

# Postapproval Changes to Drug Substances Guidance for Industry

## ***DRAFT GUIDANCE***

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Veterinary Medicine (CVM)**

**September 2018  
Pharmaceutical Quality/CMC**

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# Postapproval Changes to Drug Substances Guidance for Industry

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**TABLE OF CONTENTS**

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND .....</b>	<b>2</b>
<b>A.</b>	<b>Established Conditions and Reporting Categories .....</b>	<b>2</b>
<b>B.</b>	<b>Reporting Responsibilities.....</b>	<b>3</b>
<b>III.</b>	<b>GENERAL CONSIDERATIONS .....</b>	<b>4</b>
<b>A.</b>	<b>Assessment of Risk.....</b>	<b>4</b>
<b>B.</b>	<b>Other Relevant Guidances .....</b>	<b>6</b>
<b>IV.</b>	<b>ASSESSMENT OF CHANGE .....</b>	<b>6</b>
<b>A.</b>	<b>Drug Substance .....</b>	<b>6</b>
1.	<i>Equivalence of Impurity Profiles .....</i>	<i>7</i>
2.	<i>Equivalence of Physical Properties.....</i>	<i>9</i>
<b>B.</b>	<b>Drug Product.....</b>	<b>13</b>
1.	<i>Drug Product Manufacturing and Release Data.....</i>	<i>13</i>
2.	<i>Drug Product In Vitro Data.....</i>	<i>14</i>
3.	<i>Stability Data .....</i>	<i>15</i>
<b>V.</b>	<b>TYPES OF CHANGES AND DOCUMENTATION.....</b>	<b>16</b>
<b>VI.</b>	<b>FACILITY, SCALE, AND EQUIPMENT CHANGES .....</b>	<b>16</b>
<b>A.</b>	<b>Facility Changes.....</b>	<b>16</b>
<b>B.</b>	<b>Scale Changes.....</b>	<b>17</b>
<b>C.</b>	<b>Equipment Changes.....</b>	<b>18</b>
<b>D.</b>	<b>Recommended Documentation for the Drug Substance in a Master File or an Approved Application .....</b>	<b>18</b>
<b>E.</b>	<b>Recommended Documentation for the Drug Product in an Approved Application.....</b>	<b>20</b>
<b>VII.</b>	<b>SPECIFICATION CHANGES.....</b>	<b>21</b>
<b>A.</b>	<b>Specification Changes to Raw Materials and Intermediates .....</b>	<b>21</b>
<b>B.</b>	<b>Specification Changes to Drug Substances.....</b>	<b>22</b>
<b>C.</b>	<b>Recommended Documentation for the Drug Substance in a Master File or an Approved Application .....</b>	<b>22</b>
1.	<i>Documentation for Specification Changes to Raw Materials and Intermediates.....</i>	<i>22</i>
2.	<i>Documentation for Specification Changes to Drug Substances .....</i>	<i>23</i>
<b>D.</b>	<b>Recommended Documentation for the Drug Product in an Approved Application.....</b>	<b>24</b>
1.	<i>Documentation for Specification Changes to Raw Materials and Intermediates.....</i>	<i>24</i>

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2. Documentation for Specification Changes to Drug Substances .....	24
<b>VIII. MANUFACTURING PROCESS CHANGES.....</b>	<b>25</b>
A. Changes That Do Not Involve the Route of Synthesis .....	25
B. Changes in Route of Synthesis in One or More Steps .....	26
C. Establishing a Reprocessing Procedure as Part of the Established Manufacturing Process	26
D. Recommended Documentation for the Drug Substance in a Master File or an Approved Application .....	26
E. Recommended Documentation for the Drug Product in an Approved Application.....	28
<b>IX. STARTING MATERIAL CHANGES.....</b>	<b>28</b>
A. Recommended Documentation for the Drug Substance in a Master File or an Approved Application .....	29
B. Recommended Documentation for the Drug Product in an Approved Application.....	30
<b>X. CONTAINER CLOSURE SYSTEM CHANGES.....</b>	<b>31</b>
<b>XI. MULTIPLE CHANGES .....</b>	<b>31</b>
<b>XII. REPORTING CATEGORY .....</b>	<b>31</b>
<b>XIII. GLOSSARY.....</b>	<b>32</b>
<b>APPENDIX A. CHANGES TO DRUG SUBSTANCE MANUFACTURE.....</b>	<b>36</b>
<b>APPENDIX B: REPORTING CATEGORIES FOR ADDITIONAL EXAMPLES OF CHANGES.....</b>	<b>37</b>

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**Postapproval Changes to Drug Substances  
Guidance for Industry<sup>1</sup>**

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.<sup>2</sup> 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.

<sup>1</sup> 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.

<sup>2</sup> 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.

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39 This guidance does not address postapproval changes to peptides,<sup>3</sup> oligonucleotides,  
40 radiopharmaceuticals; or drug substances isolated from natural sources or produced by  
41 procedures involving biotechnology; or nonsynthetic steps (such as fermentation) for  
42 semisynthetic drug substances. This guidance also does not address complex active ingredients  
43 as defined in the Generic Drug User Fee Act Reauthorization Performance Goals and Program  
44 Enhancements Fiscal Years 2018-2022, known as the GDUFA II Commitment Letter.<sup>4</sup>  
45

46 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
47 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
48 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
49 the word *should* in Agency guidances means that something is suggested or recommended, but  
50 not required.  
51

## **52**

### **53 II. BACKGROUND**

54

55 As part of the reauthorization of the Generic Drug User Fee Amendments (GDUFA II), FDA  
56 committed to issuing a guidance on postapproval changes to Type II API DMFs and submission  
57 mechanisms for ANDA holders who reference such DMFs.<sup>5</sup> This guidance is intended to fulfill that  
58 commitment, and describes the recommended documentation for master file holders or drug  
59 substance manufacturers, as appropriate. The guidance also outlines the recommended  
60 documentation to be submitted by the approved application holder, as well as references the  
61 appropriate pathways for such submissions.  
62

#### **63 A. Established Conditions and Reporting Categories**

64

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

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<sup>3</sup> 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>.

<sup>4</sup>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](http://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.

<sup>5</sup> See GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018–2022, page 19.

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68 (i.e., changes that require submission of a prior approval supplement (PAS));<sup>6</sup> moderate changes  
69 (i.e., changes that require submission of a changes being effected in 30 days (CBE-30)  
70 supplement or a changes being effected (CBE-0) supplement);<sup>7</sup> and changes that must be  
71 reported in an annual report.<sup>8</sup> The reporting category for a change is based on the potential risk  
72 for the change to have an adverse effect on the identity, strength, quality, purity, or potency of  
73 the drug product as these factors may relate to its safety or effectiveness. This guidance provides  
74 recommendations on the information that should be provided to CDER, CBER, or CVM to  
75 ensure continued drug substance quality and drug product quality and performance  
76 characteristics. For the most up-to-date information on reporting categories for postapproval  
77 changes, see the referenced guidances in section XII, Reporting Category.

### **B. Reporting Responsibilities**

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

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

95 The responsibility for reporting the types of changes described in this guidance could lie with a  
96 single party or with several parties, depending on whether the drug substance synthesis or  
97 processing is described in an application or in one or more master files. The notification to FDA  
98 should include reference to the section of this guidance under which the change is made and all  
99 pertinent information to ensure the quality of the drug substance and drug product. For example,  
100 when a master file holder makes a manufacturing process change, the change should be  
101 described in an amendment to the master file, and the application holder should provide

---

<sup>6</sup> See 21 CFR 314.70(b), 314.97(a), and 514.8(b)(2).

<sup>7</sup> See 21 CFR 314.70(c), 314.70(c)(3), 314.70(c)(6), and 514.8(b)(3), 514.8(b)(3)(iv).

<sup>8</sup> See 21 CFR 314.70(d), 314.81(b)(2), and 514.8(b)(4).

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

<sup>10</sup> See 21 CFR 314.420(c).

<sup>11</sup> Ibid.

<sup>12</sup> 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.

<sup>13</sup> See 21 CFR 314.70 and 514.8.

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102 notification of the change (citing section VIII of this guidance) in a supplement or annual report,  
103 as appropriate. The data to support the process change should be provided in an amendment to  
104 the master file or supplement to the approved NDA or ANDA when no master file is referenced.  
105

106

### 107 **III. GENERAL CONSIDERATIONS**

108

#### 109 **A. Assessment of Risk**

110

111 Any modification to drug substance manufacturing carries some risk of causing an adverse  
112 impact on quality, either in the physical properties of the drug substance or in the level or nature  
113 of impurities present, and, in some cases, to the bioequivalence or safety profile of the drug.  
114 Certain kinds of modifications (e.g., equipment or facility changes) are viewed as less likely to  
115 result in an adverse impact than others (e.g., changes in the synthetic route). However, each drug  
116 substance manufacturer will need to assess the particular modification for their drug substance to  
117 determine the risk associated with the change.<sup>14</sup> This guidance applies to changes made  
118 throughout the drug substance manufacturing process, i.e., from the starting material through the  
119 final drug substance. Late-stage changes in the drug substance manufacturing process are  
120 generally viewed as more likely to have an adverse impact on the quality of the drug substance  
121 and, consequently, on the drug product. Some late-stage changes should be evaluated not only by  
122 comparing pre- and post-modification drug substance, but also by comparing drug product  
123 prepared from pre- and post-modification drug substance. Finished drug product manufacturers  
124 should ensure that drug substances used in their products meet established specifications and, for  
125 compendial drug substances, meet United States Pharmacopeia (USP) standards.  
126

127

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

136

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

139

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

142

---

<sup>14</sup> See 21 CFR 314.70(a)(2).

<sup>15</sup> 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>.



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- 143           ○ Changes implemented at the same facility with experienced personnel may pose less  
144 risk than a change implemented at a new facility with inexperienced personnel or  
145 involvement of a third-party vendor.
- 146
- 147           ● Complexity of the manufacturing steps involved in the change.
- 148
- 149           ○ Changes implemented to homogeneous reactions using common chemistry and  
150 reaction conditions may pose less risk than a change implemented to heterogeneous  
151 reaction steps involving unusually complex or sensitive chemistry, and/or unusual  
152 equipment or reaction conditions.
- 153
- 154           ● Physical and chemical stability of the material (intermediate or drug substance) involved  
155 in the change.
- 156
- 157           ○ Changes implemented for a molecule that is physically and chemically stable may  
158 pose less risk than a change implemented for a molecule that degrades easily or has  
159 multiple or unstable physical forms.
- 160
- 161           ● Complexity of the molecule.
- 162
- 163           ○ Changes implemented for a small molecule with minimal structural or stereochemical  
164 isomerism may pose less risk than a change implemented for a large molecule with  
165 multiple structural or stereochemical isomers.
- 166
- 167           ● Equivalence of the entire impurity profile.<sup>16</sup>
- 168
- 169           ○ Batches of post-modification material that have levels of identified impurities  
170 comparable to historical data may pose less risk than batches with higher levels of  
171 identified impurities and/or new identified impurities.
- 172
- 173           ○ Batches of post-modification material that have a number and level of unidentified  
174 impurities comparable to historical data may pose less risk than batches with a larger  
175 number and/or levels of unidentified impurities.
- 176
- 177           ● Comparability of physical properties when they may impact drug product performance or  
178 manufacturability (typically changes made to the drug substance at or after the final  
179 solution step would be the most likely to impact physical properties).
- 180
- 181           ○ Post-modification material that has the same physical properties may pose less risk  
182 than post-modification material with different physical properties (e.g., solid state  
183 form, particle size, solubility, bulk/tapped density).
- 184

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<sup>16</sup> See section IV.A. The impurity profile includes specified identified impurities, specified unidentified impurities, unspecified impurities, and total impurities.

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### 185 **B. Other Relevant Guidances**

186  
187 This guidance aligns with existing FDA guidance, including the ICH guidances for industry *Q7*  
188 *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, *Q7 Good*  
189 *Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Questions and*  
190 *Answers*, *Q8(R2) Pharmaceutical Development*, *Q9 Quality Risk Management*, *Q10*  
191 *Pharmaceutical Quality System*, *Q11 Development and Manufacture of Drug Substances*, *Q11*  
192 *Development and Manufacture of Drug Substances (Chemical Entities and*  
193 *Biotechnological/Biological Entities)—Questions and Answers*, and *M7 Assessment and Control*  
194 *of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic*  
195 *Risk*. In addition to ICH Q10, which describes key systems that help establish and maintain a  
196 state of control for process performance and product quality, the FDA guidances for industry  
197 *Quality Systems Approach to Pharmaceutical CGMP Regulations* and *Process Validation:*  
198 *General Principles and Practices* address the current good manufacturing practice (CGMP)  
199 requirement for change control. Change control is generally understood to be the responsibility  
200 of the quality control unit.<sup>17</sup> Effective change control activities are key components of any  
201 quality system. Although this guidance does not repeat the concepts and principles explained in  
202 those guidances, FDA encourages the use of modern pharmaceutical development concepts,  
203 quality risk management, and an effective pharmaceutical quality system at all stages of the  
204 manufacturing process life cycle.

205

206

### 207 **IV. ASSESSMENT OF CHANGE**

208

#### 209 **A. Drug Substance**

210

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

218

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

---

<sup>17</sup> See guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations*.

<sup>18</sup> See 21 CFR 314.70(a)(2).

<sup>19</sup> 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.

<sup>20</sup> 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*.

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223  
224 Some manufacturing changes can be made without this full set of data (see specific changes  
225 listed in sections VI-XI). In other cases, factors in addition to those listed above should be  
226 considered in evaluating equivalence. For example, if the drug substance is defined as a mixture  
227 of active isomers or analogs, the ratios after the change should be within the stated acceptance  
228 criteria, or if not stated, within the upper and lower statistical limits<sup>21</sup> of historical data. There  
229 should be no structural changes to the drug substance, as supported by structural analysis data  
230 when appropriate.

231  
232 *1. Equivalence of Impurity Profiles*

233  
234 The impact of manufacturing modifications on the impurity profile (including impurities  
235 addressed by ICH M7) is evaluated by determining levels of existing and new impurities. It is  
236 important to determine the stage in the manufacturing process at which impurities should be  
237 evaluated and to establish the adequacy of the analytical procedures used for this purpose. Levels  
238 of residual solvents and inorganic substances should also be considered during evaluation of the  
239 impurity profile.

240  
241 If the impurity profile of an isolated material (i.e., isolated intermediate, unfinished drug  
242 substance, or drug substance) following the change is equivalent to that of pre-change material,  
243 the drug substance's impurity profile will be considered unaffected by the modification. If the  
244 manufacturing modification occurs at an upstream step before the final intermediate is produced,  
245 and equivalence cannot be demonstrated for the intermediate isolated immediately following the  
246 change, the impurity search should be extended to the next downstream intermediate. The  
247 impurity search should also be expanded to include appropriate downstream impurities that may  
248 be formed during the manufacturing process. The evaluation process should be repeated on  
249 downstream intermediates up to and including the drug substance. Equivalence should not be  
250 established by mixing pre- and post-modification materials or materials from different batches  
251 during manufacturing operations.

252  
253 The analytical procedures used to evaluate the change should be adequate for quantitating both  
254 existing and new impurities. The same analytical procedure should be used when comparing  
255 impurity levels in pre- and post-modification batches. When the same method cannot be used  
256 and new drug substance analytical procedures are developed for this purpose, a summary of  
257 validation data for the new procedures should be provided.

258  
259 The level of impurities should generally be assessed by comparing three consecutive, pilot or  
260 commercial-scale, post-modification batches with the historical data from three or more  
261 consecutive, representative, pre-modification batches. The assessment of impurities should  
262 normally be carried out soon after manufacture. However, retained samples can be used for the  
263 comparison, provided such samples reveal no adverse trend in the level of any impurity.

264

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<sup>21</sup> For information on statistical limits, see *historical data* in the glossary.

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

- 268
- 269 • At an intermediate level, any new impurity—including any unspecified impurity—  
270 observed above the reporting threshold is evaluated and the control strategy for it and its  
271 downstream impurities are justified.
- 272
- 273 • At the drug substance level, no new impurity is observed above the identification  
274 threshold of impurities as described in the ICH guidance for industry *Q3A Impurities in*  
275 *New Drug Substances*.<sup>22</sup>
- 276
- 277 • Total impurities are within the stated limit or, if not stated, are at or below the upper  
278 statistical limit of historical data.
- 279
- 280 • Each existing residual solvent is within its acceptance criterion or, if not previously  
281 specified, is at or below the limit in ICH guidance for industry *Q3C Impurities: Residual*  
282 *Solvents* or VICH guidance for industry GL18(R), *Impurities: Residual Solvents in New*  
283 *Veterinary Medicinal Products, Active Substances and Excipients*. Limits on solvents not  
284 covered under ICH Q3C or VICH GL18(R) should be established based on safety  
285 considerations.
- 286

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

293

294 Other principles regarding equivalence of impurity profiles are outlined below:

- 295
- 296 • Non-isolated materials (e.g., solutions containing either intermediates or unfinished drug  
297 substances) are generally not appropriate for demonstrating equivalence.
- 298
- 299 • When a manufacturing change is made to an outsourced operation, either the vendor or  
300 the customer can establish equivalence.
- 301
- 302 • Scale changes should be evaluated using data from pre- and post-modification material,  
303 which should be at commercial-scale.

---

<sup>22</sup>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.

<sup>23</sup> USP references in this guidance refer to USP 40–NF 35.

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- 304  
305 • Additional purification procedures (or routine repetition of an existing procedure) to  
306 achieve equivalence with pre-change material should be fully described. Such a change in  
307 purification procedure, in combination with the change that created a need for additional  
308 purification, should be submitted together as a multiple change (see section XI).

309  
310 2. *Equivalence of Physical Properties*

311  
312 Two physical properties of the drug substance—solid state form<sup>24</sup> and particle size—are  
313 considered critical for evaluation when a manufacturing change is made, but other  
314 physiochemical characteristics also may be identified as critical in individual cases. The  
315 manufacturing changes most likely to affect the physical properties of a drug substance are those  
316 that involve the final solution step or processing operations that fall after the final solution step.  
317 Examples include changes to the following:

- 318  
319 • Process for the final precipitation of the drug substance.  
320 • Operations in which a drug substance is slurried in a solvent in which it is partly soluble.  
321 • How a drug substance is isolated from a suspension.  
322 • How a drug substance is dried.  
323 • Operations that manipulate particle size (e.g., micronization).  
324 • Mixing operations for solids.

325  
326 Changes in physical properties can also result from facility, scale, equipment, and other process  
327 changes. Testing of physical properties, when they are relevant to finished dosage form  
328 performance or manufacturability, is usually appropriate when a change is made to or after the  
329 final solution step.

330  
331 When new impurities or higher levels of existing impurities are carried over into the final  
332 solution step, the physical properties can be affected. Although minor differences in the impurity  
333 profile at this stage are unlikely to cause physical property modifications to the drug substance,  
334 the possibility of such changes should be considered when the physical properties are relevant to  
335 finished dosage form performance or manufacturability.

336  
337 a. *Equivalence of solid state form*

338  
339 Establishing equivalence with regard to the solid state form of drug substances is usually  
340 possible through testing of the drug substance. For dosage forms that fall under Category Two in  
341 Table 1 below, testing should be conducted when the manufacturing change has a moderate or  
342 high potential to adversely affect the physical properties of the drug substance.

343  
344 The solid state form of the drug substance will be considered equivalent after a given change if  
345 the post-modification batches of the finished drug substance conform to established acceptance

---

<sup>24</sup> For purposes of this guidance, solid state form includes hydrates, solvates, cocrystals, polymorphic crystalline, and amorphous states.

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

350  
351 For dosage forms that fall under Category One in Table 1, testing of the solid state form is also  
352 recommended when the drug substance manufacturing change has a moderate or high potential  
353 to adversely affect the physical properties of the drug substance, and when the drug substance  
354 physical properties can have an impact on the manufacturing and performance of the drug  
355 product. For these dosage forms found in Category One of Table 1, it is usually not necessary for  
356 the solid state form to remain the same. If a new solid state form is found, the drug product  
357 manufacturer should evaluate whether it is appropriate for use in making the dosage form, and  
358 the relevant properties of the form should be reported (e.g., solubility, stability).

### b. Equivalence of particle size distribution

361  
362 Establishing equivalence of pre- and post-modification drug substance particle size distribution  
363 can be challenging for a number of reasons, including the influence of particle shape on different  
364 measurement techniques, incomplete knowledge about the effect of changes in particle size  
365 distribution or particle shape on specific drug substances and drug products, and the absence of  
366 standardized benchmarks for equivalence. Because of these difficulties, particle size data alone  
367 may be insufficient to establish equivalence for certain kinds of changes made to the process up  
368 to or after the production of the final intermediate. These include changes that could affect the  
369 physicochemical properties or bioavailability of the drug product and changes that could affect  
370 its content uniformity.

371  
372 Three approaches to the evaluation of particle size data are possible:

- 373  
374 1) No comparison of particle size distribution data need be performed.  
375  
376 2) Particle size distribution data should generally be obtained for three consecutive post-  
377 modification batches of the drug substance and compared to three or more consecutive,  
378 representative, pre-modification batches.  
379  
380 3) Particle size distribution data should be obtained as described in 2). In addition, the drug  
381 product should be manufactured and tested to more fully evaluate equivalence.

382  
383 The approach that is most appropriate for a given change will depend on the type of dosage form  
384 the drug substance will be used to manufacture, the nature of the change in the drug substance  
385 manufacturing process, and the drug product's manufacturing method.

### c. Effect of particle size on physicochemical properties or bioavailability

388  
389 If, based on the risk assessment, the application holder determines that a comparison of data  
390 from both the drug substance and drug product is needed, equivalence should be demonstrated  
391 for both, and such data should be provided. If a drug product has a history of performance

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*Draft — Not for Implementation*

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

396

397

### d. Effect of particle size on content uniformity

398

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

410

411

### e. Drug substance physical properties considerations

412

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

419

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420 **Table 1: Relevance of Physical Properties to Dosage Form Performance**  
421

<b>Category One: Physical Properties Are Unlikely To Be Critical</b>	<b>Category Two: Physical Properties May Be Critical</b>
<ul style="list-style-type: none"><li>• Dosage forms in which the drug substance is in solution when administered</li><li>• Dosage forms in which the drug substance is completely dissolved during the manufacture of the dosage form</li><li>• Oral dosage forms containing a highly soluble drug substance*</li></ul>	<ul style="list-style-type: none"><li>• Solid oral dosage forms containing drug substances that are not highly soluble*</li><li>• Oral suspensions containing drug substances that are not highly soluble*</li><li>• Non-oral dosage forms in which the drug substance is a solid when administered (e.g., suspension injection, powder for inhalation, some transdermal systems)</li><li>• Dosage forms whose manufacturability is affected by changes in the drug substance’s physical properties (e.g., particle size, flowability, tapped density)</li><li>• Suppositories in which the drug substance particles are designed to remain undissolved</li><li>• Powders, sprinkles, and granules for oral use (e.g., some anti-infectives)</li><li>• Powders for topical application (typically antibacterials, antifungals)</li><li>• Some modified-release products</li></ul>

\* 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*.



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422  
423 **Table 2: Potential for Postapproval Changes To Adversely Affect the Physical Properties of**  
424 **a Drug Substance**  
425

<b>Low Potential</b>	<b>Moderate Potential</b>	<b>High Potential</b>
<ul style="list-style-type: none"><li>• Manufacturing process, equipment, scale, or facility change before the final solution step</li><li>• Changes in DS* drying equipment within the same operating principle</li><li>• Changes in DS isolation equipment within the same operating principle</li><li>• Establishment of a reprocessing operation as part of the manufacturing process</li><li>• Redefinition of a starting material with no change in the DS impurity profile</li></ul>	<ul style="list-style-type: none"><li>• Facility changes that include the final solution step with no significant concurrent changes in scale, equipment, or manufacturing process</li><li>• Scale changes after the final solution step with no significant concurrent changes in equipment or manufacturing process</li><li>• Change in DS particle size reduction equipment to equipment of the same operating principle but a different design</li><li>• Changes in DS drying equipment involving a change in operating principle</li><li>• Changes in DS isolation equipment involving a change in operating principle</li><li>• Changes to the equipment operating parameters during or after the final solution step</li></ul>	<ul style="list-style-type: none"><li>• Most manufacturing process changes after the final solution step</li><li>• Equipment changes after the final solution step</li><li>• Changes to a new source of DS**</li><li>• Change in DS particle size reduction equipment to equipment of a different operating principle and different design</li><li>• Redesignation of a starting material with a change in the DS impurity profile</li></ul>

426 \* DS=drug substance.

427 \*\* See section XI.

428  
429 **B. Drug Product**

430  
431 *1. Drug Product Manufacturing and Release Data*  
432

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

<sup>25</sup> Section 506A(b) of the FD&C Act.

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

443

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

445

446 • Qualification of impurities, if appropriate.

447

448 • Manufacturing and release data for one or more batches of the drug product made with  
449 the post-modification drug substance.

450

451 • In vitro testing (e.g., dissolution, in vitro release) demonstrating the equivalence of the  
452 drug product made from the post-modification drug substance to the drug product made  
453 from the pre-modification drug substance. In some cases, in vivo bioequivalence studies  
454 may be needed.

455

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

464

### 465 2. *Drug Product In Vitro Data*

466

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

477

478

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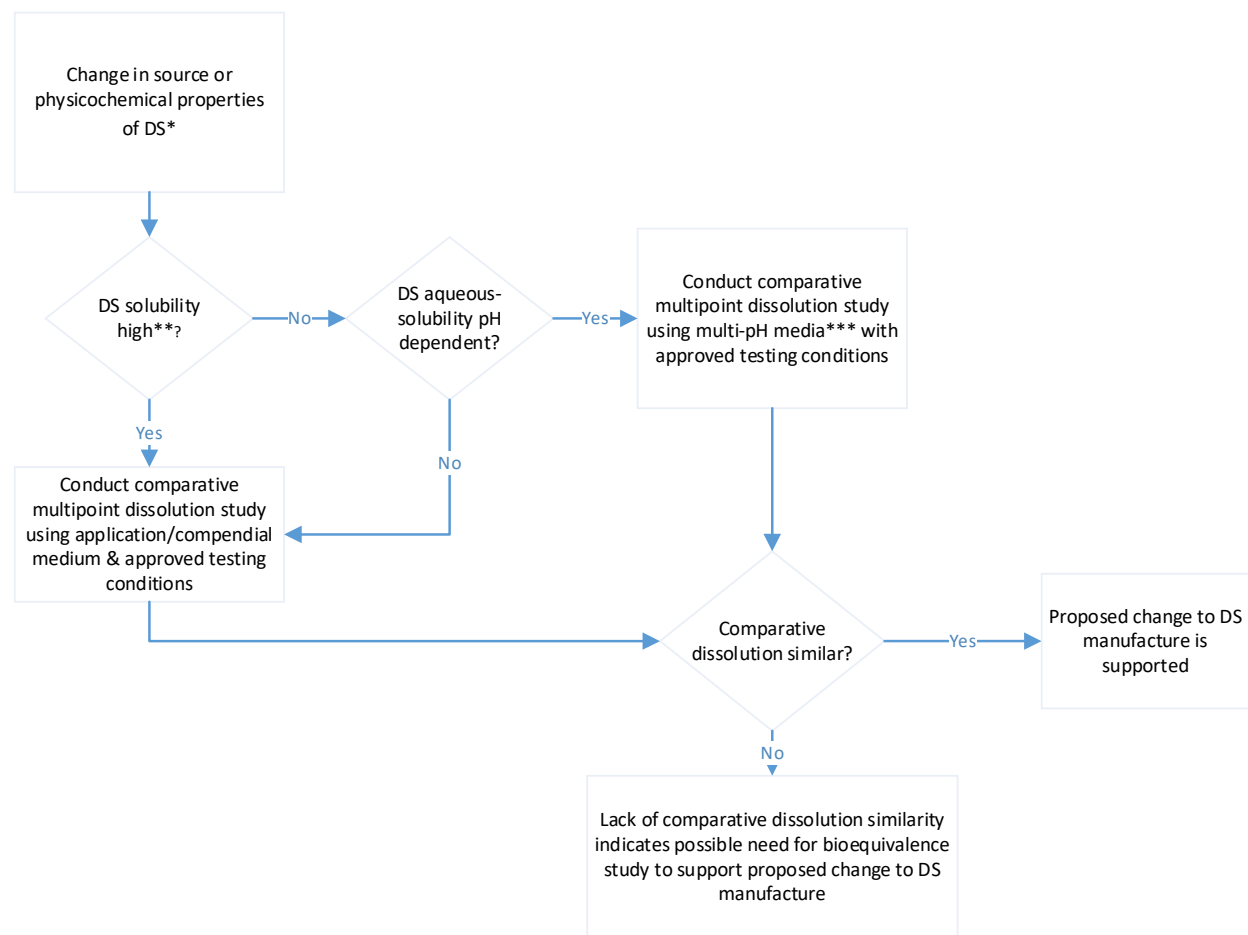
<sup>26</sup> See the following SUPAC guidances for industry: *Immediate Release Solid Oral Dosage Forms* (SUPAC-IR), *Modified Release Solid Oral Dosage Forms* (SUPAC-MR), and *Nonsterile Semisolid Dosage Forms* (SUPAC-SS). SUPAC=Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls,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

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480  
481

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



482  
483  
484

\* 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.

491

492

493

494

### 3. Stability Data

495

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.

499

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### **V. TYPES OF CHANGES AND DOCUMENTATION**

501  
502  
503 The discussion of the change being reported should be accompanied by (1) a risk assessment for  
504 FDA review (see section III, General Considerations) and (2) recommended documentation as  
505 outlined in sections VI–XI below. These sections contain general recommendations for the types  
506 of data that should be submitted to support a proposed change in facility, scale, and equipment;  
507 specification; manufacturing process; starting materials and container closure system as well as  
508 general recommendations to consider when making multiple changes.

509  
510 The amount of data submitted to justify a change and the type of reporting category chosen  
511 should be fully supported by the outcome of the risk assessment. The risk assessment need not be  
512 a lengthy, complex document but should show how the risk was evaluated and explain how the  
513 accompanying data demonstrate the risk was addressed or mitigated to support the selected  
514 reporting category.

515  
516 Recommended drug substance documentation should be submitted as an amendment to the  
517 referenced master file, or in the drug substance section (3.2.S) in a supplement to the approved  
518 application when no master file is referenced. Recommended drug product documentation should  
519 be submitted as an annual report or supplement to the approved application depending on the risk  
520 associated with the change. For more information on reporting categories, see section XII.

521

522

### **VI. FACILITY, SCALE, AND EQUIPMENT CHANGES**

523

524  
525 The manufacturing facility, scale, and equipment changes discussed in this section do not include  
526 modifications to the synthetic pathway (i.e., the same starting materials, intermediates, and  
527 unfinished drug substances are involved with only minor variations in solvents and reagents).  
528 Adjustments in process parameters should be limited to those needed to accommodate new  
529 equipment.

530

#### **A. Facility Changes**

531

532

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

542

---

<sup>27</sup> See 21 CFR 314.70(a) and 514.8(b)(1).

<sup>28</sup> 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.

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- 543 • The addition of a new contract manufacturing facility for an intermediate by the drug  
544 substance manufacturer or an existing contract manufacturer.  
545
- 546 • The addition or relocation of an in-house intermediate manufacturing facility to a  
547 different campus.  
548
- 549 • Transfer of an additional manufacturing step to a facility already being used for other  
550 manufacturing steps.  
551
- 552 • Change of facility for the final purification or final manipulation of the drug substance.  
553
- 554 • Addition of an alternate manufacturing facility for the drug substance.  
555

556 A change from one drug substance manufacturer to another is considered a change in the source  
557 of the drug substance, not a change of facility. If a facility change also involves changes in the  
558 manufacturing process, scale, or equipment, this should be considered a multiple change for  
559 purposes of data recommendations and reporting category (see section XII).  
560

561 Since intermediates are to be manufactured in compliance with CGMP regulations, when there  
562 are multiple manufacturing facilities for an intermediate, it is recommended that the same  
563 specification and analytical procedure(s) be used at each facility to ensure equivalent quality.  
564

565 For recommended documentation, see [section VI.D–E](#).  
566

### **B. Scale Changes**

567  
568  
569 Scale changes refer to changes in the batch size outside the validated scale for intermediates, the  
570 unfinished drug substance, or the drug substance. This section is relevant to scale changes that  
571 use the same equipment as listed in the current master batch record (MBR), equipment that  
572 differs only in capacity from the equipment listed in the current MBR, or equipment of the same  
573 construction material, design, and operating principle as the equipment listed in the current  
574 MBR. Changes to equipment with a different construction material or design and operating  
575 principle should be considered equipment changes (see section VI.C). Adjustments in process  
576 parameters should be limited to those needed to accommodate changes in equipment. In general,  
577 scale changes before the final intermediate is produced are less likely to impact the impurity  
578 profile or physical characteristics of the final drug substance and less supporting data may be  
579 necessary to support the change. For reaction steps that are known to be sensitive to scale from  
580 previous experience (e.g., scale-up of pilot- to commercial-scale batches), the risk to product  
581 quality is higher and a greater amount of supporting data may be necessary. A change to new  
582 equipment, even if it uses the same construction material, design, and operating principle, could  
583 still affect the impurity profile or physical properties of the drug substance. For example, if the  
584 equipment is used during or after the final solution step to reduce the particle size, or to dry or  
585 isolate the drug substance (e.g., filtration), the impact on the impurity profile and physical  
586 properties of the drug substance could be greater.  
587

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

592  
593 Drug substances used to establish equivalence should be manufactured with materials  
594 manufactured at the new scale. A significant change in scale that results in the use of new  
595 equipment and changes in process parameters during or after the final synthetic step should be  
596 considered a multiple change (see section XI).

597  
598 For recommended documentation, see [section VI.D–E](#).

599

### **C. Equipment Changes**

600  
601  
602 This section pertains to equipment changes involving new equipment that is of a different  
603 construction material, design, or operating principle than the equipment listed in the current  
604 MBR. Changes in equipment at an existing manufacturing facility should be reported. When a  
605 contract manufacturer is used, a quality agreement<sup>29</sup> should ensure that changes in equipment  
606 that take place at the contract manufacturer are reported to the holder of the master file or  
607 application. A significant change in scale that results in the use of new equipment and changes in  
608 process parameters during or after the final synthetic step should be considered a multiple change  
609 (see section XI).

610  
611 A change to new equipment with different construction material, design, or operating principle  
612 has the greatest potential to adversely affect the physical properties of the drug substance if the  
613 equipment is used during or after the final solution step or after subsequent processing  
614 procedures, such as:

- 615
- 616 • Isolating the drug substance (e.g., changing from filtration to centrifugation).
  - 617
  - 618 • Drying the drug substance (e.g., changing from vacuum tray dryer to fluid bed dryer).
  - 619
  - 620 • Reducing the particle size of the drug substance (e.g., changing from dry milling to  
621 fluidized bed jet milling).
  - 622

623 For recommended documentation, see [section VI.D–E](#).

624

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

625  
626  
627  
628 Submissions to master files and the drug substance section in an approved application should  
629 include a description of the change. More specifically:

630

---

<sup>29</sup> See guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*.

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- 631       • For **facility changes**, provide:
- 632
- 633           ○ The name, address, and contact person’s information (name, phone number, email
- 634           address) for the new facility, its DUNS number, and FEI number, if available.
- 635
- 636           ○ A concise description of the manufacturing steps being transferred and a summary
- 637           of variations in equipment or process parameters.
- 638
- 639           ○ A statement that the synthetic pathway is identical at the new facility for a master
- 640           file.<sup>30</sup>
- 641
- 642       • For **scale changes**, provide a concise description of the change, including a comparison
- 643       to the current/approved process and a summary with justification for variations in
- 644       equipment or process controls.
- 645
- 646       • For **equipment changes**, provide a concise description of the change, including a
- 647       comparison to the equipment that is being replaced and a summary with justification for
- 648       variations in process controls.
- 649

650   Regardless of the type of change—facility, scale, or equipment—submissions to master files and

651   the drug substance section in an approved application should also include the following

652   documentation:

653

- 654       • A comparison of the impurity profile of pre- and post-modification material to establish
- 655       equivalence per the guidelines in section IV, Assessment of Change. Comparative data
- 656       and certificates of analysis (COA) from at least three consecutive batches of the material
- 657       manufactured after implementation of the change should be provided. The data may be
- 658       generated for an intermediate or the drug substance depending on which step of the
- 659       manufacturing process is being performed as a result of the change.
- 660
- 661       • If the impurity profile is demonstrated to be equivalent for an intermediate or for the drug
- 662       substance:
- 663
- 664           ○ An evaluation of the impurities in the pre- and post-modification material and a
- 665           discussion of purging data or the results from spike/purge studies.
- 666
- 667           ○ A statement of commitment to put the first commercial-scale batch of the drug
- 668           substance into the stability program.
- 669
- 670       • If the equivalence of the impurity profile or physical properties is not demonstrated in the
- 671       drug substance and a revised specification is proposed, see section VII, Specification
- 672       Changes. In addition, provide:

---

<sup>30</sup> 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).

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682
- 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.

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

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

686  
687  
688  
689  
690 Submissions to approved applications should include the following documentation if not already  
691 provided in the drug substance section of the application:

- 692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702
- 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.

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

- 706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716
- 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.



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- 717 • Three months of accelerated and available long-term stability data for one batch of drug  
718 product using the post-modification drug substance, and a statement of commitment to  
719 submit long-term data in an annual report.  
720

721

722

### **VII. SPECIFICATION CHANGES**

723

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

728

#### **A. Specification Changes to Raw Materials and Intermediates**

729

730 Specification changes to raw materials and intermediates generally fall into one of the following  
731 categories:  
732

733

- 734 • Specification changes made to comply with compendial changes, including the  
735 following:
- 736 ○ USP Monograph or other compendial monographs<sup>31</sup> for a raw material become  
737 available.
  - 738 ○ USP Monograph or other compendial monographs for a raw material is updated.
  - 739
  - 740 • Specification changes that provide greater assurance of quality, including the following:
  - 741
  - 742 ○ Tightening acceptance criteria.
  - 743
  - 744 ○ Adding a new impurity control.
  - 745
  - 746 ○ Revising an existing analytical procedure with an improved procedure.
  - 747
  - 748 ○ Revising specifications associated exclusively with improved analytical procedures.
  - 749
  - 750 • Other specification changes, including the following:
  - 751
  - 752 ○ Relaxing acceptance criteria.
  - 753
  - 754 ○ Deleting a test.
  - 755
  - 756
  - 757

---

<sup>31</sup> Refer to MAPP 5310.7 *Acceptability of Standards from Alternative Compendia (BP/EP/JP)* 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>.

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- 758           ○ Replacing an existing analytical procedure with a new procedure.  
759  
760           ○ Revising specifications associated with changes in supplier/grade of reagents or  
761           solvents, including the use of recycled solvents.  
762

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

- 766
- 767           • Elimination of redundant testing (e.g., deletion of a boiling point test for a solvent if a  
768           chromatographic assay test is routinely performed).  
769
  - 770           • Elimination of testing that is no longer required (e.g., testing for an impurity that is no  
771           longer present because of a change in the supplier of a starting material).  
772
  - 773           • Minor specification changes (e.g., change in the concentration of a reagent that would  
774           subsequently be diluted before use).  
775

776 The common factor in these three examples is that the ability to assess the chemical purity of the  
777 material is not adversely affected by the change and therefore evaluation is not needed.  
778

### **B.       Specification Changes to Drug Substances**

779  
780  
781 Specification changes to the drug substance or unfinished drug substance, including additions,  
782 deletions, or changes to analytical procedures, are covered in this section.  
783

784 When a USP monograph becomes available or is updated, the drug substance's specifications  
785 should be updated to comply with the compendial standards as appropriate. Deleting an existing  
786 test or changing from the routine test to a skip test should be justified. Relaxing an acceptance  
787 criterion in final drug substance specifications should be justified as appropriate. Impurities that  
788 are listed in the compendium but cannot be formed in the manufacturing process do not need to  
789 be included in the specification; however, a footnote should be added to the specification and  
790 COA of the final drug substance that states that the impurity cannot be formed. If compendial  
791 impurities are controlled upstream or as unknown impurities in the drug substance, a footnote  
792 should also be added to the specification and COA of the final drug substance.  
793

### **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*

794  
795  
796  
797  
798  
799 For specification changes involving raw materials and intermediates, submissions to master files  
800 or to the drug substance section of approved applications should include the following  
801 documentation:

- 802
- 803           • A description of and rationale for the proposed change.

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- 827
- 828
- 829
- 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.

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

833

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

### 838

### 839 2. *Documentation for Specification Changes to Drug Substances*

### 840

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

- 843
- 844
- 845
- 846
- 847
- 848
- 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.

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- 849           ○ If the original analytical procedures are changed to compendial methods for assay  
850           and/or related substances, the method verification for the compendial methods should  
851           be provided. If an impurity is included in the original specification but not in the  
852           compendial impurity profile, it should be demonstrated that this impurity is controlled  
853           appropriately. A method validation report showing that the analytical procedure is  
854           appropriate for the noncompendial impurity should be provided.  
855
- 856           ○ If in-house methods are used for assay and/or related substances, method equivalency  
857           should be established between the in-house and compendial methods. All  
858           compendial-specified impurities should be included in the method equivalency study  
859           or justify its exclusion, if appropriate.  
860
- 861           ● If a test is deleted or changed from a routine test to a skip test, the rationale for the  
862           proposed change, historical data, and a description of the source of the historical data.  
863
  - 864           ● An updated COA with a revised drug substance specification.  
865
  - 866           ● Justification for new or revised acceptance criteria with supporting data.  
867
  - 868           ● Evaluation of physical properties, if appropriate.  
869
  - 870           ● If such changes involve stability-indicating tests or methods, stability data using the new  
871           specification to support the retest/expiry period of the drug substance.  
872

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

873  
874  
875  
876   This information would be submitted by the applicant only if the specification change requires  
877   the submission of a supplement or inclusion in an annual report.  
878

#### *1.       Documentation for Specification Changes to Raw Materials and Intermediates*

879  
880  
881   For specification changes involving raw materials and intermediates, submissions for  
882   applications should include the following documentation:  
883

- 884           ● A general description of the specification change.  
885
- 886           ● The drug substance manufacturer's COA for the drug substance made with the  
887           intermediate that was manufactured in accordance with the proposed specification  
888           change, if available.  
889

#### *2.       Documentation for Specification Changes to Drug Substances*

890  
891  
892   For specification changes involving drug substances, submissions for applications should include  
893   the following documentation:  
894

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- 895 • A description of the specification changes.  
896
- 897 • The drug substance manufacturer's COA for the drug substance tested according to the  
898 proposed specification changes.  
899
- 900 • An updated COA from the drug product manufacturer for the drug substance using the  
901 revised specification.  
902
- 903 • Method description and transfer report for a drug substance manufacturer's analytical  
904 procedure adopted by the drug product manufacturer.  
905
- 906 • The updated drug product specification and COAs, if the new or revised drug substance  
907 acceptance criteria impacts the drug product specification.  
908  
909

### **VIII. MANUFACTURING PROCESS CHANGES**

911  
912 This category encompasses a wide range of process-related changes, such as a change in the  
913 route of synthesis or an addition of a reprocessing procedure. Changes to the manufacturing  
914 process at or after the final solution step are considered to have a high potential to adversely  
915 affect the impurity profile and physical properties of the drug substance.  
916

917 New specifications may be needed when new solvents, reagents, starting materials, or  
918 intermediates are involved in a change to the manufacturing process. (See also section VII).  
919 When the process changes involve concurrent facility, scale, or equipment changes (e.g.,  
920 changing the method of isolating the drug substance from filtration to centrifugation, changing  
921 from tray to fluid bed drying), the changes are considered a multiple change (see section XI).  
922

#### **A. Changes That Do Not Involve the Route of Synthesis**

923  
924  
925 Examples include the following types of changes that might be made in one or more steps of the  
926 synthetic procedure, in purification processes, or in reprocessing operations:  
927

- 928 • Changes in unit operations (e.g., addition, deletion, change in the order, or repetition of  
929 an existing unit operation on a routine basis).  
930
- 931 • Addition or deletion of raw materials (e.g., solvents, reagents) or ancillary materials (e.g.,  
932 resins, processing aids).  
933
- 934 • Changes in solvent composition (other than for an analytical procedure, which is covered  
935 in section VII, Specification Changes).  
936
- 937 • Changes to process parameters (e.g., temperature, pH, reagent stoichiometry, time). See  
938 section VI for changes to operating conditions that are scale or equipment related.  
939

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

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

944  
945  
946 In general, changes in route of synthesis are considered to have a moderate to high potential to  
947 adversely affect the impurity profile of the drug substance. The manufacturing process should be  
948 validated using the new route of synthesis. Impurity carryover studies and spike/purge studies  
949 should be conducted as appropriate. Control of mutagenic impurities in or expected to be in the  
950 final drug substance should be evaluated according to ICH M7 (section 4.1).  
951

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

952  
953  
954  
955  
956 Reprocessing is not considered a routine event. If frequent reprocessing is expected, the  
957 procedures should be included as part of the established manufacturing process described in an  
958 application. If an application is approved without reprocessing procedures in the manufacturing  
959 process, the procedures can be added postapproval as an amendment to the DMF or as a  
960 supplement to the NDA or ANDA. Establishing a reprocessing operation as part of the  
961 manufacturing process has a low potential to adversely affect the physical properties of the drug  
962 substance. This category does not cover the addition of new steps beyond the established  
963 manufacturing process, which is considered reworking. Reworking increases the potential to  
964 affect the drug substance properties and needs more evaluation and testing according to ICH Q7.  
965

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

966  
967  
968  
969 For changes involving the manufacturing process, submissions to master files and the drug  
970 substance section of approved applications should include the following documentation:

- 971
- 972 • A description of and rationale for the proposed change.
  - 973
  - 974 • Specifications for new materials (e.g., starting materials, reagents, solvents,  
975 intermediates) as well as representative COAs. If new specifications are necessary in  
976 conjunction with a process change, this would be considered a multiple change (see  
977 section XI).
  - 978
  - 979 • Executed batch records should be provided for master files referenced in support of an  
980 ANDA application.
  - 981
  - 982 • Evaluation of the impurity profile (for intermediates or drug substance) and physical  
983 properties (for drug substance), including:  
984

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- 985           ○ A comparison of the impurity profile of pre- and post-modification material to  
986           establish equivalence as described in section IV, Assessment of Change. Historical  
987           data for comparison may be submitted, if applicable, along with a description of the  
988           source of the historical data. Data and COAs from at least three consecutive batches  
989           of the material manufactured using the alternate manufacturing process should be  
990           provided. These data may be for intermediates or drug substances depending on  
991           which part of the manufacturing process is being modified.  
992  
993           ○ A description of new or revised analytical procedures that are used for the  
994           intermediate or drug substance analysis to evaluate the presence or absence of  
995           impurities. If the analytical procedure is used for drug substance testing, a summary  
996           of validation/verification data should be provided for new or revised methods and for  
997           existing methods if their use is being extended beyond their original purpose.  
998  
999           ○ If an intermediate specification change is a result of the process change that  
1000           introduces the use of a new reagent, solvent, catalyst, or raw material, and such  
1001           change will not result in a change in drug substance specification, data to justify test  
1002           exclusion for new impurities as the result of the change.  
1003  
1004           ○ Carryover studies that were conducted to justify upstream control of impurities  
1005           should be repeated if applicable to the portion of the process being changed.  
1006

1007 If the impurity profile is demonstrated to be equivalent in an intermediate or in the drug  
1008 substance, the submission should include:

- 1009
- 1010           • An evaluation of the impurities in the pre- and post-modification material and a  
1011           discussion of purging data or the results from spike/purge studies.
  - 1012
  - 1013           • A commitment to put the first commercial-scale batch of the drug substance into the  
1014           stability program.

1015

1016 If impurity profile equivalence is not demonstrated in an intermediate or in the drug substance  
1017 and a revised or new in-process control or specification is proposed, see section VII,  
1018 Specification Changes.

1019

1020 If the drug substance impurity profile or physical properties are not equivalent, then 3 months of  
1021 accelerated and 3 months of long-term stability data from three batches should be provided in the  
1022 submission. A commitment to continue the stability study through the retest/expiry date of the  
1023 drug substance should also be included.

1024

1025 If the changes involve the route of synthesis, the submission should contain additional  
1026 information, which includes but is not limited to:

- 1027
- 1028           • A detailed description of the new synthetic procedures, including the operating  
1029           conditions, controls of critical steps, and intermediates.

1030

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- 1031       • For master files, a summary of the process validation batch data for the new synthetic  
1032 procedure, including in-process controls, intermediate, and drug substance analysis, if the  
1033 process validation activities have been conducted.

1034

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

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1038

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

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1051

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:

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## **IX. STARTING MATERIAL CHANGES**

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

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<sup>32</sup> 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*.

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



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1071 affect a drug substance’s impurity profile depending on the starting material and its proximity to  
1072 the drug substance. Changes to the route of synthesis or manufacturing process of the starting  
1073 material that result in changes to the starting material specification could have a higher level of  
1074 risk.

1075  
1076 The drug substance manufacturer is responsible for managing changes to the manufacturing  
1077 process upstream of the starting material under its pharmaceutical quality system and for  
1078 selecting and qualifying additional vendors of the starting material (ICH Q11 Q&A 5.15 and  
1079 ICH Q7 Q&A 12.3). If there are changes to the vendor, the updated vendor list should be  
1080 reported in the DMF and/or application. The specifications and analytical procedures used at all  
1081 sites should ensure the same degree of quality, regardless of vendor, manufacturing process, or  
1082 site of use. The designation of a proposed starting material should be justified per the ICH Q11  
1083 general principles for selection of starting materials.

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

1084  
1085  
1086  
1087  
1088 For changes involving the starting material, submissions to master files and the drug substance  
1089 section of approved applications should include the following documentation:

- 1090  
1091 • The name, address, and contact person’s information (name, phone number, email  
1092 address) for the new facility/vendor.
- 1093  
1094 • In-house and vendor COAs for the starting material, if applicable.
- 1095  
1096 • Additional documentation may be needed for a change in the synthetic route of a starting  
1097 material designated at a late stage in the manufacture of a drug substance.

#### *Redesignated Starting Materials*

1098  
1099  
1100  
1101 The guidance ICH *Q11 Development and Manufacture of Drug Substances – Questions and*  
1102 *Answers* states that, “Generally, it is anticipated that API starting materials that have already  
1103 been accepted by regulatory authorities (e.g., for use in authorized medicinal products) would not  
1104 need to be re-justified against the ICH Q11 general principles or the recommendations included  
1105 in this Q&A document, unless significant changes are made to the manufacturing processes and  
1106 controls.” For FDA, this is understood to mean significant changes to the manufacturing process  
1107 and controls are those that are made between the introduction of the starting material and the  
1108 finished drug substance (e.g., when many unit operations that remove impurities are deleted from  
1109 the manufacturing process after introduction of the starting material). In such a situation, ICH  
1110 Q11, ICH Q11Q&A, and ICH Q7 should be consulted.

1111  
1112 There is a potential relationship between the risk for adverse impact to drug substance quality  
1113 and the number of synthetic steps that occur between introduction of the starting material and the  
1114 end of drug substance synthesis. Factors such as the formation, fate, and purge of impurities near  
1115 the end of the synthetic pathway increase the risk for adverse impact to the drug substance  
1116 quality. If a starting material is re-designated such that the number of steps from the end of the

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1117 manufacturing process is reduced, the carryover of impurities into the drug substance is more  
1118 likely. FDA and the approved drug application holder(s) referenced in the master file should be  
1119 informed of the changes, and comparative batch analysis data for the drug substance should be  
1120 provided.

1121  
1122 If the changes involve a re-designation of the starting material, the submission should contain at  
1123 a minimum the following information (not an exhaustive list) in addition to the documentation  
1124 described in section IX.A.:

- 1125
- 1126 • The rationale for re-designating the starting material addressing ICH Q11 principles.
- 1127 • The list of sources of the re-designated starting material and the full name and address for  
1128 each source.
- 1129 • For non-commodity chemicals, the complete manufacturing process information from  
1130 each source, including the complete synthetic scheme and a brief process description  
1131 (such as when there is a new starting material specification). Reagents and solvents used  
1132 in the starting material process should be clearly indicated in these documents.
- 1133 • Updated specifications for the re-designated starting material, which include controls for  
1134 impurities and residual solvents. Justification and a discussion of the control strategy for  
1135 solvents and possible impurities should be included. Information from each source  
1136 regarding whether a class 1 solvent as described in ICH Q3C has been used or may be  
1137 present because of the manufacturing process should also be included.
- 1138 • A description of analytical procedures for the re-designated starting material.
- 1139 • The vendor's COAs from each source of starting material.
- 1140 • Starting material COAs for the re-designated starting material generated by the drug  
1141 substance manufacturer using material obtained from each source.
- 1142 • When multiple sources are used, a comparison of batch data for re-designated starting  
1143 material generated from each source.
- 1144 • Comparative batch analysis data for downstream isolated materials, either the  
1145 intermediate or the drug substance.

### 1146 1147 **B. Recommended Documentation for the Drug Product in an Approved** 1148 **Application**

1149  
1150 For changes in the vendor or manufacturing process of the starting material, no information need  
1151 be submitted by the applicant, unless the change triggers other changes addressed in this  
1152 guidance.

1153  
1154 For redesignation of the starting material, the applicant should submit the drug substance  
1155 manufacturer's COA for the drug substance manufactured with the new or changed starting  
1156 material.

1157  
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### 1159 **X. CONTAINER CLOSURE SYSTEM CHANGES**

1160

1161 Please see the guidance for industry *Container Closure Systems for Packaging Human Drugs*  
1162 *and Biologics*.<sup>34</sup>

1163

### 1164 **XI. MULTIPLE CHANGES**

1165

1166 Multiple changes are those that involve various combinations of the changes described in this  
1167 guidance. This includes changing to a new source of drug substance, which brings with it a  
1168 change in facility, and any number of changes in the manufacturing process, potentially  
1169 including an entirely different route of synthesis. The applicant should submit the drug substance  
1170 information as outlined in the Quality section of the CTD for the new drug substance source.<sup>35</sup>  
1171 Even if there is significant technology sharing or a common source of technology (e.g., if two  
1172 firms manufacture the drug substance via the same licensed process), significant differences may  
1173 exist in facilities, controls, and standard operating procedures. A change to a new source of the  
1174 drug substance is considered to have a high potential to have an adverse effect on the drug  
1175 substance's impurity profile and physical properties. A new source of drug substance should be  
1176 supported by submission of three pilot or commercial scale batches of drug substance. Twelve  
1177 months of long-term and 6 months accelerated stability data for the drug substance should be  
1178 provided. If less than 12 months data are available at the time of submission, additional data  
1179 should be provided for review prior to approval. At least one batch of pilot or commercial scale  
1180 drug product should be manufactured; however, depending on the extent of drug product  
1181 understanding and complexity of the dosage form, up to three batches of drug product may be  
1182 requested. A minimum of 3 months long-term and 3 months accelerated drug product stability  
1183 data should be provided in the submission.

1184

1185 The recommended documentation for multiple changes should be the sum of the  
1186 recommendations for individual changes and the reporting category should be the most  
1187 restrictive of the categories recommended for the individual changes.

1188

1189

### 1190 **XII. REPORTING CATEGORY**

1191

1192 For manufacturing site, equipment, and process changes pertaining to non-commercially  
1193 available starting materials, drug substance intermediates, final intermediates, and drug  
1194 substance, the potential for an adverse effect to the drug product depends on the extent of  
1195 changes to the impurity profile and physical properties of the post-modification drug substance  
1196 and the type of dosage form it is used in. Therefore, the recommended reporting categories may  
1197 differ depending on these factors.

1198

1199 For guidance on reporting categories and examples, use the following sources of information, in  
1200 the listed order, for postapproval changes:

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

<sup>35</sup> See ICH guidance for industry *MAQ: The CTD — Quality*.

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- 1201 1. 21 CFR 314.70, 21 CFR 314.81, or 21 CFR 514.8, as appropriate.
- 1202 2. This guidance, which provides the most specific recommendations for the particular drug  
1203 substance manufacturing process change at issue.
- 1204 3. The guidance for industry *Changes to an Approved NDA or ANDA or Chemistry,*  
1205 *Manufacturing, and Controls Changes to an Approved NADA or ANADA*, as appropriate.
- 1206 4. The guidance for industry *Changes to an Approved NDA or ANDA Questions and*  
1207 *Answers*.
- 1208 5. The guidance for industry *CMC Postapproval Manufacturing Changes to Be*  
1209 *Documented in Annual Reports*.
- 1210 6. The draft guidance for industry *Established Conditions: Reportable CMC Changes for*  
1211 *Approved Drug and Biologic Products*.<sup>36</sup>  
1212

1213 See appendix B for additional examples of changes not included in the above guidances.  
1214

1215 If you have a question regarding a DMF,<sup>37</sup> NDA, or ANDA for which you are the master file or  
1216 application holder, please contact the regulatory project manager or regulatory business project  
1217 manager assigned to the application.  
1218

### 1219 1220 XIII. GLOSSARY

1221  
1222 **Acceptance Criteria:** Numerical limits, ranges, or other criteria for the test described.  
1223

1224 **Batch:** “[A] specific quantity of [an intermediate or drug substance] that is intended to have  
1225 uniform character and quality, within specified limits, and is produced according to a single  
1226 manufacturing order during the same cycle of manufacture” (21 CFR 210.3(b)(2)). A batch may  
1227 also mean a specific quantity of material or drug substance produced in one process or series of  
1228 processes so that it could be expected to be homogeneous.  
1229

1230 **Drug Product:** “[A] finished dosage form, e.g., tablet, capsule, or solution, that contains a drug  
1231 substance, generally, but not necessarily, in association with one or more other ingredients”  
1232 (21 CFR 314.3(b)).  
1233

1234 **Drug Substance:** “[An] active ingredient that is intended to furnish pharmacological activity or  
1235 other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to  
1236 affect the structure or any function of the human body, but does not include intermediates used in  
1237 the synthesis of such ingredient” (§ 314.3(b)).  
1238

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<sup>36</sup> 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>.

<sup>37</sup> See footnote 9.

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1239 **Final Intermediate:** In reference to synthetic and semisynthetic drug substances, the last  
1240 compound synthesized before the chemical reaction that produces the molecule or ion  
1241 responsible for the physiological or pharmacological action of the drug substance. The chemical  
1242 reaction that transforms the final intermediate into a form of the drug substance involves more  
1243 than a change in salt form (including a salt with hydrogen or coordination bonds) or other  
1244 noncovalent derivatives (such as complex chelates or clathrates).

1245  
1246 **Final Solution Step:** The solution from which the drug substance is isolated in pure form.

1247  
1248 **Historical Data:** For purposes of this guidance, data on impurities or physical attributes from  
1249 three or more consecutive representative pre-modification batches. The upper statistical limit of  
1250 an impurity should be based on the mean plus three times the standard deviation. A lower  
1251 statistical limit can be similarly defined, where appropriate (e.g., the level of an active  
1252 component, moisture content in a hydrate).

1253  
1254 **Impurity:** Any component of the drug substance that is not the entity defined as the drug  
1255 substance (ICH Q3A or VICH GL10(R)).

1256  
1257 **Impurity Profile:** A description of the identified and unidentified impurities present in a drug  
1258 substance (ICH Q3A or VICH GL10(R)) or drug product (ICH Q3B(R2) or VICH GL11(R)).

1259  
1260 **Intermediate:**

- 1261
- 1262 • For synthetic drug substances, a material produced during steps of the synthesis of a drug  
1263 substance that undergoes further molecular change or purification before it becomes a  
1264 drug substance. Intermediates may or may not be isolated (ICH Q7 and ICH Q3A or  
1265 VICH GL10(R)).
  - 1266 • For drug substances derived from a biological source, a material produced during the  
1267 manufacturing process of a drug substance that undergoes further purification or  
1268 molecular modification before it becomes a drug substance.

1269  
1270  
1271 **Isolated Intermediate:** An intermediate that is obtained after workup of a reaction step in the  
1272 synthetic scheme for the drug substance. The isolation or purification procedure should be part of  
1273 the validated process. An aliquot of a reaction product that is worked up or purified for purposes  
1274 of characterization does not constitute an isolated intermediate.

1275  
1276 **Method Validation:** The process of proving that an analytical test procedure is suitable for its  
1277 intended use.

1278  
1279 **Operating Parameters:** Conditions that can be adjusted to control the manufacturing process  
1280 (e.g., temperature, pressure, pH, time, mixing speed).

1281  
1282 **Particle Size Distribution:** A measurement of the relative proportion of particles in a sample as  
1283 a function of size.

1284

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- 1285 **Person:** Includes individual, partnership, corporation, and association. (Section 201(e) of the  
1286 FD&C Act).
- 1287
- 1288 **Physical Properties:** Attributes such as physical state, melting point, boiling point, solubility,  
1289 hygroscopicity, color, density, refractive index, partition coefficient, crystal shape, solid state  
1290 form, and particle size distribution.
- 1291
- 1292 **Pilot Scale:** The manufacture of a bulk drug substance or intermediate on a reduced scale by  
1293 processes representative of those to be applied on a larger, commercial manufacturing scale.
- 1294
- 1295 **Polymorphism:** The occurrence of different crystalline forms of the same drug substance  
1296 (ICH Q3A or VICH GL10(R)).
- 1297
- 1298 **Process Validation:** Establishing documented evidence that provides a high degree of assurance  
1299 that a specific process will consistently produce a product meeting its predetermined  
1300 specification and quality characteristics.
- 1301
- 1302 **Representative Pre-modification Batches:** Commercial-scale batches of a drug substance or  
1303 commercial-scale batches of an intermediate or unfinished drug substance that have been  
1304 successfully used to produce the drug substance.
- 1305
- 1306 **Same Manufacturing Facility:** Unbroken site or set of buildings in adjacent city blocks.
- 1307
- 1308 **Semisynthetic Drug Substance:** A drug substance produced by fermentation and synthesis or  
1309 synthesized from a precursor or structural element of natural origin (e.g., a product of natural or  
1310 plant origin).
- 1311
- 1312 **Single Drug Substance Manufacturing Process:** The same starting materials and intermediates  
1313 with minor variations being allowed in solvents and raw materials as long as the type of chemical  
1314 transformation in each step is unchanged. For example, palladium/carbon could be used at one  
1315 facility while platinum/carbon could be used at another. However, substitution of lithium  
1316 aluminum hydride at a facility would not be permissible as the chemical mechanism for that  
1317 transformation would be different and could generate a different impurity profile for the drug  
1318 substance.
- 1319
- 1320 **Solid State Forms:** Different crystalline forms of the same drug substance. These can include  
1321 solvation or hydration products (also known as pseudo-polymorphs) and amorphous forms (ICH  
1322 guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New  
1323 Drug Substances and New Drug Products: Chemical Substances* or VICH guidance for industry  
1324 *GL39, Specifications: Test Procedures And Acceptance Criteria For New Veterinary Drug  
1325 Substances And New Medicinal Products: Chemical Substances*; and ICH Q3A or VICH  
1326 GL10(R)).
- 1327
- 1328 **Specification:** The quality standard (i.e., tests, analytical procedures, and acceptance criteria)  
1329 provided in an application to confirm the quality of drug substances, drug products,  
1330 intermediates, raw materials, reagents, and other components, including the container closure

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1331 system and in-process materials. According to ICH Q6A, a specification includes the list of tests,  
1332 reference to analytical procedures, and acceptance criteria.

1333  
1334 **Starting Material:** A material used in the synthesis of a drug substance that is incorporated as  
1335 an element into the structure of an intermediate or of the drug substance. A starting material can  
1336 be an article of commerce, a material purchased from one or more suppliers under contract or  
1337 commercial agreement, or produced in-house. The chemical and physical properties, structure,  
1338 and impurity profile of a starting material are well-defined in the chemical literature.

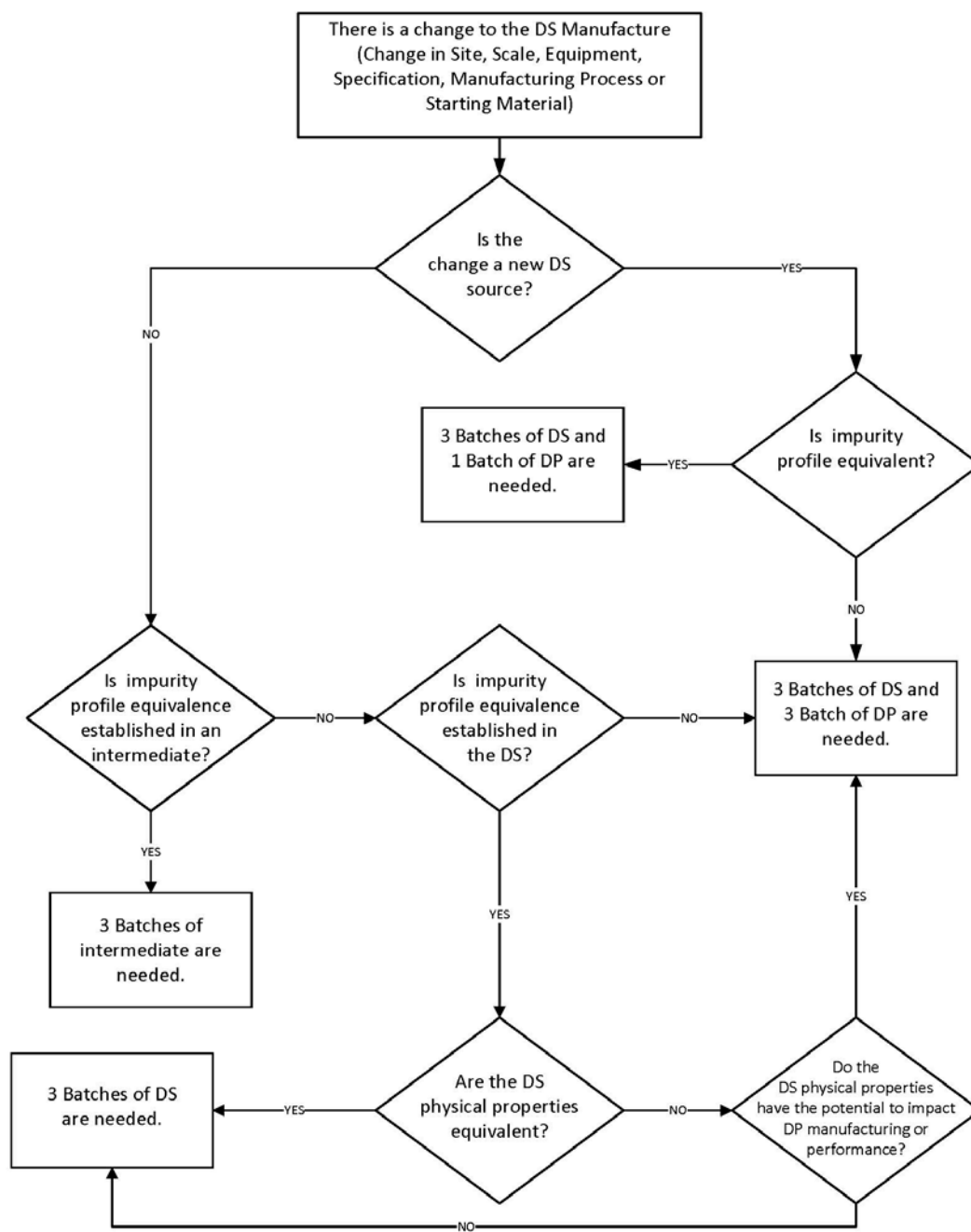
1339  
1340 **Total Impurities:** The sum of all impurities observed above the reporting limit.

1341  
1342 **Unfinished Drug Substance:** A form of the drug substance that is further processed to produce  
1343 the form of the drug substance used to manufacture the drug product. The unfinished drug  
1344 substance can differ from the drug substance. For example, the solid state form of the unfinished  
1345 drug substance could be different from the finished drug substance or the counter ion for the  
1346 unfinished drug substance could be different from the actual drug substance. Although firms  
1347 have sometimes referred to such materials as intermediates, these materials do not meet the  
1348 definitions of *intermediate* and *final intermediate* provided in this guidance for synthetic or  
1349 semisynthetic drug substances.

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1350 **APPENDIX A. CHANGES TO DRUG SUBSTANCE MANUFACTURE**  
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1354 \_\_\_\_\_

1355 \* DS=drug substance. Changes involve changes in facility, scale, equipment, specification, manufacturing process,  
1356 or starting materials.

1357 \*\*DP=drug product.



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### **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.

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### 1404 **Reporting Category for Manufacturing Process Changes**

1405

1406 *PAS*

1407

1408 • Changes that result in a change to the route of synthesis for the final intermediate or drug  
1409 substance.

1410

1411 • Redefinition of a starting material resulting in a change in the impurity profile of the drug  
1412 substance.

1413

1414 • Changes made after the formation of the final intermediate (e.g., new recrystallization  
1415 solvent).

1416

1417 • Changes in the synthesis with adverse effect to the impurity profile (e.g., introduction of  
1418 genotoxic impurity).