Guidance for Industry

BACPAC I: Intermediates in Drug Substance Synthesis Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation

"Note: This guidance replaces the version dated February 2001. The document has been revised to reflect that the information provided on the chemistry, manufacturing, and controls of drug substances is now only applicable to animal drugs."

Comments and suggestions regarding this document should be sent to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the exact title of the document.

For questions regarding this document, contact Dennis Bensley, Center for Veterinary Medicine (HFV-143), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, (240) 276-8268, E-mail: dennis.bensley@fda.hhs.gov.

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
June 1, 2006

TABLE OF CONTENTS

Contains Nonbinding Recommendations

GUIDANCE FOR INDUSTRY[1]

BACPAC I: Intermediates in Drug Substance Synthesis

Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation

This guidance represents the Food and Drug Administration's (FDA'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. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to holders of new animal drug applications (NADAs), abbreviated new animal drug applications (ANADAs), or veterinary master files (VMFs) who intend, during the postapproval period, to change the (1) site of manufacture, (2) scale of manufacture, (3) equipment, (4) ***specification(s)***,[2] and/or (5) manufacturing process of ***intermediates*** in the synthetic pathway leading to the ***drug substance***.[3]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Bulk Actives Postapproval Changes (BACPAC) Working Group of the Drug Substance Technical Committee operating under the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER), with participation by the Center for Veterinary Medicine (CVM), at the Food and Drug Administration (FDA).

[2] Terms in bold italics are defined in the glossary.

[3] The FDA solicited early input on this topic through a public meeting sponsored by the American Association of Pharmaceutical Scientists in conjunction with the FDA. The meeting, held March 25-27, 1997, provided a forum for FDA to hear public opinion on postapproval changes in the manufacture of drug substances.

II. BACKGROUND

Under section 506A of the Federal Food, Drug, and Cosmetic Act (the Act), the holder of an NADA or ANADA must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The Act provides for four reporting categories: (1) Prior Approval Supplement, (2) Supplement – Changes Being Effected in 30 days, (3) Supplement – Changes Being Effected, and (4) Annual Report. The reporting category for a change is based on the potential for the change to have an adverse effect on the identity, strength, quality, purity, or potency of the ***drug product*** as these factors may relate to the safety or effectiveness of the drug product. This guidance provides recommendations on reporting categories for postapproval changes relating to intermediates in drug substance synthesis based on a determination by the Center for Veterinary Medicine (CVM) of the potential for a specified change to have an adverse effect on the drug product. It also provides recommendations on the information that should be provided to CVM to ensure continued drug substance quality and drug product quality and performance characteristics.

This guidance describes chemistry, manufacturing, and controls information and documentation in support of each change and provides recommendations on reporting categories. The guidance applies to synthetic drug substances and the synthetic steps involved in the preparation of ***semisynthetic drug substances***. It is limited to structurally well-characterized drug substances for which ***impurities*** can be monitored at the levels recommended. The guidance covers: (1) site, scale, and equipment changes involving the synthetic steps up to and including the step that produces the ***final intermediate***, (2) specification changes for raw materials, ***starting materials***, and intermediates, except the final intermediate, and (3) manufacturing process changes involving the synthetic steps up to and including the final intermediate.[4]

Postapproval changes affecting the following are not addressed in this document:

- Synthetic peptides
- Oligonucleotides
- Radiopharmaceuticals
- Drug substances derived exclusively by isolation from natural sources or produced by procedures involving biotechnology
- Nonsynthetic steps for semisynthetic drug substances

Also excluded from *BACPAC I* are certain changes in (1) specification and process (e.g., virus or adventitious agent removal process) associated with the use of raw materials, starting materials, and intermediates derived from natural sources (e.g., plants, bovine serum) or biotechnology (e.g., enzymes, monoclonal antibody reagents) used in the synthetic and/or semisynthetic process, and (2) source material (e.g., plants, microorganisms) of substances derived from natural sources that are the intermediates that begin the synthetic part of a semisynthetic process.

[4] Changes to the final intermediate and manufacturing changes after the final intermediate will be covered in a forthcoming BACPAC II guidance. Also note the limited exceptions that follow for specification and process changes relating to the use of raw materials and starting materials derived from natural sources or biotechnology.

Until the CVM guidance entitled *Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA* is finalized, applicants with questions about related issues are encouraged to contact CVM for advice.[5]

The following changes are excluded from *BACPAC I*:

- Any specification change for a raw material, starting material, or intermediate derived from a biotechnology process
- Changes related to testing for viruses or adventitious agents: (1) relaxing an acceptance criterion, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure previously described
- Changes in virus or adventitious agent removal or inactivation methods
- Changes in source material, cell line, or supplier of raw materials, starting materials, or intermediates derived from a biotechnology process
- Changes in source material (e.g., plant species, geographic location of plant harvesting, microorganism) or supplier of substances derived from natural sources that are the intermediates that begin the synthetic part of a semisynthetic process[6]

This guidance does not comment on or otherwise affect compliance or inspection documentation that has been defined by the Office of Compliance or FDA's Office of Regulatory Affairs.

In general, an applicant should use the following sources of information, in the listed order, for guidance on recommended reporting categories for postapproval changes that are within the scope of this guidance. *BACPAC I*, which provides the most specific guidance, should be the first source of information.

1. *BACPAC I* (except as specified above for changes relating to naturally sourced or biotechnology derived materials)

2. 21 CFR 514.8 (when the final rule publishes)[7]

Applicants can contact the appropriate chemistry review teams for guidance on postapproval changes not addressed in these information sources.

[5] A notice of availability of a draft version of this guidance was published in the *Federal Register* on October 1, 1999 (64 FR 53393).

[6] This exclusion from *BACPAC I* is intended to focus on those substances derived from natural sources that are the intermediates that begin the synthetic part of a semisynthetic process. The recommendations in *BACPAC I* can be used for widely available (i.e., used more than just to produce pharmaceuticals) starting materials derived from natural sources, such as glucose or tartaric acid, that may be used in a synthetic process.

[7] A proposed rule was published in the *Federal Register* on October 1, 1999 (64 FR 53281).

III. GENERAL CONSIDERATIONS

Any modification to the method of manufacture of a drug substance carries some risk of causing adverse impact, either in the physical properties of the drug substance or in the level or nature of impurities present. The risk of adverse change is generally acknowledged to be greater when a modification occurs near the end of a drug substance manufacturing process rather than the beginning. Also, certain kinds of modifications (e.g., equipment or site changes) are viewed as less likely to result in adverse change than others (e.g., changes in the synthetic route). However, there are no simple rules for determining how much risk is associated with any particular modification. This guidance is limited to changes made up to and including the final intermediate because these early modifications are generally viewed as less likely to have an adverse impact on the drug substance and, consequently, on the drug product. The final intermediate was chosen as the break point in this attempt to categorize risk because (1) it is typically the most well characterized material in the synthetic scheme, except for the drug substance itself, and (2) physical properties of the drug substance usually will not be affected by changes made up to that point.

The responsibility for reporting changes of the type described in this guidance can lie with a single party or with several parties, depending on whether the drug substance synthesis is described in an application or in one or more master files. If the holder of a master file makes a *BACPAC I* change, a description of the change should be submitted to the master file and all persons authorized to reference the master file who are affected by the change should be notified by the master file holder that the change has been made. The notification should include reference to the section of this guidance under which the change is made and all pertinent information to ensure the quality of the drug product. For example, when the holder of a master file makes a site change for an intermediate other than the final intermediate, the change should be described in an amendment to the master file, and the drug product applicant should file information describing the change in the next annual report (i.e., notification). The data to support the site change can be provided in either the master file amendment or in the annual report to the drug product application.

IV. ASSESSMENT OF CHANGE

A holder of an approved application must ***assess the effects of the change*** before distributing a drug product made with a manufacturing change (section 506A(b) of the Act). A central tenet of this guidance is that a given change in the drug substance manufacturing process can be adequately assessed by comparing pre- and postchange materials and demonstrating that the postchange material is equivalent to the prechange material (i.e., of the same or better quality, as described below). When equivalence cannot be demonstrated, applicants should submit a prior approval supplement and should consider appropriate tests for qualification of impurities, demonstration of bioequivalence, and assessment of stability. This document does not call for the submission of stability data or routine stability commitments. However, the stability of some drug products can be affected by small changes in impurities (e.g., increases in the trace levels of heavy metals). For drug products with a potential for stability problems, the first production

batch of drug product made with postchange drug substance should be included in the applicant's stability testing program.

Two major factors for determining equivalence in the drug substance are the ***impurity profile*** and physical properties. For the purposes of this guidance, only these factors will be discussed. However, other factors that can be important in individual cases should be evaluated to demonstrate equivalence. For example, if the drug substance is defined as a mixture of active isomers or analogs, the ratios after the change should be within the stated ***acceptance criteria***, or if not stated, within the upper and lower statistical limits[8] of ***historical data***. There should be no structural changes to the final intermediate or to the drug substance, as supported by structural analysis data when appropriate.

A. Equivalence of Impurity Profiles

The impact of manufacturing modifications on the impurity profile is evaluated by determining levels of existing impurities and new impurities. It is important to determine the stage in the manufacturing process at which impurities should be evaluated and to establish the adequacy of the analytical procedures used for this purpose. Levels of residual solvents and inorganic substances should also be considered during evaluation of the impurity profile.

Ideally, impurities should be evaluated in ***isolated intermediates*** immediately following the process step in which the manufacturing modification is made. If it can be shown that the impurity profile of an isolated intermediate following the modified step is equivalent (as defined below), the impurity profile of the drug substance will be considered unaffected by the modification. If equivalence cannot be demonstrated at the isolated intermediate immediately following the change, the impurity search can be extended to the next downstream intermediate and the evaluation process repeated until the final intermediate is reached. The Agency recognizes that it may not always be possible to establish equivalence prior to or at the final intermediate. For example, adequate analytical procedures may not be available, cannot be developed, or, in some cases, historical data may not exist. When it is not feasible to evaluate impurities in intermediates, or when equivalence cannot be demonstrated at these stages, the testing can be carried out on the drug substance itself. Equivalence can be demonstrated on any single intermediate or on the drug substance. Equivalence should not be established by combining results from multiple intermediates.

The analytical procedures used to evaluate the change should be adequate for quantitating both existing and new impurities at the recommended levels. Development of new analytical procedures may be called for. When new analytical procedures are developed for this purpose, a summary of validation data should be provided. The same analytical procedure should be used when comparing impurity levels in pre- and postmodification batches.

The level of impurities should be assessed by comparing three consecutive postmodification batches to the historical data from three or more consecutive representative premodification

[8] See information on statistical limits included in the definition of ***historical data*** in the glossary.

batches. For the purposes of *BACPAC I*, representative premodification batches are production scale batches of drug substance that meet all acceptance criteria in the specification, or production scale batches of an intermediate that have been successfully used in a subsequent process. The assessment of impurities should normally be carried out soon after manufacture. However, retained samples can be used for the comparison, provided there is no trend toward the level of any impurity increasing over time.

The impurity profile will be considered equivalent after a given change if three consecutive postmodification batches of either an isolated intermediate or the drug substance are evaluated and the test data for each batch demonstrate that:

- For evaluation at an intermediate, no new impurity is observed above 0.1% (or above 0.2% in an intermediate with only veterinary use).

For evaluation at the drug substance, no new impurity is observed above the ***qualification threshold*** of impurities as described in the Veterinary International Conference on Harmonisation (VICH) guidance *GL10 Impurities in New Veterinary Drug Substances*.[9]

- Each existing impurity is within its stated limit or, if not stated, is at or below the upper statistical limit of historical data.

- ***Total impurities*** are within the stated limit or, if not stated, are at or below the upper statistical limit of historical data.

- Each existing residual solvent is within its stated limit or, if not stated, is at or below the upper statistical limit of historical data.

- New residual solvents, in either an intermediate or the drug substance, are at or below the levels recommended[10] in the VICH guidance *GL18 Impurities: Residual Solvents*, when finalized.[11]

Additional principles regarding equivalence of impurity profiles are outlined below.

[9] Although these criteria (i.e., 0.1%, 0.2%, ***qualification threshold***) are based on ICH guidances that are intended for registration applications of new drug substances, they are considered appropriate for the purpose of evaluating the equivalence of impurity profiles under *BACPAC I*.

[10] Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. This should be considered when proposing limits for new residual solvents in the drug substance.

[11] A notice of availability of the September 1999 draft version of this guidance was published in the *Federal Register* on October 12, 1999 (64 FR 55296). Until this guidance is finalized, applicants with questions about levels of new residual solvents are encouraged to contact CVM for advice.

- Equivalence of the impurity profile can be established by testing any isolated intermediate following the change, including the final intermediate or the drug substance. Equivalence should not be established by combining results from multiple intermediates.

- ***In situ intermediates*** are generally not appropriate for demonstrating equivalence.

- The batches of the intermediate or drug substance used for testing should be synthesized using exclusively the material that has been subjected to the change(s) (i.e., without blending with prechange material).

- When a manufacturing change is made to an outsourced intermediate, either the vendor or the customer can establish equivalence. However, in addition to assessing equivalence of the impurity profile, release testing by the vendor or acceptance testing by the customer, as appropriate, should be conducted.

- Changes can be evaluated using data from ***pilot scale*** batches. If equivalence is demonstrated by using pilot batches, the first production batch should also be evaluated for equivalence. The production batch equivalence data should be kept on file at the manufacturing site.

If equivalence cannot be demonstrated on the production batch, this would be considered evidence of an adverse effect on the identity, strength, quality, purity, and/or potency of the drug product, and the change should not be implemented (i.e., the drug product affected by the change should not be distributed). An applicant still wishing to institute such a change can contact the appropriate chemistry review teams for guidance on any additional information that should be provided in support of the change and reporting of the change.

- Additional purification procedures (or repetition of an existing procedure on a routine basis) to achieve equivalence with prechange material after the final intermediate are not covered under *BACPAC I*. However, modified purification procedures prior to the final intermediate can be submitted under *BACPAC I* (see section V.C for process changes and section V.D for multiple changes).

B. Equivalence of Physical Properties

In general, physical properties of the drug substance are not likely to be affected by changes made before the final intermediate because most synthetic schemes involve dissolution of the crude drug substance in a suitable solvent before the drug substance is isolated by crystallization or precipitation. This ***final solution step***, and not a preceding step, usually determines the physical properties of the drug substance. Generally, the only way changes before the final intermediate can affect the physical properties of the drug substance is by carryover of new impurities or higher levels of existing impurities into the final solution step. Although minor differences in the impurity profile at this stage are unlikely to cause physical property modifications to the drug substance, the possibility of such changes in physical properties should be considered. Consequently, physical properties of the drug substance, when they are relevant to finished dosage form performance, should be evaluated unless equivalence of the impurity

profile can be demonstrated prior to the final solution step (e.g., on the crude drug substance or an earlier intermediate).

Generally, only two physical properties of the drug substance, morphic form[12] and particle size, are considered critical for evaluation of equivalence. However, other physical properties can be important in individual cases. The physical properties of the drug substance will be considered equivalent after a given change if three consecutive postmodification batches of the finished drug substance are compared to three or more consecutive representative premodification batches and the test data for each batch demonstrate:

- Conformance to established acceptance criteria for morphic form or, where acceptance criteria do not exist, the isolation of the same form or mixture of forms within the range of historical data

- Conformance to historical particle size distribution profile

The BACPAC I Decision Tree (Attachment A) incorporates the approaches described above for the evaluation of impurity profiles and physical properties and is a general guide for the assessment of changes.

V. TYPES OF CHANGE

A. Site, Scale, and Equipment Changes

The manufacturing site, scale of manufacture, and manufacturing equipment changes discussed in this section do not include any modifications to the synthetic pathway (i.e., the same starting materials, intermediates, solvents, and reagents are involved). Adjustments in operating conditions (e.g., temperature, pressure) should be limited to those that accommodate new equipment. Under these constraints, the changes in this category should not usually give rise to different impurity profiles for either the intermediates following the change or the drug substance.

1. Site Changes

Site changes include changes in location of the site of manufacture of intermediates, including the final intermediate, for both company-owned and contract manufacturing facilities. Site changes can involve the addition of new contract manufacturing facilities or the relocation of manufacturing facilities approved in the referenced application(s). Transfer of an existing manufacturing step to a facility approved for other manufacturing steps should be considered a site change.

Changes to a different manufacturing site should be reported. Changes within the ***same manufacturing site*** need not be submitted to the Agency, and equivalence testing as

[12] For purposes of this guidance, morphic form also includes hydrates, solvates, and amorphous materials.

described in this document need not be carried out.[13] Changes in supplier of starting materials need not be submitted to the Agency except for those situations described in section I or when a firm has made a commitment to the Agency to do so.

The new site should have similar environmental controls (e.g., temperature, humidity, cross contamination). Manufacturing facilities should operate in accordance with the principles of current good manufacturing practice.

Test documentation (submitted as amendments to master files and/or in annual reports or supplements to the applications, as appropriate) should include:

- The name and address of the new facility
- A concise description of the manufacturing steps being transferred, a summary of any variation in equipment or operating conditions, and a statement that the synthetic pathway is identical at the new site
- Evaluation of the impurity profile and physical properties. This evaluation should include:

  – A report on changes in impurities with a description of analytical procedures
  – Data on three consecutive batches made at the new site
  – Historical data for comparison
  – A description of the source of the historical data.

A summary of validation data should be provided for any new analytical procedures and also for existing procedures if their use is being extended beyond their original purpose.

If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is necessary.

If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, applicants still wishing to make the change should submit a prior approval supplement. When equivalence is not established, applicants should consider conducting an assessment of the effect of the change on the safety and effectiveness of the drug product (e.g., qualification of impurities, bioequivalence studies). The additional data that should be submitted will depend on the individual case, and the appropriate chemistry teams can be contacted for guidance.

[13] Here and in several other places in *BACPAC I,* it is stated that a change need not be submitted to the Agency, and/or equivalence testing as defined in *BACPAC I* need not be conducted. These statements do not relieve the responsible party from the obligation to have compliance or inspection documentation, which has been defined by the Office of Compliance or FDA's Office of Regulatory Affairs, available on site, nor does it relieve a holder of an approved application from assessing the effects of the change before distributing a drug product made with a manufacturing change (506A(b) of the Act). In the rare instance there is evidence that such a change results in nonequivalence of production batches, the drug product affected by the change should not be placed into distribution (see section IV.A under additional principles – bullet 5).

2. Reporting Category:

- Annual Report if the site change does not involve the final intermediate
- Supplement :Changes Being Effected if the site change involves the final intermediate

3. Scale Changes

Scale changes include increases and decreases in the batch size of intermediates, including the final intermediate, beyond those approved in the original application. No attempt is made to classify scale changes according to the magnitude of the change. Scale changes need not be submitted to the Agency.

4. Equipment Changes

A change to new equipment need not be submitted to the Agency, even where equipment is specified in the approved application.

B. Specification Changes

Specification changes for release of an intermediate for further processing, raw materials (e.g., solvents and reagents), and starting materials are covered in this section. Changes to controls of critical steps (e.g., tests for monitoring reaction progress or for control of reaction events) are also covered in this section. Changes to operating conditions are covered under Manufacturing Changes (section V.C).

Specification changes for the final intermediate are not included in this guidance, nor are certain specification changes for raw materials, starting materials, and intermediates derived from natural sources or biotechnology (see section I).

1. Specification Changes Made to Comply with Compendial Changes

Test documentation (submitted in amendments to master files and/or in annual reports to the applications, as appropriate) should include:

- A description of the change
- Updated specifications

Reporting Category:

- Annual Report.

2. Specification Changes That Provide Greater Assurance of Quality

Examples:

- Tightening of acceptance criteria
- Replacing an existing analytical procedure with an improved procedure
- Revised specifications associated exclusively with improved analytical procedures

Test documentation (submitted as amendments to master files and/or in annual reports to the applications, as appropriate) should include:

- Rationale for the proposed change and a brief description of any new analytical procedures, including a discussion of improvements over existing procedures.
- Updated specifications.

Reporting Category:

- Annual Report.

3. Other Specification Changes

Examples:

- Relaxing acceptance criteria
- Deleting a test
- Replacing an existing analytical procedure with a new procedure that does not qualify as an improvement
- Revised specifications associated with changes in supplier/grade of starting materials, reagents, or solvents

Generally, if there is a specification change that falls under this category, the effect of the change on the impurity profile of a later intermediate or on the impurity profile and/or physical properties of the drug substance should be evaluated. For example, if the stereochemistry at a position in an intermediate is induced through the use of a chiral reagent, a change in the acceptance criterion for the enantiomeric purity of the reagent from NLT 95% to NLT 90% should be evaluated. The evaluation should be conducted using material that challenges the specification change. For example, if an assay acceptance criterion for a starting material has been relaxed from a 98-102% range to a 90-102% range, the equivalence of an intermediate or drug substance should be demonstrated for batches made using starting material with an assay value near the new lower limit (i.e., 90%).

Some specification changes that fall within the scope of section V.B.3 would clearly not affect the quality of downstream intermediates or the drug substance and therefore no evaluation of equivalence would be needed. Examples include:

- Elimination of a redundant test (e.g., deletion of a boiling point test for a solvent where a chromatographic assay test is routinely performed)

- Elimination of a test that is no longer necessary (e.g., testing for an impurity that is no longer present due to a change in the supplier of a starting material)

- Inconsequential quality changes (e.g., change in the concentration of a reagent which would subsequently be diluted prior to use)

The common factor in these examples is that the ability to assess the chemical purity of the material is not being negatively altered by the change. Evaluation is not needed for such changes.

Test documentation (submitted as amendments to master files and/or in annual reports or supplements to the applications, as appropriate) should include

- Rationale for the proposed change and a brief description of any new analytical procedures
- Evaluation of the impurity profile and physical properties, if appropriate (see above). This evaluation should include:

  – A report on changes in impurities with a description of analytical procedures
  – Data on three consecutive batches made using material that justifies the revised specifications
  – Historical data for comparison
  – A description of the source of the historical data

  A summary of validation data should be provided for any new analytical procedures and also for existing procedures if their use is being extended beyond their original purpose.

  If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is necessary.

  If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, applicants still wishing to make the change should submit a prior approval supplement. When equivalence is not established, applicants should consider conducting an assessment of the effect of the change on the safety and effectiveness of the drug product (e.g., qualification of impurities, bioequivalence studies). The additional data that should be submitted will depend on the individual case, and the appropriate chemistry teams can be contacted for guidance.

  - Rationale for not providing an evaluation of equivalence, if applicable
  - Certificates of Analysis for raw materials and batch release data for intermediates, as appropriate

- Updated specifications

Reporting Category:

- Annual Report if an evaluation of the effect of the change on impurity profile and/or physical properties is not necessary
- Supplement: Changes Being Effected if the effect of the change on impurity profile and/or physical properties should be demonstrated

C. Manufacturing Process Changes

This category encompasses a wide range of process-related changes. New specifications may be called for when different solvents, reagents, starting materials, or intermediates are involved (see also section V.B, Specification Changes). Process changes that result in the formation of a different final intermediate are outside the scope of this guidance. Also, certain process changes for raw materials, starting materials, and intermediates derived from natural sources or biotechnology are not included in this guidance (see section I).

1. Changes That Do Not Involve New Starting Materials[14] or Intermediates

Examples include the following types of changes that might be made in one or more steps of the synthetic process, purification processes, or reprocessing operations:

- Changes in unit operations (e.g., addition, deletion, change in the order, repetition of an existing unit operation on a routine basis)
- Addition or deletion of raw materials (e.g., solvents, reagents) or ancillary materials (e.g., resins, processing aids)
- Changes in solvent composition (other than for an analytical procedure, which would be covered under Specification Changes)
- Operating conditions (e.g., temperature, pH, reagent stoichiometry, time)[15]

Documentation of equivalence is recommended for most, but not all, cases. For example, if the amount of charcoal used in a process is increased, equivalence testing may not be warranted. However, if the amount of charcoal is decreased, there is the possibility of an increase in impurities; therefore, equivalence testing should be performed. If applicants/DMF holders have questions on whether equivalence testing should be conducted to support a change, the appropriate chemistry review teams can be consulted.

Test documentation (submitted as amendments to master files and/or in annual reports or supplements to the applications, as appropriate) should include:

[14] Changes in a supplier of starting materials need not be submitted to the Agency except for those situations described in section I or when a firm has made a commitment to the Agency to do so.

[15] Changes to operating conditions that are scale- or equipment-related or are within established or validated ranges need not be reported.

- Description of change
- Specifications for new reagents and solvents and Certificates of Analysis from the suppliers, if applicable
- Evaluation of the impurity profile and physical properties. This evaluation should include:

  – A report on changes in impurities with a description of analytical procedures
  – Data on three consecutive batches made using material produced by the changed process
  – Historical data for comparison
  – A description of the source of the historical data

A summary of validation data should be provided for any new analytical procedures and also for existing procedures if their use is being extended beyond their original purpose.

If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is necessary.

When a new solvent is introduced into the synthetic process, the possibility of carryover into the drug substance should be assessed. Tests and acceptance criteria should be established, as appropriate. See section IV.A for additional guidance on evaluating equivalence when new residual solvents are present in an intermediate or the drug substance.

If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, applicants still wishing to make the change should submit a prior approval supplement. When equivalence is not established, applicants should consider conducting an assessment of the effect of the change on the safety and effectiveness of the drug product (e.g., qualification of impurities, bioequivalence studies). The additional data that should be submitted will depend on the individual case, and the appropriate chemistry teams can be contacted for guidance.

Reporting Category:

- Annual Report if equivalence is demonstrated prior to the final intermediate.

- Supplement: Changes Being Effected if equivalence is demonstrated at the final intermediate or drug substance.

2. Changes in the Route of Synthesis in One or More Steps Involving Different Starting Materials and/or Intermediates (except the final intermediate)

Test documentation (submitted as amendments to master files and/or in supplements to the applications, as appropriate) should include:

- Description of the change with details of the new synthetic procedure, the operating conditions, and controls of critical steps and intermediates
- Appropriate structural characterization data for new intermediates
- Specifications for any new starting materials and/or intermediates
- Evaluation of the impurity profile and physical properties. This evaluation should include:

  – A report on changes in impurities with a description of analytical procedures
  – Data on three consecutive batches made using material produced by the changed process
  – Historical data for comparison
  – A description of the source of the historical data.

A summary of validation data should be provided for any new analytical procedures and also for existing procedures if their use is being extended beyond their original purpose.

If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is necessary.

When a new solvent is introduced as a result of a change in the route of synthesis, the possibility of carryover into the drug substance should be assessed. Tests and acceptance criteria should be established as appropriate. See section IV.A for additional guidance on evaluating equivalence when new residual solvents are present in an intermediate or the drug substance.

If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent in the drug substance, applicants still wishing to make the change should submit a prior approval supplement. When equivalence is not established, applicants should consider conducting an assessment of the effect of the change on the safety and effectiveness of the drug product (e.g., qualification of impurities, bioequivalence studies). The additional data that should be submitted will depend on the individual case, and the appropriate chemistry teams can be contacted for guidance.

Reporting Category:

- Supplement: Changes Being Effected in 30 Days if equivalence is demonstrated prior to the final intermediate.
- Prior approval supplement if equivalence is demonstrated at the final intermediate or drug substance.

3. Changes in Which an Intermediate Is Redefined as a Starting Material

This change is often in response to an increase in commercial availability of the proposed starting material. In general, the specification for the proposed starting material should be more comprehensive (e.g., additional tests and/or tighter acceptance criteria) than for the intermediate. Redefinition of a final intermediate as a starting material is not covered under *BACPAC I.*

Test documentation (submitted as amendments to master files and/or in supplements to the applications, as appropriate) should include:

- Rationale for the proposed change and overview of current synthetic procedure
- Evidence that the intermediate complies with the current definition and/or expected characteristics of a starting material.

- A new or revised specification, a description of new or revised analytical procedures for the redefined starting material, and, if appropriate, additional tests and/or tightened acceptance criteria for downstream intermediates
- A list of sources of the redefined starting material
- A description of how the suitability of a new supplier or revised process from an existing supplier will be assessed
- Evaluation of the impurity profile and physical properties. This evaluation should include:

  – A report on changes in impurities with a description of analytical procedures
  – Data on three consecutive batches made using material that justifies the new or revised specifications
  – Historical data for comparison
  – A description of the source of the historical data.

A summary of validation data should be provided for any new analytical procedures and also for existing procedures if their use is being extended beyond their original purpose.

If equivalence of the impurity profile is established at any intermediate following the change, no testing of the drug substance is necessary.

When a new solvent is introduced into the synthetic process, the possibility of carryover into the drug substance should be assessed. Tests and acceptance criteria should be established, as appropriate. See section IV.A for additional guidance on evaluating equivalence when new residual solvents are present in an intermediate or the drug substance.

If testing is performed on the drug substance, equivalence should be established for (1) the impurity profile and (2) the physical properties, if relevant to the finished dosage form performance. If either the impurity profile or physical properties are not equivalent

in the drug substance, applicants still wishing to make the change should submit a prior approval supplement. When equivalence is not established, applicants should consider conducting an assessment of the effect of the change on the safety and effectiveness of the drug product (e.g., qualification of impurities, bioequivalence studies). The additional data that should be submitted will depend on the individual case, and the appropriate chemistry teams can be contacted for guidance.

- Certificates of Analysis from the suppliers for the proposed starting material.

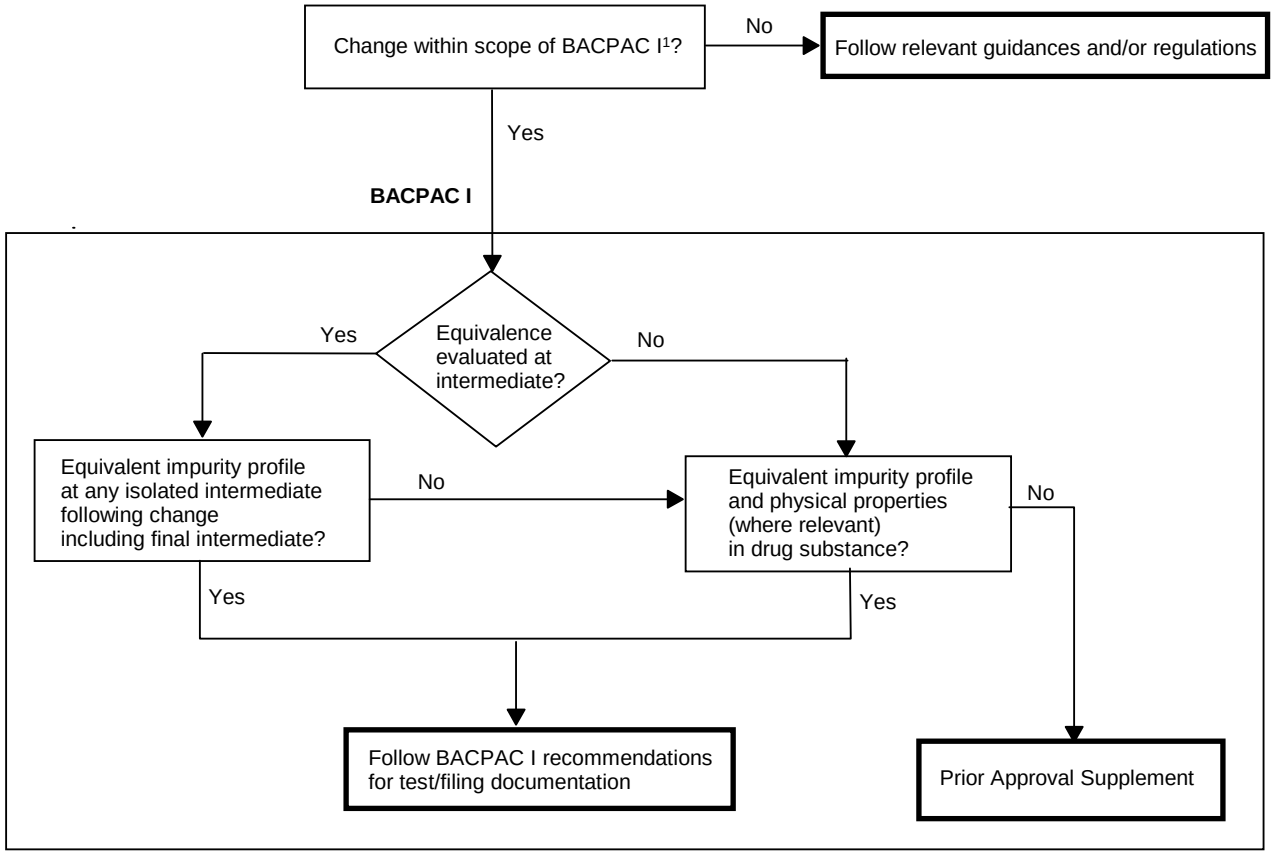
Reporting Category:

- Supplement: Changes Being Effected in 30 Days.

D. Multiple Changes

Multiple changes are those that involve various combinations of the changes described in sections V.A, B, and C. The test documentation should be the sum of the recommendations for individual changes and the reporting category should be the most restrictive. For example, a change in the route of synthesis where equivalence is demonstrated at the final intermediate (prior approval supplement) and change in the manufacturing site of the final intermediate (Supplement: Changes Being Effected) should be submitted as a prior approval supplement, and the applicant should provide the listed test documentation for both changes.

ATTACHMENT A: BACPAC I DECISION TREE



[1] Site, scale, and equipment changes involving the synthetic steps up to and including the step that produces the final intermediate; specification changes for raw materials, starting materials, and intermediates, except the final intermediate; manufacturing process changes involving the synthetic steps up to and including the step that produces the final intermediate

ATTACHMENT B: GLOSSARY

Acceptance Criteria: Numerical limits, ranges, or other criteria for the test described.

Assess the Effects of the Change: To evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

Batch: A specific quantity of an intermediate or drug substance intended to have uniform character and quality, within specified limits, and produced according to a single manufacturing order during the same cycle of manufacture. A batch can also mean a specific quantity of material or drug substance produced in one process or series of processes so that it could be expected to be homogeneous (21 CFR 210.3(b)(2)).

Drug Product: A finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)(4)).

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Final Intermediate: For the purposes of this guidance, the last compound synthesized before the reaction that produces the drug substance. The final step forming the new drug substance involves covalent bond formation; ionic bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

Final Solution Step: The solution from which the drug substance is isolated in pure form by either crystallization or precipitation. Where the purification procedure for the crude drug substance involves several crystallization or precipitation steps, final solution step refers only to the last of these steps.

Historical Data: For purposes of this guidance, data on impurities or physical attributes from three or more consecutive representative premodification batches. The upper statistical limit of an impurity should be based on the mean plus three times the standard deviation. A lower statistical limit can be similarly defined, where appropriate (e.g., the level of an active component, moisture content in a hydrate).

Impurity: Any component of the drug substance that is not the entity defined as the drug substance.

Impurity profile: A description of the identified and unidentified impurities present in a drug substance.

In Situ Intermediate: An intermediate that is not isolated. It is normally, but not necessarily, in solution (see the CDER guidance on *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, February 1987).

Intermediate: A material produced during steps of the synthesis of a drug substance that undergoes further molecular change before it becomes a drug substance.

Isolated Intermediate: An intermediate that is obtained as the product after workup of a reaction step in the synthetic scheme for the drug substance. The isolation or purification procedure should be part of the validated process. An aliquot of a reaction product that is worked up and/or purified for purposes of characterization does not constitute an isolated intermediate.

Pilot Scale: The manufacture of a bulk drug substance or intermediate on a reduced scale by processes representative of and simulating that to be applied on a larger, production manufacturing scale.

Same Manufacturing Site: Continuous or unbroken site or a set of buildings in adjacent city blocks.

Semisynthetic Drug Substance: A drug substance produced by fermentation or biotechnology and synthesis or synthesized from a precursor or structural element of natural origin (e.g., from a plant).

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in the approved application to confirm the quality of drug substances, drug products, intermediates, raw material reagents, components, in-process material, container closure systems, and other materials used in the production of the drug substance or drug product.

Starting Material: A material used in the synthesis of a drug substance that is incorporated as an important element into the structure of the drug substance. Starting materials are usually available from commercial sources. See the CDER guidance on *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (February 1987) (or current version of the drug substance guidance) for guidance on the factors that should be considered when evaluating whether a material can be classified as a starting material.

Total Impurities: The sum of all impurities observed.