Postapproval Changes to Drug Substances

Guidance for Industry

DRAFT GUIDANCE

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Postapproval Changes to Drug Substances Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to holders of approved new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), and abbreviated new animal drug applications (ANADAs) and holders of drug master files (DMFs) and veterinary master files (VMFs) who want to make a change to the drug substance manufacturing process during the drug product application's postapproval period.[2] It does not address holders of biologics license applications (BLAs) or holders of any master files cross-referenced in BLAs.

The guidance applies to synthetic drug substances and the synthetic steps involved in preparing semisynthetic drug substances. The guidance covers the following changes:

- Facility, scale, and equipment changes associated with all steps of drug substance manufacturing.
- Specification changes to starting materials, raw materials, intermediates, and the unfinished and final drug substance.
- Synthetic manufacturing process changes.
- Changes in the source of the drug substance.
- Changes to the container closure system for the drug substance.

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Center for Veterinary Medicine at the Food and Drug Administration.

[2] In general, when this guidance refers to NDAs, ANDAs, and DMFs, we are also referring to NADAs, ANADAs, and VMFs, respectively. Further, the use of the term "master files" includes both DMFs and VMFs.

This guidance does not address postapproval changes to peptides,[3] oligonucleotides, radiopharmaceuticals; or drug substances isolated from natural sources or produced by procedures involving biotechnology; or nonsynthetic steps (such as fermentation) for semisynthetic drug substances. This guidance also does not address complex active ingredients as defined in the Generic Drug User Fee Act Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022, known as the GDUFA II Commitment Letter.[4]

In general, FDA's guidance documents 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.

II. BACKGROUND

As part of the reauthorization of the Generic Drug User Fee Amendments (GDUFA II), FDA committed to issuing a guidance on postapproval changes to Type II API DMFs and submission mechanisms for ANDA holders who reference such DMFs.[5] This guidance is intended to fulfill that commitment, and describes the recommended documentation for master file holders or drug substance manufacturers, as appropriate. The guidance also outlines the recommended documentation to be submitted by the approved application holder, as well as references the appropriate pathways for such submissions.

A. Established Conditions and Reporting Categories

Under 21 CFR 314.70, 314.97, and 514.8, application holders must notify FDA about changes to conditions established in approved applications beyond the variations already provided for in their applications. FDA's regulations identify three broad reporting categories: major changes

[3] See the guidance for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs or Biologics guidance web pages at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

[4] See GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018–2022. All public documents cited in this guidance may be found on the FDA website (www.fda.gov). *Complex Product* generally includes: 1) Products with complex active ingredients (e.g., peptides, polymeric compounds, complex mixtures of active pharmaceutical ingredients (APIs), naturally sourced ingredients); complex formulations (e.g., liposomes, colloids); complex routes of delivery (e.g., locally acting drugs such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions or gels) or complex dosage forms (e.g., transdermals, metered dose inhalers, extended release injectables); 2) Complex drug-device combination products (e.g., auto injectors, metered dose inhalers); and 3) Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

[5] See GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018–2022, page 19.

(i.e., changes that require submission of a prior approval supplement (PAS));[6] moderate changes (i.e., changes that require submission of a changes being effected in 30 days (CBE-30) supplement or a changes being effected (CBE-0) supplement);[7] and changes that must be reported in an annual report.[8] The reporting category for a change is based on the potential risk 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 its safety or effectiveness. This guidance provides recommendations on the information that should be provided to CDER, CBER, or CVM to ensure continued drug substance quality and drug product quality and performance characteristics. For the most up-to-date information on reporting categories for postapproval changes, see the referenced guidances in section XII, Reporting Category.

B. Reporting Responsibilities

Where drug substance information is provided in a DMF, a letter(s) of authorization must be provided to allow the applicant to reference the DMF.[9] Any addition, change, or deletion of information in the master file must be submitted to the master file[10] in the form of an amendment. Further, the master file holder must notify each person authorized to reference the DMF of the nature of the changes,[11] and should provide as much detail as is consistent with the confidentiality agreement between the master file holder and the authorized person, so that the authorized person can determine how to report the changes in the approved application. In turn, application holders must notify FDA of each change in each condition established in an approved application, excluding the variations already provided for in the application.[12]

When drug substance information is contained in an application, rather than in a referenced DMF, such changes must be submitted to FDA in the form of a supplement to the approved application or in an annual report, whichever is appropriate for the change being made.[13]

The responsibility for reporting the types of changes described in this guidance could lie with a single party or with several parties, depending on whether the drug substance synthesis or processing is described in an application or in one or more master files. The notification to FDA 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 substance and drug product. For example, when a master file holder makes a manufacturing process change, the change should be described in an amendment to the master file, and the application holder should provide

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[6] See 21 CFR 314.70(b), 314.97(a), and 514.8(b)(2).

[7] See 21 CFR 314.70(c), 314.70(c)(3), 314.70(c)(6), and 514.8(b)(3), 514.8(b)(3)(iv).

[8] See 21 CFR 314.70(d), 314.81(b)(2), and 514.8(b)(4).

[9] 21 CFR 314.420(b). See FDA's DMF web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/UCM2007046.

[10] See 21 CFR 314.420(c).

[11] Ibid.

[12] See 21 CFR 314.70 (supplements and other changes to an approved NDA), and 21 CFR 314.97, requiring that ANDA holders comply with the requirements of 21 CFR 314.70 regarding the submission of supplemental ANDAs and other changes to an approved ANDA. For animal drugs, see 21 CFR 514.8.

[13] See 21 CFR 314.70 and 514.8.

notification of the change (citing section VIII of this guidance) in a supplement or annual report, as appropriate. The data to support the process change should be provided in an amendment to the master file or supplement to the approved NDA or ANDA when no master file is referenced.

III. GENERAL CONSIDERATIONS

A. Assessment of Risk

Any modification to drug substance manufacturing carries some risk of causing an adverse impact on quality, either in the physical properties of the drug substance or in the level or nature of impurities present, and, in some cases, to the bioequivalence or safety profile of the drug. Certain kinds of modifications (e.g., equipment or facility changes) are viewed as less likely to result in an adverse impact than others (e.g., changes in the synthetic route). However, each drug substance manufacturer will need to assess the particular modification for their drug substance to determine the risk associated with the change.[14] This guidance applies to changes made throughout the drug substance manufacturing process, i.e., from the starting material through the final drug substance. Late-stage changes in the drug substance manufacturing process are generally viewed as more likely to have an adverse impact on the quality of the drug substance and, consequently, on the drug product. Some late-stage changes should be evaluated not only by comparing pre- and post-modification drug substance, but also by comparing drug product prepared from pre- and post-modification drug substance. Finished drug product manufacturers should ensure that drug substances used in their products meet established specifications and, for compendial drug substances, meet United States Pharmacopeia (USP) standards.

Risk assessment principles are outlined in International Council for Harmonisation (ICH) guidance for industry *Q9 Quality Risk Management* (ICH Q9).[15] As noted in ICH Q9, the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk. A risk assessment should be performed by the drug substance manufacturer to assess the effect of the change, as well as by the drug product manufacturer to evaluate the risks associated with drug substance manufacturing modifications. A reduction in the number of drug substance and/or drug product batches from the recommendations provided in this guidance (see sections VI – XI) may also be acceptable if an adequate justification is provided based on the risk assessment.

The following are examples of factors to consider when conducting a risk assessment on a change to the drug substance:

- Experience of the manufacturing facility and/or personnel involved in the portion of the process that encompasses the proposed change.

[14] See 21 CFR 314.70(a)(2).

[15] ICH guidances can be found on FDA Drugs or Biologics guidance web pages at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

- Changes implemented at the same facility with experienced personnel may pose less risk than a change implemented at a new facility with inexperienced personnel or involvement of a third-party vendor.

- Complexity of the manufacturing steps involved in the change.

  - Changes implemented to homogeneous reactions using common chemistry and reaction conditions may pose less risk than a change implemented to heterogeneous reaction steps involving unusually complex or sensitive chemistry, and/or unusual equipment or reaction conditions.

- Physical and chemical stability of the material (intermediate or drug substance) involved in the change.

  - Changes implemented for a molecule that is physically and chemically stable may pose less risk than a change implemented for a molecule that degrades easily or has multiple or unstable physical forms.

- Complexity of the molecule.

  - Changes implemented for a small molecule with minimal structural or stereochemical isomerism may pose less risk than a change implemented for a large molecule with multiple structural or stereochemical isomers.

- Equivalence of the entire impurity profile.[16]

  - Batches of post-modification material that have levels of identified impurities comparable to historical data may pose less risk than batches with higher levels of identified impurities and/or new identified impurities.

  - Batches of post-modification material that have a number and level of unidentified impurities comparable to historical data may pose less risk than batches with a larger number and/or levels of unidentified impurities.

- Comparability of physical properties when they may impact drug product performance or manufacturability (typically changes made to the drug substance at or after the final solution step would be the most likely to impact physical properties).

  - Post-modification material that has the same physical properties may pose less risk than post-modification material with different physical properties (e.g., solid state form, particle size, solubility, bulk/tapped density).

[16] See section IV.A. The impurity profile includes specified identified impurities, specified unidentified impurities, unspecified impurities, and total impurities.

B. Other Relevant Guidances

This guidance aligns with existing FDA guidance, including the ICH guidances for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Questions and Answers, Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management, Q10 Pharmaceutical Quality System, Q11 Development and Manufacture of Drug Substances, Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)—Questions and Answers*, and *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*. In addition to ICH Q10, which describes key systems that help establish and maintain a state of control for process performance and product quality, the FDA guidances for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* and *Process Validation: General Principles and Practices* address the current good manufacturing practice (CGMP) requirement for change control. Change control is generally understood to be the responsibility of the quality control unit.[17] Effective change control activities are key components of any quality system. Although this guidance does not repeat the concepts and principles explained in those guidances, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and an effective pharmaceutical quality system at all stages of the manufacturing process life cycle.

IV. ASSESSMENT OF CHANGE

A. Drug Substance

After making manufacturing changes, DMF holders or drug substance manufacturers should assess the effects of the changes to the drug substance.[18] A central principle underlying this draft guidance is that a change in the drug substance manufacturing process can be adequately assessed by comparing three consecutive pilot or commercial scale batches of pre- and post-modification material to determine if the quality of the post-modification material is equivalent to or better than the quality of the pre-change material.[19,20] Evaluation of the manufacturing change may include but is not limited to:

- A comparison of impurities in pre- and post-modification intermediates, the unfinished drug substance, and/or the drug substance.
- A comparison of the drug substance's physical properties before and after modification.
- Drug substance stability data.

[17] See guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations*.

[18] See 21 CFR 314.70(a)(2).

[19] Whenever possible, changes in site, equipment, or manufacturing process (including changes in the source of the drug substance) should be evaluated using data from commercial-scale batches.

[20] Such a comparison does not in and of itself constitute full process performance qualification as described in the guidance for industry *Process Validation: General Principles and Practices*.

Some manufacturing changes can be made without this full set of data (see specific changes listed in sections VI-XI). In other cases, factors in addition to those listed above should be considered in evaluating 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[21] of historical data. There should be no structural changes to the drug substance, as supported by structural analysis data when appropriate.

1. Equivalence of Impurity Profiles

The impact of manufacturing modifications on the impurity profile (including impurities addressed by ICH M7) is evaluated by determining levels of existing 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.

If the impurity profile of an isolated material (i.e., isolated intermediate, unfinished drug substance, or drug substance) following the change is equivalent to that of pre-change material, the drug substance's impurity profile will be considered unaffected by the modification. If the manufacturing modification occurs at an upstream step before the final intermediate is produced, and equivalence cannot be demonstrated for the intermediate isolated immediately following the change, the impurity search should be extended to the next downstream intermediate. The impurity search should also be expanded to include appropriate downstream impurities that may be formed during the manufacturing process. The evaluation process should be repeated on downstream intermediates up to and including the drug substance. Equivalence should not be established by mixing pre- and post-modification materials or materials from different batches during manufacturing operations.

The analytical procedures used to evaluate the change should be adequate for quantitating both existing and new impurities. The same analytical procedure should be used when comparing impurity levels in pre- and post-modification batches. When the same method cannot be used and new drug substance analytical procedures are developed for this purpose, a summary of validation data for the new procedures should be provided.

The level of impurities should generally be assessed by comparing three consecutive, pilot or commercial-scale, post-modification batches with the historical data from three or more consecutive, representative, pre-modification batches. The assessment of impurities should normally be carried out soon after manufacture. However, retained samples can be used for the comparison, provided such samples reveal no adverse trend in the level of any impurity.

[21] For information on statistical limits, see *historical data* in the glossary.

The impurity profile will be considered equivalent if the post-modification batches of an isolated intermediate, unfinished drug substance, or drug substance are evaluated and the test data for each batch demonstrate that:

- At an intermediate level, any new impurity—including any unspecified impurity—observed above the reporting threshold is evaluated and the control strategy for it and its downstream impurities are justified.

- At the drug substance level, no new impurity is observed above the identification threshold of impurities as described in the ICH guidance for industry *Q3A Impurities in New Drug Substances*.[22]

- 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 acceptance criterion or, if not previously specified, is at or below the limit in ICH guidance for industry *Q3C Impurities: Residual Solvents* or VICH guidance for industry GL18(R), *Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients.* Limits on solvents not covered under ICH Q3C or VICH GL18(R) should be established based on safety considerations.

If a new solvent is introduced during drug substance manufacturing, the solvent's residual concentration in the drug substance should be evaluated. An appropriate test and acceptance criterion should be added to the drug substance specification; if such a test is not added, justification should be provided. Limits on new residual solvents should be established based on safety considerations and USP General Chapter <467> *Residual Solvents*, ICH Q3C, or VICH GL18(R) as applicable.[23]

Other principles regarding equivalence of impurity profiles are outlined below:

- Non-isolated materials (e.g., solutions containing either intermediates or unfinished drug substances) are generally not appropriate for demonstrating equivalence.

- When a manufacturing change is made to an outsourced operation, either the vendor or the customer can establish equivalence.

- Scale changes should be evaluated using data from pre- and post-modification material, which should be at commercial-scale.

[22]Although these criteria (i.e., identification thresholds) are based on ICH Q3A and ICH guidance for industry Q3B(R2) *Impurities in New Drug Products*, which are not intended to apply to drug substances used in existing marketed drug products, they are considered appropriate for evaluating the equivalence of impurity profiles. For animal drugs, these criteria are described in VICH guidances for industry GL10(R), *Impurities in New Veterinary Drug Substances*, and GL11(R), *Impurities in New Veterinary Medicinal Products*. VICH=International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

[23] USP references in this guidance refer to USP 40–NF 35.

- Additional purification procedures (or routine repetition of an existing procedure) to achieve equivalence with pre-change material should be fully described. Such a change in purification procedure, in combination with the change that created a need for additional purification, should be submitted together as a multiple change (see section XI).

2. Equivalence of Physical Properties

Two physical properties of the drug substance—solid state form[24] and particle size—are considered critical for evaluation when a manufacturing change is made, but other physiochemical characteristics also may be identified as critical in individual cases. The manufacturing changes most likely to affect the physical properties of a drug substance are those that involve the final solution step or processing operations that fall after the final solution step. Examples include changes to the following:

- Process for the final precipitation of the drug substance.
- Operations in which a drug substance is slurried in a solvent in which it is partly soluble.
- How a drug substance is isolated from a suspension.
- How a drug substance is dried.
- Operations that manipulate particle size (e.g., micronization).
- Mixing operations for solids.

Changes in physical properties can also result from facility, scale, equipment, and other process changes. Testing of physical properties, when they are relevant to finished dosage form performance or manufacturability, is usually appropriate when a change is made to or after the final solution step.

When new impurities or higher levels of existing impurities are carried over into the final solution step, the physical properties can be affected. 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 should be considered when the physical properties are relevant to finished dosage form performance or manufacturability.

a. Equivalence of solid state form

Establishing equivalence with regard to the solid state form of drug substances is usually possible through testing of the drug substance. For dosage forms that fall under Category Two in Table 1 below, testing should be conducted when the manufacturing change has a moderate or high potential to adversely affect the physical properties of the drug substance.

The solid state form of the drug substance will be considered equivalent after a given change if the post-modification batches of the finished drug substance conform to established acceptance

[24] For purposes of this guidance, solid state form includes hydrates, solvates, cocrystals, polymorphic crystalline, and amorphous states.

criteria for the solid state form. If acceptance criteria do not exist, the isolation of the same form or a mixture of forms within the range of historical data (as determined from three or more consecutive, representative, pre-modification batches) will serve to demonstrate equivalence. If equivalence is demonstrated, refer to section XII. Reporting Category.

For dosage forms that fall under Category One in Table 1, testing of the solid state form is also recommended when the drug substance manufacturing change has a moderate or high potential to adversely affect the physical properties of the drug substance, and when the drug substance physical properties can have an impact on the manufacturing and performance of the drug product. For these dosage forms found in Category One of Table 1, it is usually not necessary for the solid state form to remain the same. If a new solid state form is found, the drug product manufacturer should evaluate whether it is appropriate for use in making the dosage form, and the relevant properties of the form should be reported (e.g., solubility, stability).

b. Equivalence of particle size distribution

Establishing equivalence of pre- and post-modification drug substance particle size distribution can be challenging for a number of reasons, including the influence of particle shape on different measurement techniques, incomplete knowledge about the effect of changes in particle size distribution or particle shape on specific drug substances and drug products, and the absence of standardized benchmarks for equivalence. Because of these difficulties, particle size data alone may be insufficient to establish equivalence for certain kinds of changes made to the process up to or after the production of the final intermediate. These include changes that could affect the physicochemical properties or bioavailability of the drug product and changes that could affect its content uniformity.

Three approaches to the evaluation of particle size data are possible:

1) No comparison of particle size distribution data need be performed.

2) Particle size distribution data should generally be obtained for three consecutive post-modification batches of the drug substance and compared to three or more consecutive, representative, pre-modification batches.

3) Particle size distribution data should be obtained as described in 2). In addition, the drug product should be manufactured and tested to more fully evaluate equivalence.

The approach that is most appropriate for a given change will depend on the type of dosage form the drug substance will be used to manufacture, the nature of the change in the drug substance manufacturing process, and the drug product's manufacturing method.

c. Effect of particle size on physicochemical properties or bioavailability

If, based on the risk assessment, the application holder determines that a comparison of data from both the drug substance and drug product is needed, equivalence should be demonstrated for both, and such data should be provided. If a drug product has a history of performance

problems indicative of a sensitivity to changes in particle size or shape (e.g., dissolution failures at release or during stability studies), and if the drug substance manufacturing change has a high potential to adversely affect the drug substance's particle size or shape, equivalence of the data from both the drug substance and drug product should be demonstrated.

d. Effect of particle size on content uniformity

For some drug products, a change in particle size or shape may affect the content uniformity of the drug product irrespective of the risk that its physicochemical properties or bioavailability could be affected. Content uniformity is more likely to be an issue when the drug substance makes up only a small percentage of the total formulation weight, the drug substance is formulated as a solid, and the drug product is manufactured by a process that can be sensitive to changes in particle size or shape (e.g., dry granulation). If it is likely that the dosage form's content uniformity will be affected by a change in particle size or shape, and if the drug substance manufacturing change has a high potential to adversely affect the drug substance's particle size or shape, then comparison of the data from both the drug substance and drug product should be used to evaluate the change. The drug product should meet the appropriate acceptance criteria for uniformity of dosage units as outlined in USP <905>.

e. Drug substance physical properties considerations

The following tables summarize the factors to consider in evaluating the equivalence of physical properties. The amount of data submitted by the drug product manufacturer should be commensurate with criticality and risk as outlined in Table 1. Table 1 categorizes dosage forms based on their potential to be affected by a change in the drug substance's physical properties (including particle size). Table 2 summarizes the potential for various changes to adversely affect the drug substance's physical properties.

Table 1: Relevance of Physical Properties to Dosage Form Performance

Category One: Physical Properties Are Unlikely To Be Critical	Category Two: Physical Properties May Be Critical
• Dosage forms in which the drug substance is in solution when administered • Dosage forms in which the drug substance is completely dissolved during the manufacture of the dosage form • Oral dosage forms containing a highly soluble drug substance*	• Solid oral dosage forms containing drug substances that are not highly soluble* • Oral suspensions containing drug substances that are not highly soluble* • Non-oral dosage forms in which the drug substance is a solid when administered (e.g., suspension injection, powder for inhalation, some transdermal systems) • Dosage forms whose manufacturability is affected by changes in the drug substance's physical properties (e.g., particle size, flowability, tapped density) • Suppositories in which the drug substance particles are designed to remain undissolved • Powders, sprinkles, and granules for oral use (e.g., some anti-infectives) • Powders for topical application (typically antibacterials, antifungals) • Some modified-release products

* As defined in the guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.

Table 2: Potential for Postapproval Changes To Adversely Affect the Physical Properties of a Drug Substance

Low Potential	Moderate Potential	High Potential
• Manufacturing process, equipment, scale, or facility change before the final solution step • Changes in DS* drying equipment within the same operating principle • Changes in DS isolation equipment within the same operating principle • Establishment of a reprocessing operation as part of the manufacturing process • Redefinition of a starting material with no change in the DS impurity profile	• Facility changes that include the final solution step with no significant concurrent changes in scale, equipment, or manufacturing process • Scale changes after the final solution step with no significant concurrent changes in equipment or manufacturing process • Change in DS particle size reduction equipment to equipment of the same operating principle but a different design • Changes in DS drying equipment involving a change in operating principle • Changes in DS isolation equipment involving a change in operating principle • Changes to the equipment operating parameters during or after the final solution step	• Most manufacturing process changes after the final solution step • Equipment changes after the final solution step • Changes to a new source of DS** • Change in DS particle size reduction equipment to equipment of a different operating principle and different design • Redesignation of a starting material with a change in the DS impurity profile

* DS=drug substance.

** See section XI.

B. Drug Product

1. Drug Product Manufacturing and Release Data

The manufacture of a batch of drug product using the post-modification drug substance is not always required. However, when, as a result of the change, the drug substance equivalence cannot be established, and the drug substance physical properties can affect manufacturability or performance of the drug product, application holders must assess the drug product made with the post-modification drug substance before distributing the drug product.[25] In such cases a batch of

[25] Section 506A(b) of the FD&C Act.

drug product should be manufactured to fully evaluate the effect of a change in drug substance manufacturing. The drug product batch may be of reduced size, though usually not less than 10 percent of a normal commercial-scale batch.[26] Release testing and the results of in-process testing (e.g., in-process data collected during tablet compression, blend uniformity data) should be provided for the drug product batch.

Evaluation of the manufacturing change may include, but is not limited to:

- Qualification of impurities, if appropriate.
- Manufacturing and release data for one or more batches of the drug product made with the post-modification drug substance.
- In vitro testing (e.g., dissolution, in vitro release) demonstrating the equivalence of the drug product made from the post-modification drug substance to the drug product made from the pre-modification drug substance. In some cases, in vivo bioequivalence studies may be needed.

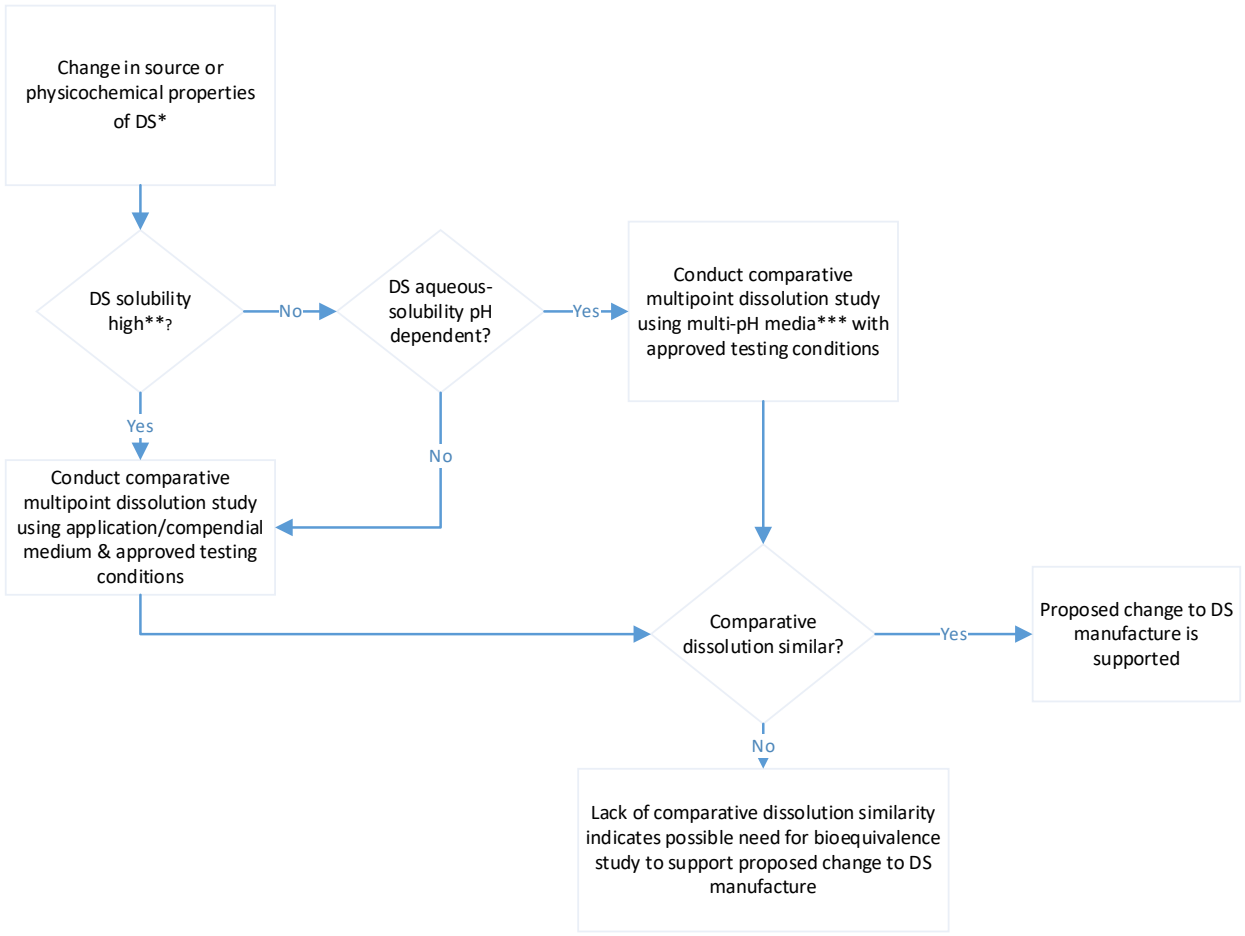
When the drug product is available in multiple strengths (including different formulations), a batch of only one strength may be manufactured. The strength chosen for evaluation should be the strength most sensitive to changes in the drug substance's physical properties. If there is no evidence of one strength being more sensitive than another, the lowest strength should be used for low-dose drug products; the highest strength should be used for all other products. A scientific rationale for the strength chosen should be provided in the submission to FDA. In the case of complex dosage forms with multiple strengths, such as modified release products, one batch per strength may be needed.

2. Drug Product In Vitro Data

If a batch of drug product is manufactured because the change in drug substance manufacturing could affect the drug product's physicochemical properties or bioavailability, the equivalence of this batch relative to the drug product made from the pre-modification drug substance should be determined using an appropriate in vitro test procedure. The type of testing that will be appropriate will vary with dosage form, route of administration, and solubility of the drug substance. Figure 1 contains a decision tree that provides further reference to additional guidances that cover this information. For dosage forms not listed in Figure 1, the appropriate chemistry and biopharmaceutics or bioequivalence teams should be consulted. Please contact the regulatory project manager or regulatory business project manager assigned to the application to facilitate this communication.

[26] See the following SUPAC guidances for industry: *Immediate Release Solid Oral Dosage Forms* (SUPAC-IR), *Modified Release Solid Oral Dosage Forms* (SUPAC-MR), and *Nonsterile Semisolid Dosage Forms* (SUPAC-SS). SUPAC=Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation.

Figure 1: Decision Tree for In-Vitro Testing of Drug Products



* DS=drug substance. For changes in drug substance used in semisolid dosage forms, refer to SUPAC-SS for test documentation.
** For definitions of low and high solubility, refer to guidance for industry *Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.
*** For multi-pH media conditions, refer to SUPAC-IR and SUPAC-MR.

3. Stability Data

The need for and amount of stability data on the drug substance and drug product will depend on the type of change and its effect on the drug substance and the drug product dosage form. For specific details, see sections VI-XI.

V. TYPES OF CHANGES AND DOCUMENTATION

The discussion of the change being reported should be accompanied by (1) a risk assessment for FDA review (see section III, General Considerations) and (2) recommended documentation as outlined in sections VI–XI below. These sections contain general recommendations for the types of data that should be submitted to support a proposed change in facility, scale, and equipment; specification; manufacturing process; starting materials and container closure system as well as general recommendations to consider when making multiple changes.

The amount of data submitted to justify a change and the type of reporting category chosen should be fully supported by the outcome of the risk assessment. The risk assessment need not be a lengthy, complex document but should show how the risk was evaluated and explain how the accompanying data demonstrate the risk was addressed or mitigated to support the selected reporting category.

Recommended drug substance documentation should be submitted as an amendment to the referenced master file, or in the drug substance section (3.2.S) in a supplement to the approved application when no master file is referenced. Recommended drug product documentation should be submitted as an annual report or supplement to the approved application depending on the risk associated with the change. For more information on reporting categories, see section XII.

VI. FACILITY, SCALE, AND EQUIPMENT CHANGES

The manufacturing facility, scale, and equipment changes discussed in this section do not include modifications to the synthetic pathway (i.e., the same starting materials, intermediates, and unfinished drug substances are involved with only minor variations in solvents and reagents). Adjustments in process parameters should be limited to those needed to accommodate new equipment.

A. Facility Changes

Facility changes involve changes in location of the site of manufacture of intermediates (including the final intermediate) and unfinished and final drug substances for both company-owned and contract manufacturing facilities. FDA must be notified when a drug substance manufacturer uses a manufacturing facility that differs from that which is specified in the approved application.[27,28] The new facility, which may be in the same or different campus, should have similar environmental controls (e.g., temperature, humidity, cross contamination) as the previous facility. The applicant or DMF holder is responsible for ensuring that any new manufacturing facility is operating in accordance with CGMP regulations. Some types of facility changes include, but are not limited to:

[27] See 21 CFR 314.70(a) and 514.8(b)(1).

[28] If this change also includes a withdrawal of a facility, the Agency should be notified which facilities are being withdrawn in the submission, and which existing or new facility will take over the withdrawn facility's operations.

- The addition of a new contract manufacturing facility for an intermediate by the drug substance manufacturer or an existing contract manufacturer.

- The addition or relocation of an in-house intermediate manufacturing facility to a different campus.

- Transfer of an additional manufacturing step to a facility already being used for other manufacturing steps.

- Change of facility for the final purification or final manipulation of the drug substance.

- Addition of an alternate manufacturing facility for the drug substance.

A change from one drug substance manufacturer to another is considered a change in the source of the drug substance, not a change of facility. If a facility change also involves changes in the manufacturing process, scale, or equipment, this should be considered a multiple change for purposes of data recommendations and reporting category (see section XII).

Since intermediates are to be manufactured in compliance with CGMP regulations, when there are multiple manufacturing facilities for an intermediate, it is recommended that the same specification and analytical procedure(s) be used at each facility to ensure equivalent quality.

For recommended documentation, see section VI.D–E.

B. Scale Changes

Scale changes refer to changes in the batch size outside the validated scale for intermediates, the unfinished drug substance, or the drug substance. This section is relevant to scale changes that use the same equipment as listed in the current master batch record (MBR), equipment that differs only in capacity from the equipment listed in the current MBR, or equipment of the same construction material, design, and operating principle as the equipment listed in the current MBR. Changes to equipment with a different construction material or design and operating principle should be considered equipment changes (see section VI.C). Adjustments in process parameters should be limited to those needed to accommodate changes in equipment. In general, scale changes before the final intermediate is produced are less likely to impact the impurity profile or physical characteristics of the final drug substance and less supporting data may be necessary to support the change. For reaction steps that are known to be sensitive to scale from previous experience (e.g., scale-up of pilot- to commercial-scale batches), the risk to product quality is higher and a greater amount of supporting data may be necessary. A change to new equipment, even if it uses the same construction material, design, and operating principle, could still affect the impurity profile or physical properties of the drug substance. For example, if the equipment is used during or after the final solution step to reduce the particle size, or to dry or isolate the drug substance (e.g., filtration), the impact on the impurity profile and physical properties of the drug substance could be greater.

Some nonproportional changes may be appropriate in executing a change in batch scale; however, changes in batch size that alter the ratio of reactants, solvents, or other materials should be evaluated as a manufacturing process change and reported as a multiple change (see section XI).

Drug substances used to establish equivalence should be manufactured with materials manufactured at the new scale. A significant change in scale that results in the use of new equipment and changes in process parameters during or after the final synthetic step should be considered a multiple change (see section XI).

For recommended documentation, see section VI.D–E.

C. Equipment Changes

This section pertains to equipment changes involving new equipment that is of a different construction material, design, or operating principle than the equipment listed in the current MBR. Changes in equipment at an existing manufacturing facility should be reported. When a contract manufacturer is used, a quality agreement[29] should ensure that changes in equipment that take place at the contract manufacturer are reported to the holder of the master file or application. A significant change in scale that results in the use of new equipment and changes in process parameters during or after the final synthetic step should be considered a multiple change (see section XI).

A change to new equipment with different construction material, design, or operating principle has the greatest potential to adversely affect the physical properties of the drug substance if the equipment is used during or after the final solution step or after subsequent processing procedures, such as:

- Isolating the drug substance (e.g., changing from filtration to centrifugation).
- Drying the drug substance (e.g., changing from vacuum tray dryer to fluid bed dryer).
- Reducing the particle size of the drug substance (e.g., changing from dry milling to fluidized bed jet milling).

For recommended documentation, see section VI.D–E.

D. Recommended Documentation for the Drug Substance in a Master File or an Approved Application

Submissions to master files and the drug substance section in an approved application should include a description of the change. More specifically:

[29] See guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*.

- For **facility changes**, provide:
  - The name, address, and contact person's information (name, phone number, email address) for the new facility, its DUNS number, and FEI number, if available.
  - A concise description of the manufacturing steps being transferred and a summary of variations in equipment or process parameters.
  - A statement that the synthetic pathway is identical at the new facility for a master file.[30]
- For **scale changes**, provide a concise description of the change, including a comparison to the current/approved process and a summary with justification for variations in equipment or process controls.
- For **equipment changes**, provide a concise description of the change, including a comparison to the equipment that is being replaced and a summary with justification for variations in process controls.

Regardless of the type of change—facility, scale, or equipment—submissions to master files and the drug substance section in an approved application should also include the following documentation:

- A comparison of the impurity profile of pre- and post-modification material to establish equivalence per the guidelines in section IV, Assessment of Change. Comparative data and certificates of analysis (COA) from at least three consecutive batches of the material manufactured after implementation of the change should be provided. The data may be generated for an intermediate or the drug substance depending on which step of the manufacturing process is being performed as a result of the change.
- If the impurity profile is demonstrated to be equivalent for an intermediate or for the drug substance:
  - An evaluation of the impurities in the pre- and post-modification material and a discussion of purging data or the results from spike/purge studies.
  - A statement of commitment to put the first commercial-scale batch of the drug substance into the stability program.
- If the equivalence of the impurity profile or physical properties is not demonstrated in the drug substance and a revised specification is proposed, see section VII, Specification Changes. In addition, provide:

[30] Type II API DMFs intended for reference in a generic drug submission that are subject to the DMF fee under GDUFA I may only contain a single drug substance manufacturing process. See guidance for industry *Completeness Assessments for Type II API DMFs Under GDUFA*, pp. 4–5 and 9 (see note for item #1).

- Three months of accelerated and 3 months of long-term stability data from three batches and a statement of commitment to continue the stability study through the retest/expiry date of the drug substance.

- A description of any new analytical procedures used during batch analysis to evaluate the presence/absence of impurities. A summary of validation data should be provided for new test methods as well as for existing methods if the use is being extended beyond their original purpose.

For changes submitted to master files, method transfer data should be provided for analytical methods that are used for routine release or stability analysis of the drug substance at the new facility.

E. Recommended Documentation for the Drug Product in an Approved Application

Submissions to approved applications should include the following documentation if not already provided in the drug substance section of the application:

- A description of the change; for **facility changes**, provide the name, address, as well as FEI and DUNS numbers for the new facility/vendor.

- The drug substance manufacturer's COA for the drug substance made after implementation of the change or drug substance made with intermediates produced after implementation of the change.

- The drug product manufacturer's COA for drug substance confirming conformance to the application-approved specification and USP, if applicable.

If equivalence of the drug substance impurity profile and physical properties is not demonstrated and the physical properties are likely to affect the drug product manufacturability or performance (see Table 1), the submission should also include the following information:

- A comparison of the COA for the pre-change drug product and the COA for the three batches post-modification drug product made with the drug substance manufactured after implementation of the change.

- Dissolution data as described in section IV, Assessment of Change.

- Analytical procedure data summary to ensure adequate quantitation and absence of co-elution of chromatographic peaks for drug substance impurities for both the drug substance and drug product methods.

- Three months of accelerated and available long-term stability data for one batch of drug product using the post-modification drug substance, and a statement of commitment to submit long-term data in an annual report.

VII. SPECIFICATION CHANGES

This section addresses specification changes to raw materials (reagents and solvents), intermediates , and drug substances (including unfinished drug substances). Changes to controls for critical steps (e.g., tests for monitoring reaction progress or for control of reaction events) are also covered.

A. Specification Changes to Raw Materials and Intermediates

Specification changes to raw materials and intermediates generally fall into one of the following categories:

- Specification changes made to comply with compendial changes, including the following:
  - USP Monograph or other compendial monographs[31] for a raw material become available.
  - USP Monograph or other compendial monographs for a raw material is updated.
- Specification changes that provide greater assurance of quality, including the following:
  - Tightening acceptance criteria.
  - Adding a new impurity control.
  - Revising an existing analytical procedure with an improved procedure.
  - Revising specifications associated exclusively with improved analytical procedures.
- Other specification changes, including the following:
  - Relaxing acceptance criteria.
  - Deleting a test.

[31] Refer to MAPP 5310.7 *Acceptability of Standards from Alternative Compendia (BP/EPJP)* for information on British Pharmacopoeia (BP), European Pharmacopoeia (EP), and Japanese Pharmacopoeia (JP). To make sure you have the most recent version of a MAPP, check the CDER MAPPs web page at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

- Replacing an existing analytical procedure with a new procedure.

- Revising specifications associated with changes in supplier/grade of reagents or solvents, including the use of recycled solvents.

Some specification changes would not be expected to affect the quality of downstream intermediates or the drug substance and therefore no evaluation of equivalence would be needed. Examples include the following:

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

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

- Minor specification changes (e.g., change in the concentration of a reagent that would subsequently be diluted before use).

The common factor in these three examples is that the ability to assess the chemical purity of the material is not adversely affected by the change and therefore evaluation is not needed.

B. Specification Changes to Drug Substances

Specification changes to the drug substance or unfinished drug substance, including additions, deletions, or changes to analytical procedures, are covered in this section.

When a USP monograph becomes available or is updated, the drug substance's specifications should be updated to comply with the compendial standards as appropriate. Deleting an existing test or changing from the routine test to a skip test should be justified. Relaxing an acceptance criterion in final drug substance specifications should be justified as appropriate. Impurities that are listed in the compendium but cannot be formed in the manufacturing process do not need to be included in the specification; however, a footnote should be added to the specification and COA of the final drug substance that states that the impurity cannot be formed. If compendial impurities are controlled upstream or as unknown impurities in the drug substance, a footnote should also be added to the specification and COA of the final drug substance.

C. Recommended Documentation for the Drug Substance in a Master File or an Approved Application

1. Documentation for Specification Changes to Raw Materials and Intermediates

For specification changes involving raw materials and intermediates, submissions to master files or to the drug substance section of approved applications should include the following documentation:

- A description of and rationale for the proposed change.

- A brief description of new or revised analytical procedures and method validation/verification, as appropriate.

- An updated COA with the revised specification for raw materials or intermediates.

- Evaluation of the impurity profile (for intermediates or drug substance) and physical properties (for drug substance), including:

  - A report on the evaluation of changes in impurities with a description of the new or revised analytical procedures, with appropriate method validation/verification.

  - COAs for the three pilot or commercial scale batches made using the material with the revised specification, historical data for comparison, and a description of the source of the historical data.

  - Data to justify changes in intermediate specifications or to illustrate when manufacturing steps have been shown to remove or reduce the level of impurities to a specified level. In this case, spike/purge study data should be submitted. The additional data that should be submitted will depend on the individual case. Contact the regulatory project manager or regulatory business project manager assigned to the application for guidance.

  - Rationale for not providing an evaluation of intermediate or drug substance equivalence, if appropriate.

If impurity equivalence is demonstrated in an intermediate or in the drug substance, the submission should also include a commitment to put, at a minimum, the first commercial-scale batch of drug substance into the stability program.

If impurity equivalence is not demonstrated in an intermediate or at the drug substance, the submission should also include 3 months of accelerated and 3 months of long-term stability data from three batches. A commitment to continue the stability study through the retest/expiry date of the drug substance should also be included.

2. Documentation for Specification Changes to Drug Substances

For specification changes involving drug substances, submissions to master files and the drug substance section of approved applications should include the following documentation:

- A description of and rationale for the proposed specification change.

- A brief description of new or revised analytical procedures and method validation/verification package, as appropriate.

- If the original analytical procedures are changed to compendial methods for assay and/or related substances, the method verification for the compendial methods should be provided. If an impurity is included in the original specification but not in the compendial impurity profile, it should be demonstrated that this impurity is controlled appropriately. A method validation report showing that the analytical procedure is appropriate for the noncompendial impurity should be provided.

- If in-house methods are used for assay and/or related substances, method equivalency should be established between the in-house and compendial methods. All compendial-specified impurities should be included in the method equivalency study or justify its exclusion, if appropriate.

- If a test is deleted or changed from a routine test to a skip test, the rationale for the proposed change, historical data, and a description of the source of the historical data.

- An updated COA with a revised drug substance specification.

- Justification for new or revised acceptance criteria with supporting data.

- Evaluation of physical properties, if appropriate.

- If such changes involve stability-indicating tests or methods, stability data using the new specification to support the retest/expiry period of the drug substance.

D. Recommended Documentation for the Drug Product in an Approved Application

This information would be submitted by the applicant only if the specification change requires the submission of a supplement or inclusion in an annual report.

1. Documentation for Specification Changes to Raw Materials and Intermediates

For specification changes involving raw materials and intermediates, submissions for applications should include the following documentation:

- A general description of the specification change.

- The drug substance manufacturer's COA for the drug substance made with the intermediate that was manufactured in accordance with the proposed specification change, if available.

2. Documentation for Specification Changes to Drug Substances

For specification changes involving drug substances, submissions for applications should include the following documentation:

- A description of the specification changes.

- The drug substance manufacturer's COA for the drug substance tested according to the proposed specification changes.

- An updated COA from the drug product manufacturer for the drug substance using the revised specification.

- Method description and transfer report for a drug substance manufacturer's analytical procedure adopted by the drug product manufacturer.

- The updated drug product specification and COAs, if the new or revised drug substance acceptance criteria impacts the drug product specification.

VIII. MANUFACTURING PROCESS CHANGES

This category encompasses a wide range of process-related changes, such as a change in the route of synthesis or an addition of a reprocessing procedure. Changes to the manufacturing process at or after the final solution step are considered to have a high potential to adversely affect the impurity profile and physical properties of the drug substance.

New specifications may be needed when new solvents, reagents, starting materials, or intermediates are involved in a change to the manufacturing process. (See also section VII). When the process changes involve concurrent facility, scale, or equipment changes (e.g., changing the method of isolating the drug substance from filtration to centrifugation, changing from tray to fluid bed drying), the changes are considered a multiple change (see section XI).

A. Changes That Do Not Involve the Route of Synthesis

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

- Changes in unit operations (e.g., addition, deletion, change in the order, or 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 is covered in section VII, Specification Changes).

- Changes to process parameters (e.g., temperature, pH, reagent stoichiometry, time). See section VI for changes to operating conditions that are scale or equipment related.

Documentation of equivalence is recommended for most, but not all, cases. For example, if the amount of charcoal used in a process increases, equivalence testing may not be warranted. However, if the amount of charcoal decreases, there is the possibility of an increase in impurities; therefore, equivalence testing should be performed.

B. Changes in Route of Synthesis in One or More Steps

In general, changes in route of synthesis are considered to have a moderate to high potential to adversely affect the impurity profile of the drug substance. The manufacturing process should be validated using the new route of synthesis. Impurity carryover studies and spike/purge studies should be conducted as appropriate. Control of mutagenic impurities in or expected to be in the final drug substance should be evaluated according to ICH M7 (section 4.1).

C. Establishing a Reprocessing Procedure as Part of the Established Manufacturing Process

Reprocessing is not considered a routine event. If frequent reprocessing is expected, the procedures should be included as part of the established manufacturing process described in an application. If an application is approved without reprocessing procedures in the manufacturing process, the procedures can be added postapproval as an amendment to the DMF or as a supplement to the NDA or ANDA. Establishing a reprocessing operation as part of the manufacturing process has a low potential to adversely affect the physical properties of the drug substance. This category does not cover the addition of new steps beyond the established manufacturing process, which is considered reworking. Reworking increases the potential to affect the drug substance properties and needs more evaluation and testing according to ICH Q7.

D. Recommended Documentation for the Drug Substance in a Master File or an Approved Application

For changes involving the manufacturing process, submissions to master files and the drug substance section of approved applications should include the following documentation:

- A description of and rationale for the proposed change.

- Specifications for new materials (e.g., starting materials, reagents, solvents, intermediates) as well as representative COAs. If new specifications are necessary in conjunction with a process change, this would be considered a multiple change (see section XI).

- Executed batch records should be provided for master files referenced in support of an ANDA application.

- Evaluation of the impurity profile (for intermediates or drug substance) and physical properties (for drug substance), including:

- A comparison of the impurity profile of pre- and post-modification material to establish equivalence as described in section IV, Assessment of Change. Historical data for comparison may be submitted, if applicable, along with a description of the source of the historical data. Data and COAs from at least three consecutive batches of the material manufactured using the alternate manufacturing process should be provided. These data may be for intermediates or drug substances depending on which part of the manufacturing process is being modified.

- A description of new or revised analytical procedures that are used for the intermediate or drug substance analysis to evaluate the presence or absence of impurities. If the analytical procedure is used for drug substance testing, a summary of validation/verification data should be provided for new or revised methods and for existing methods if their use is being extended beyond their original purpose.

- If an intermediate specification change is a result of the process change that introduces the use of a new reagent, solvent, catalyst, or raw material, and such change will not result in a change in drug substance specification, data to justify test exclusion for new impurities as the result of the change.

- Carryover studies that were conducted to justify upstream control of impurities should be repeated if applicable to the portion of the process being changed.

If the impurity profile is demonstrated to be equivalent in an intermediate or in the drug substance, the submission should include:

- An evaluation of the impurities in the pre- and post-modification material and a discussion of purging data or the results from spike/purge studies.

- A commitment to put the first commercial-scale batch of the drug substance into the stability program.

If impurity profile equivalence is not demonstrated in an intermediate or in the drug substance and a revised or new in-process control or specification is proposed, see section VII, Specification Changes.

If the drug substance impurity profile or physical properties are not equivalent, then 3 months of accelerated and 3 months of long-term stability data from three batches should be provided in the submission. A commitment to continue the stability study through the retest/expiry date of the drug substance should also be included.

If the changes involve the route of synthesis, the submission should contain additional information, which includes but is not limited to:

- A detailed description of the new synthetic procedures, including the operating conditions, controls of critical steps, and intermediates.

- For master files, a summary of the process validation batch data for the new synthetic procedure, including in-process controls, intermediate, and drug substance analysis, if the process validation activities have been conducted.

E. Recommended Documentation for the Drug Product in an Approved Application

For changes involving the manufacturing process, submissions for applications should include the following documentation:

- The drug substance manufacturer's COA for the drug substance made post-modification or the drug substance made with intermediates produced after implementation of the change.

- The drug product manufacturer's COA for the drug substance confirming conformance to the application-approved specification and USP, if applicable.

In addition, if the drug substance impurity profile and physical properties equivalence are not demonstrated and the physical properties are likely to influence the drug product manufacturability or performance (see Table 1), the submission should include the following:

- COAs for the pre-change drug product compared to the COAs for three batches of post-modification drug product made with the drug substance manufactured using the alternate manufacturing process.

- Dissolution data as described in section IV, Assessment of Change.

- Analytical methods data summary to ensure adequate quantitation and absence of co-elution of chromatographic peaks for drug substance impurities for both the drug substance and drug product methods.

- Three months of accelerated and available long-term stability data for one batch of the drug product using the post-modification drug substance and a commitment to submit long-term data in an annual report.

IX. STARTING MATERIAL CHANGES

With the introduction of the API starting material, good manufacturing practice as described in ICH Q7 apply.[32,33] Changes in vendor of the starting material may have a potential to adversely

[32] However, there is an expectation that an appropriate level of controls suitable for the production of the API starting material should be applied. See guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Questions and Answers.*

[33] See guidance for industry *169 Drug Substance Chemistry, Manufacturing, and Controls Information* available at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm.

affect a drug substance's impurity profile depending on the starting material and its proximity to the drug substance. Changes to the route of synthesis or manufacturing process of the starting material that result in changes to the starting material specification could have a higher level of risk.

The drug substance manufacturer is responsible for managing changes to the manufacturing process upstream of the starting material under its pharmaceutical quality system and for selecting and qualifying additional vendors of the starting material (ICH Q11 Q&A 5.15 and ICH Q7 Q&A 12.3). If there are changes to the vendor, the updated vendor list should be reported in the DMF and/or application. The specifications and analytical procedures used at all sites should ensure the same degree of quality, regardless of vendor, manufacturing process, or site of use. The designation of a proposed starting material should be justified per the ICH Q11 general principles for selection of starting materials.

A. Recommended Documentation for the Drug Substance in a Master File or an Approved Application

For changes involving the starting material, submissions to master files and the drug substance section of approved applications should include the following documentation:

- The name, address, and contact person's information (name, phone number, email address) for the new facility/vendor.
- In-house and vendor COAs for the starting material, if applicable.
- Additional documentation may be needed for a change in the synthetic route of a starting material designated at a late stage in the manufacture of a drug substance.

Redesignated Starting Materials

The guidance ICH *Q11 Development and Manufacture of Drug Substances – Questions and Answers* states that, "Generally, it is anticipated that API starting materials that have already been accepted by regulatory authorities (e.g., for use in authorized medicinal products) would not need to be re-justified against the ICH Q11 general principles or the recommendations included in this Q&A document, unless significant changes are made to the manufacturing processes and controls." For FDA, this is understood to mean significant changes to the manufacturing process and controls are those that are made between the introduction of the starting material and the finished drug substance (e.g., when many unit operations that remove impurities are deleted from the manufacturing process after introduction of the starting material). In such a situation, ICH Q11, ICH Q11Q&A, and ICH Q7 should be consulted.

There is a potential relationship between the risk for adverse impact to drug substance quality and the number of synthetic steps that occur between introduction of the starting material and the end of drug substance synthesis. Factors such as the formation, fate, and purge of impurities near the end of the synthetic pathway increase the risk for adverse impact to the drug substance quality. If a starting material is re-designated such that the number of steps from the end of the

manufacturing process is reduced, the carryover of impurities into the drug substance is more likely. FDA and the approved drug application holder(s) referenced in the master file should be informed of the changes, and comparative batch analysis data for the drug substance should be provided.

If the changes involve a re-designation of the starting material, the submission should contain at a minimum the following information (not an exhaustive list) in addition to the documentation described in section IX.A.:

- The rationale for re-designating the starting material addressing ICH Q11 principles.
- The list of sources of the re-designated starting material and the full name and address for each source.
- For non-commodity chemicals, the complete manufacturing process information from each source, including the complete synthetic scheme and a brief process description (such as when there is a new starting material specification). Reagents and solvents used in the starting material process should be clearly indicated in these documents.
- Updated specifications for the re-designated starting material, which include controls for impurities and residual solvents. Justification and a discussion of the control strategy for solvents and possible impurities should be included. Information from each source regarding whether a class 1 solvent as described in ICH Q3C has been used or may be present because of the manufacturing process should also be included.
- A description of analytical procedures for the re-designated starting material.
- The vendor's COAs from each source of starting material.
- Starting material COAs for the re-designated starting material generated by the drug substance manufacturer using material obtained from each source.
- When multiple sources are used, a comparison of batch data for re-designated starting material generated from each source.
- Comparative batch analysis data for downstream isolated materials, either the intermediate or the drug substance.

B. Recommended Documentation for the Drug Product in an Approved Application

For changes in the vendor or manufacturing process of the starting material, no information need be submitted by the applicant, unless the change triggers other changes addressed in this guidance.

For redesignation of the starting material, the applicant should submit the drug substance manufacturer's COA for the drug substance manufactured with the new or changed starting material.

X. CONTAINER CLOSURE SYSTEM CHANGES

Please see the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics*.[34]

XI. MULTIPLE CHANGES

Multiple changes are those that involve various combinations of the changes described in this guidance. This includes changing to a new source of drug substance, which brings with it a change in facility, and any number of changes in the manufacturing process, potentially including an entirely different route of synthesis. The applicant should submit the drug substance information as outlined in the Quality section of the CTD for the new drug substance source.[35] Even if there is significant technology sharing or a common source of technology (e.g., if two firms manufacture the drug substance via the same licensed process), significant differences may exist in facilities, controls, and standard operating procedures. A change to a new source of the drug substance is considered to have a high potential to have an adverse effect on the drug substance's impurity profile and physical properties. A new source of drug substance should be supported by submission of three pilot or commercial scale batches of drug substance. Twelve months of long-term and 6 months accelerated stability data for the drug substance should be provided. If less than 12 months data are available at the time of submission, additional data should be provided for review prior to approval. At least one batch of pilot or commercial scale drug product should be manufactured; however, depending on the extent of drug product understanding and complexity of the dosage form, up to three batches of drug product may be requested. A minimum of 3 months long-term and 3 months accelerated drug product stability data should be provided in the submission.

The recommended documentation for multiple changes should be the sum of the recommendations for individual changes and the reporting category should be the most restrictive of the categories recommended for the individual changes.

XII. REPORTING CATEGORY

For manufacturing site, equipment, and process changes pertaining to non-commercially available starting materials, drug substance intermediates, final intermediates, and drug substance, the potential for an adverse effect to the drug product depends on the extent of changes to the impurity profile and physical properties of the post-modification drug substance and the type of dosage form it is used in. Therefore, the recommended reporting categories may differ depending on these factors.

For guidance on reporting categories and examples, use the following sources of information, in the listed order, for postapproval changes:

[34] For the purpose of post-approval changes to the container/closure system of drug substances, the Container Closure Guidance also applies to animal drugs.

[35] See ICH guidance for industry *M4Q: The CTD — Quality*.

1. 21 CFR 314.70, 21 CFR 314.81, or 21 CFR 514.8, as appropriate.

2. This guidance, which provides the most specific recommendations for the particular drug substance manufacturing process change at issue.

3. The guidance for industry *Changes to an Approved NDA or ANDA* or *Chemistry, Manufacturing, and Controls Changes to an Approved NADA or ANADA*, as appropriate.

4. The guidance for industry *Changes to an Approved NDA or ANDA Questions and Answers.*

5. The guidance for industry *CMC Postapproval Manufacturing Changes to Be Documented in Annual Reports*.

6. The draft guidance for industry *Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products*.[36]

See appendix B for additional examples of changes not included in the above guidances.

If you have a question regarding a DMF,[37] NDA, or ANDA for which you are the master file or application holder, please contact the regulatory project manager or regulatory business project manager assigned to the application.

XIII. GLOSSARY

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

Batch: "[A] specific quantity of [an intermediate or drug substance] that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture" (21 CFR 210.3(b)(2)). A batch may 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.

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)).

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" (§ 314.3(b)).

[36] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[37] See footnote 9.

Final Intermediate: In reference to synthetic and semisynthetic drug substances, the last compound synthesized before the chemical reaction that produces the molecule or ion responsible for the physiological or pharmacological action of the drug substance. The chemical reaction that transforms the final intermediate into a form of the drug substance involves more than a change in salt form (including a salt with hydrogen or coordination bonds) or other noncovalent derivatives (such as complex chelates or clathrates).

Final Solution Step: The solution from which the drug substance is isolated in pure form.

Historical Data: For purposes of this guidance, data on impurities or physical attributes from three or more consecutive representative pre-modification 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 (ICH Q3A or VICH GL10(R)).

Impurity Profile: A description of the identified and unidentified impurities present in a drug substance (ICH Q3A or VICH GL10(R)) or drug product (ICH Q3B(R2) or VICH GL11(R)).

Intermediate:

- For synthetic drug substances, a material produced during steps of the synthesis of a drug substance that undergoes further molecular change or purification before it becomes a drug substance. Intermediates may or may not be isolated (ICH Q7 and ICH Q3A or VICH GL10(R)).

- For drug substances derived from a biological source, a material produced during the manufacturing process of a drug substance that undergoes further purification or molecular modification before it becomes a drug substance.

Isolated Intermediate: An intermediate that is obtained 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 or purified for purposes of characterization does not constitute an isolated intermediate.

Method Validation: The process of proving that an analytical test procedure is suitable for its intended use.

Operating Parameters: Conditions that can be adjusted to control the manufacturing process (e.g., temperature, pressure, pH, time, mixing speed).

Particle Size Distribution: A measurement of the relative proportion of particles in a sample as a function of size.

Person: Includes individual, partnership, corporation, and association. (Section 201(e) of the FD&C Act).

Physical Properties: Attributes such as physical state, melting point, boiling point, solubility, hygroscopicity, color, density, refractive index, partition coefficient, crystal shape, solid state form, and particle size distribution.

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

Polymorphism: The occurrence of different crystalline forms of the same drug substance (ICH Q3A or VICH GL10(R)).

Process Validation: Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality characteristics.

Representative Pre-modification Batches: Commercial-scale batches of a drug substance or commercial-scale batches of an intermediate or unfinished drug substance that have been successfully used to produce the drug substance.

Same Manufacturing Facility: Unbroken site or set of buildings in adjacent city blocks.

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

Single Drug Substance Manufacturing Process: The same starting materials and intermediates with minor variations being allowed in solvents and raw materials as long as the type of chemical transformation in each step is unchanged. For example, palladium/carbon could be used at one facility while platinum/carbon could be used at another. However, substitution of lithium aluminum hydride at a facility would not be permissible as the chemical mechanism for that transformation would be different and could generate a different impurity profile for the drug substance.

Solid State Forms: Different crystalline forms of the same drug substance. These can include solvation or hydration products (also known as pseudo-polymorphs) and amorphous forms (ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* or VICH guidance for industry GL39, *Specifications: Test Procedures And Acceptance Criteria For New Veterinary Drug Substances And New Medicinal Products: Chemical Substances;* and ICH Q3A or VICH GL10(R)).

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including the container closure

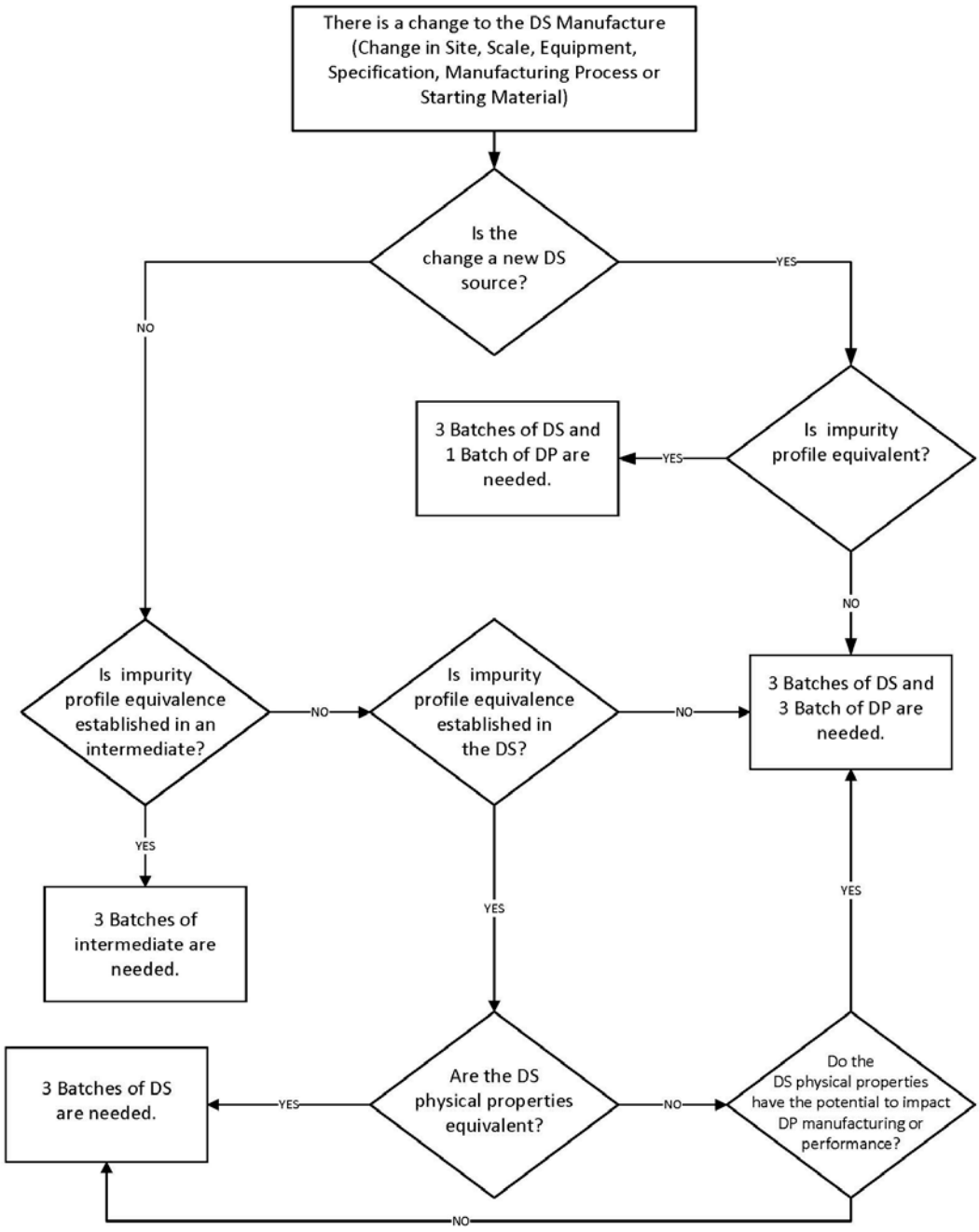
system and in-process materials. According to ICH Q6A, a specification includes the list of tests, reference to analytical procedures, and acceptance criteria.

Starting Material: A material used in the synthesis of a drug substance that is incorporated as an element into the structure of an intermediate or of the drug substance. A starting material can be an article of commerce, a material purchased from one or more supplies under contract or commercial agreement, or produced in-house. The chemical and physical properties, structure, and impurity profile of a starting material are well-defined in the chemical literature.

Total Impurities: The sum of all impurities observed above the reporting limit.

Unfinished Drug Substance: A form of the drug substance that is further processed to produce the form of the drug substance used to manufacture the drug product. The unfinished drug substance can differ from the drug substance. For example, the solid state form of the unfinished drug substance could be different from the finished drug substance or the counter ion for the unfinished drug substance could be different from the actual drug substance. Although firms have sometimes referred to such materials as intermediates, these materials do not meet the definitions of *intermediate* and *final intermediate* provided in this guidance for synthetic or semisynthetic drug substances.

APPENDIX A. CHANGES TO DRUG SUBSTANCE MANUFACTURE



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* DS=drug substance. Changes involve changes in facility, scale, equipment, specification, manufacturing process, or starting materials.

**DP=drug product.

APPENDIX B: REPORTING CATEGORIES FOR ADDITIONAL EXAMPLES OF CHANGES

Reporting Categories for Facility Changes

Change Being Effected in 30 Days (CBE-30) Supplement

- A change to an alternate manufacturing facility within the same master file or within the same corporate ownership (without a change in the existing manufacturing process), such as a facility transfer for the last step in the manufacturing of the drug substance.

- A change in the manufacturing facility for a drug substance intermediate, including the final intermediate (CBE-30 at a minimum; see next entry for exception).

Prior Approval Supplement (PAS)

- A change in the facility for manufacture of a drug substance intermediate, including the final intermediate, if the change in manufacturing involves a new route of synthesis or the proposed facility does not have an acceptable CGMP inspectional history.

Reporting Categories for Equipment Changes

CBE-30

- A change from one type of drying process to another (e.g., oven tray to fluid bed or rotary cone vacuum dryer) for a thermally stable intermediate or drug substance.

- A change in drying process of the isolated wet crude final intermediate to using an agitated nutsche filter dryer in place of a fluid bed drier or a centrifugation for a thermally stable compound.

- Changes to equipment used for particle size reduction in drug substances that are not affected by particle size if the circumstances of the changes are such that an evaluation of the drug substance's physical properties is not required.

PAS

- Changes in drug substance drying equipment to equipment of a different operating principle and different design for a non-thermally stable intermediate or drug substance.

- Changes to equipment used for particle size reduction to equipment of a different operating principle and different design.

- Equipment changes made during or after the final solution step.

Reporting Category for Manufacturing Process Changes

PAS

- Changes that result in a change to the route of synthesis for the final intermediate or drug substance.

- Redefinition of a starting material resulting in a change in the impurity profile of the drug substance.

- Changes made after the formation of the final intermediate (e.g., new recrystallization solvent).

- Changes in the synthesis with adverse effect to the impurity profile (e.g., introduction of genotoxic impurity).