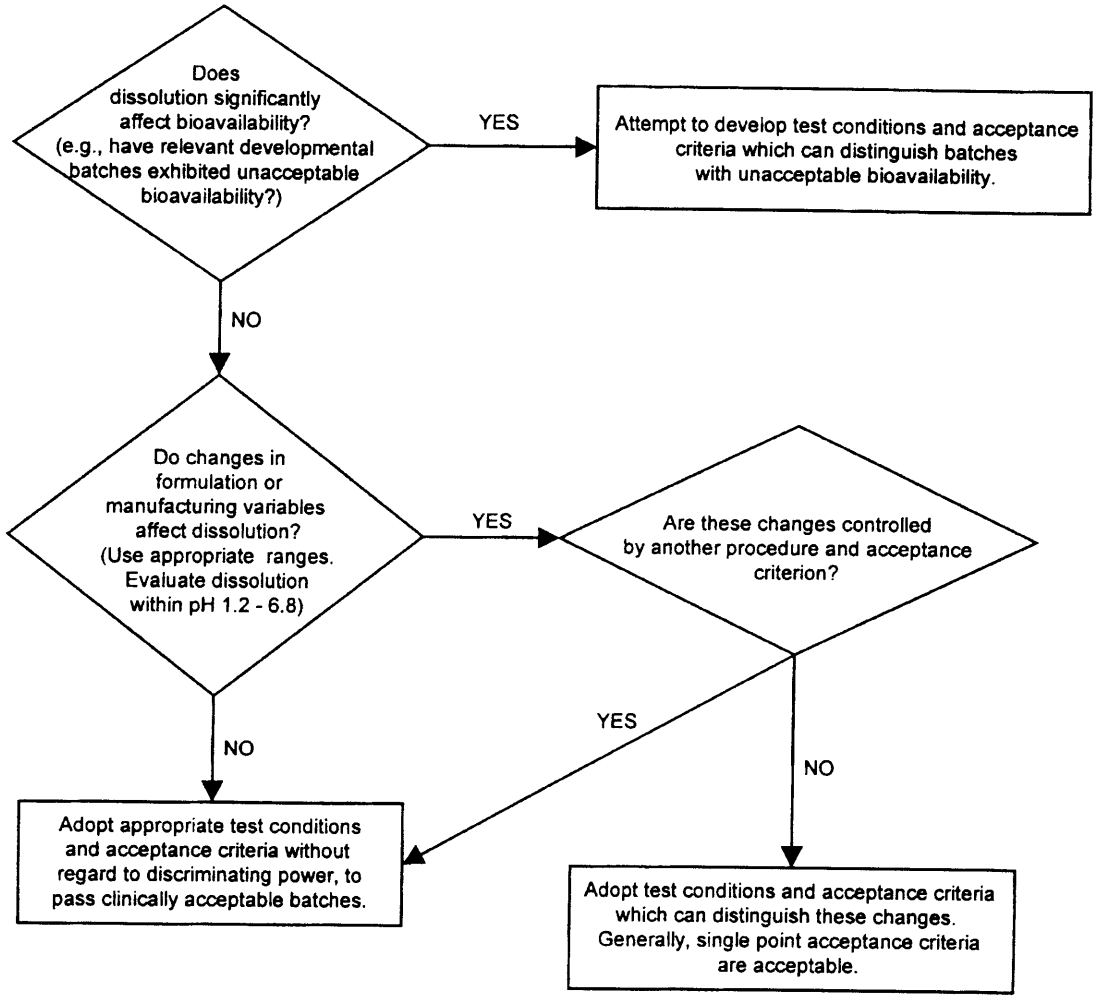
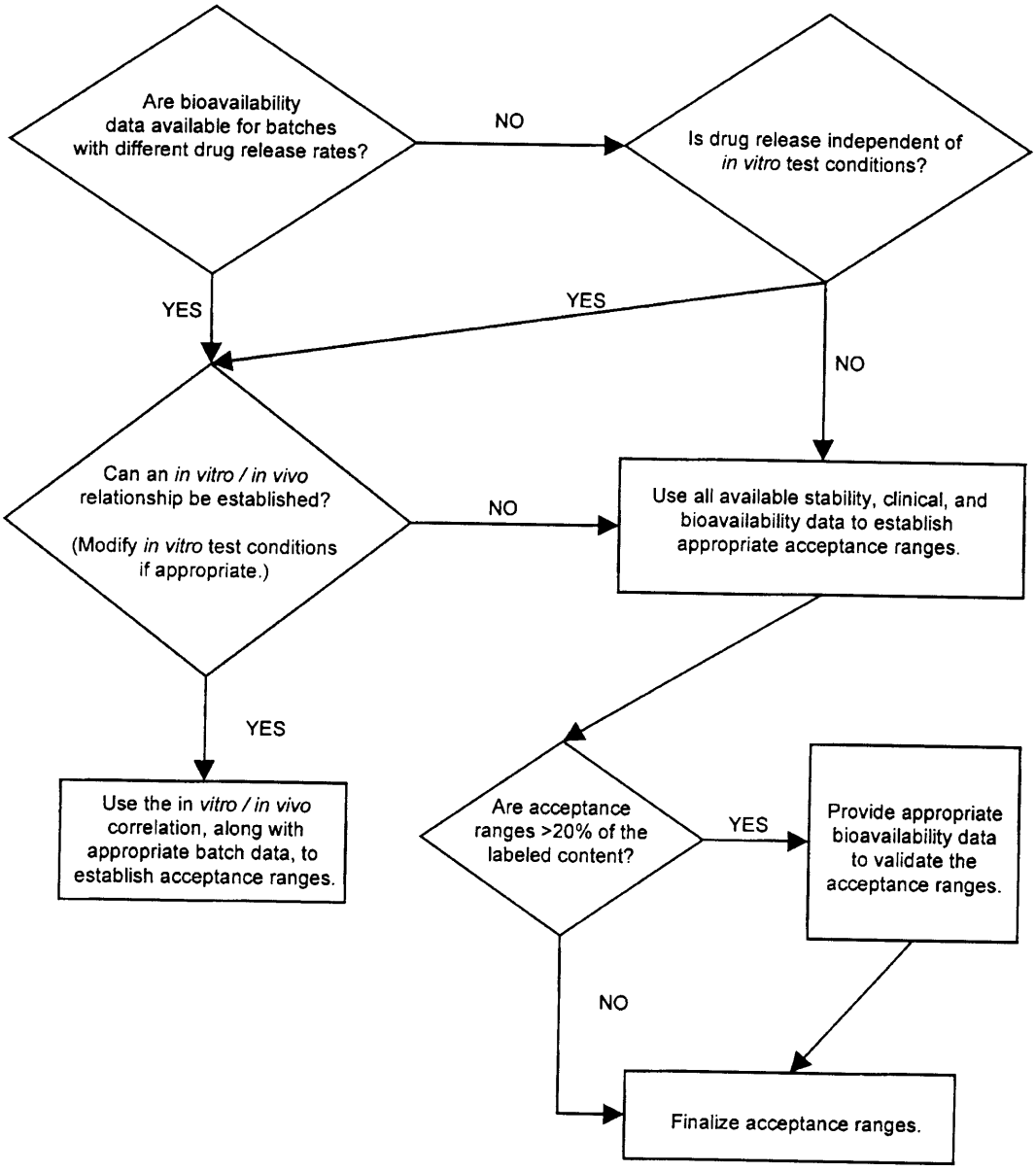
DECISION TREES #7: SETTING ACCEPTANCE CRITERIA
FOR DRUG PRODUCT DISSOLUTION

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

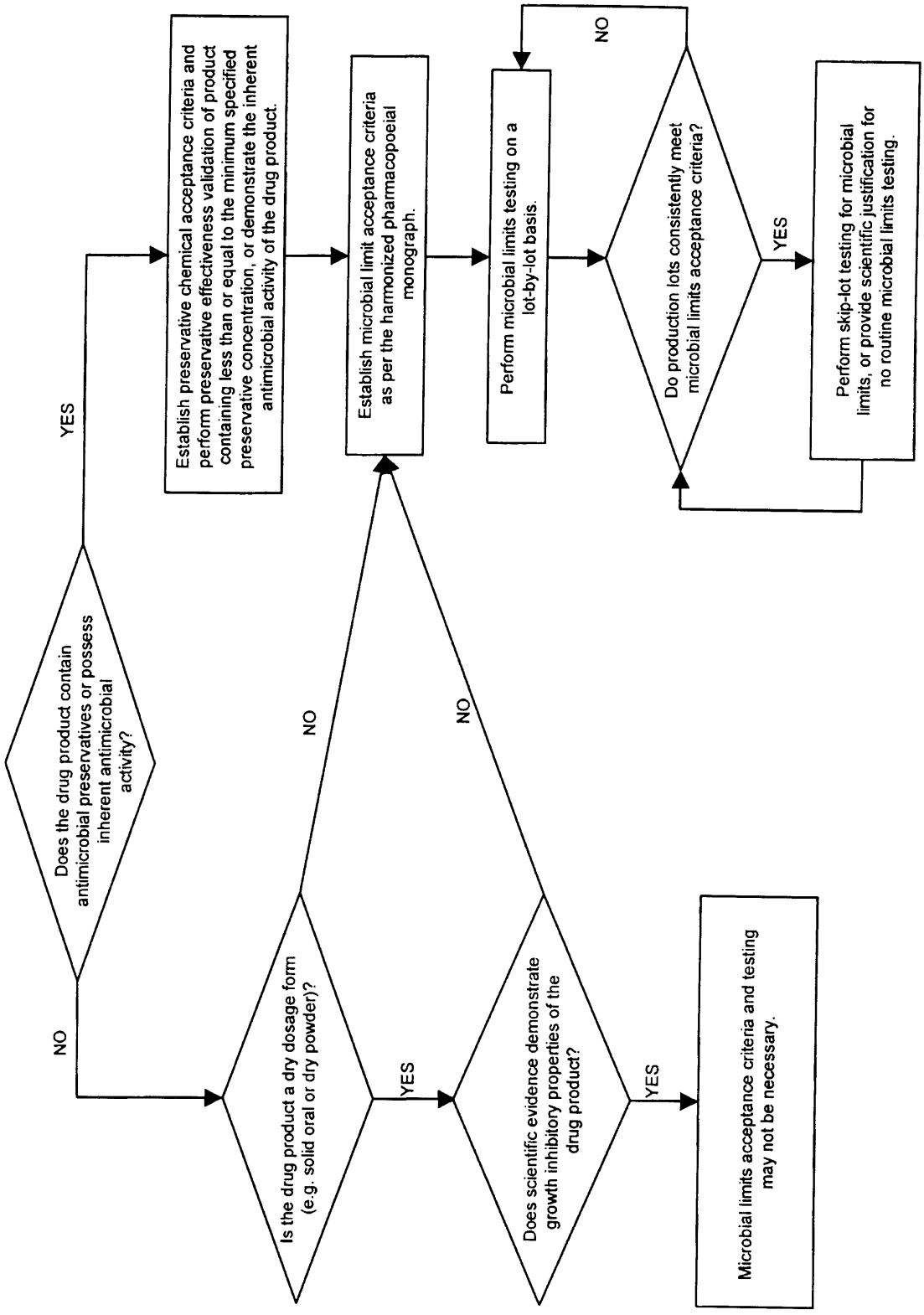


DECISION TREES #7: SETTING
ACCEPTANCE CRITERIA
FOR DRUG PRODUCT DISSOLUTION

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



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



Dated: December 20, 2000.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 00–33369 Filed 12–28–00; 8:45 am]

BILLING CODE 4160–01–C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Cooperative Arrangement Between the United States Food and Drug Administration and Therapeutic Goods Administration, Republic of Australia Regarding the Exchange of Information on Current Good Manufacturing Practice Inspections of Human Pharmaceutical Facilities

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing notice of cooperative arrangement between the Food and Drug Administration, Department of Health and Human Services, United States of America and the Therapeutic Goods Administration, Department of Health and Aged Care, Commonwealth of Australia. The purpose of the arrangement is to enable each administration to obtain information that will enable it to make its own independent facility and/or product regulatory decisions in the assessment of current good manufacturing practices compliance, public health protection, and approval of new drugs. It also will facilitate more efficient use of resources for each organization in meeting their statutory requirements without reduction of public safety or regulatory responsibilities.

DATES: The arrangement became effective October 11, 2000.

FOR FURTHER INFORMATION CONTACT: Merton V. Smith, Office of International Programs, International Agreements Staff (HFG–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0910.

SUPPLEMENTARY INFORMATION: This cooperative arrangement is subject to FDA's regulations in 21 CFR 20.108 for cooperative agreements. Therefore, in accordance with 21 CFR 20.108(c), which states that all written agreements and memoranda of understanding between FDA and others shall be published in the **Federal Register**, the agency is publishing notice of this written arrangement.

Dated: December 20, 2000.

Margaret M. Dotzel,

Associate Commissioner for Policy.

The arrangement is set forth in its entirety as follows:

BILLING CODE 4160–01–F