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# Guidance for Industry

## Drug Substance

**Chemistry, Manufacturing, and Controls Information**

### ***DRAFT GUIDANCE***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 Review (CBER)  
Center for Veterinary Medicine (CVM)**

**January 2004  
CMC**

# Guidance for Industry

## Drug Substance

### **Chemistry, Manufacturing, and Controls Information**

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<sup>1</sup> Alphanumeric designations in parentheses that follow headings show where information should be placed in applications that are submitted in Common Technical Document (CTD) format.

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**GUIDANCE FOR INDUSTRY<sup>2</sup>**

**Drug Substance**

**Chemistry, Manufacturing, and Controls Information**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale and/or justification for the proposed revision.*
- *Identify specific comments by line numbers; use the pdf version of the document whenever possible.*
- *If possible, e-mail an electronic copy (Word) of the comments you have submitted to the docket to [cummingsd@cder.fda.gov](mailto:cummingsd@cder.fda.gov).*

**I. INTRODUCTION**

Information on the chemistry, manufacturing, and controls (CMC) for the drug substance must be submitted to support the approval of original new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), and abbreviated new animal drug applications (ANADAs).<sup>3</sup> This guidance provides recommendations on the CMC information for drug substances that should be submitted to support these applications. The guidance is structured to facilitate the preparation of applications submitted in Common Technical Document (CTD) format.

This guidance addresses the information to be submitted for drug substances to ensure continued drug substance and drug product quality (i.e., the identity, strength, quality, purity, and potency).

<sup>2</sup> This guidance has been prepared by Drug Substance Technical Subcommittee of the Chemistry Manufacturing and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluations and Research (CBER) and the Center for Veterinary Medicine (CVM) at the FDA.

<sup>3</sup> See 21 CFR 314.50(d)(1) and 514.1(b)

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35 This guidance provides recommendations on the information that should be included for the  
36 following topics:

37

- 38 • Nomenclature, structure, and general drug substance properties
- 39 • Manufacture
- 40 • Characterization
- 41 • Control of drug substance
- 42 • Reference standards or materials
- 43 • Container closure system
- 44 • Stability

45

46 The recommendations provided in this guidance apply to the following types of drug substances:

47

- 48 • Drug substances manufactured by chemical synthesis
- 49 • Highly purified and well characterized drug substances derived from plants or animals<sup>4</sup>
- 50 • Semisynthetic drug substances manufactured by the chemical modification of a highly  
51 purified and well characterized intermediate derived from plants or animals
- 52 • The synthetic portion of the manufacturing process for semisynthetic drug substances  
53 manufactured by the chemical modification of an intermediate produced by conventional  
54 fermentation.

55

56 The guidance does not provide specific recommendations relating to the following:

57

- 58 • Monoclonal antibodies
- 59 • Peptides
- 60 • Oligonucleotides
- 61 • Radiopharmaceuticals
- 62 • Medical gases
- 63 • Drug substances that are not well characterized (e.g., botanicals, some proteins) derived  
64 from plants or animals
- 65 • Drug substances derived using transgenic technology
- 66 • Drug substances derived directly from or manufacturing operations involving  
67 fermentation (conventional fermentation or using rDNA technology) or tissue or cell  
68 culture.

69

70 More detailed guidance on the content of an application may be available in separate guidance  
71 documents for specific types of drug substances (see section II.C). Applicants with drug  
72 substances not specifically covered by this (*Drug Substance* guidance) or another guidance can  
73 apply the content recommendations in this guidance, as scientifically appropriate, and/or can  
74 contact the appropriate chemistry review teams for guidance.

75

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<sup>4</sup> For purposes of this guidance, *drug substances derived from plants or animals* does not include materials produced by plant cell fermentation, animal cell or tissue culture, or through use of transgenic technology (e.g., biotechnology-derived protein drug products).

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

81  
82 This guidance, when finalized, will replace the guidance entitled *Submitting Supporting*  
83 *Documentation in Drug Applications for the Manufacture of Drug Substances* (February 1987).

## **II. BACKGROUND**

### **A. The Common Technical Document — Quality (CTD-Q) Format**

84  
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86  
87  
88  
89  
90 In November 2000, the International Conference on Harmonisation of Technical  
91 Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued  
92 harmonized guidance for the format of drug product applications (i.e., Common  
93 Technical Document (CTD)). The CTD describes a format for applications that  
94 (supplemented with regional information) can be used for submission to the regulatory  
95 authorities in the United States, European Union, and Japan. One focus of this effort was  
96 harmonizing the format for quality information (i.e., chemistry, manufacturing, and  
97 controls) that will be submitted in an application. FDA's guidance on *M4Q: The CTD —*  
98 *Quality* describes the format for the quality information submitted in Module 3 of an  
99 application and provides additional information on formatting aspects of an application.  
100 Applicants can submit NDAs, ANDAs, NADAs, and ANADAs using the CTD-Q  
101 format.<sup>5</sup> Applicants should review FDA's guidance on *M4Q: The CTD — Quality* and  
102 other related CTD guidance documents for detailed formatting recommendations on  
103 preparing an application in CTD format.

104  
105 Module 3 of each NDA and ANDA should include the specified CTD sections: Drug  
106 Substance (3.2.S), Drug Product (3.2.P), Appendices (3.2.A), Regional Information  
107 (3.2.R), and Literature References (3.3). In some cases, the majority of information to  
108 address the drug substance sections will be incorporated by reference from a master file  
109 (see section II.D.2). However, an applicant should still provide information to address  
110 some of the drug substance subsections. Recommendations on the content of the drug  
111 product section (3.2.P) of Module 3 will be the provided in the guidance *Drug Product —*  
112 *Chemistry, Manufacturing, and Controls Information (Drug Product guidance)*, when  
113 finalized.<sup>6</sup> The Appendices, Regional Information, and Literature References sections  
114 include information for both drug substance and drug product, as appropriate.

---

<sup>5</sup> The information in animal drug applications is commonly presented in the order of the required CMC information specified under section § 514.1(b)(4) and (5). Although the CTD-Q format was developed for human drugs, the drug substance information to support NADAs and ANADAs can be formatted according to the CTD-Q format or any alternative format that provides the appropriate information to support the application.

<sup>6</sup> A draft version of this guidance published on January 28, 2003 (68 FR 4219).

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116 This *Drug Substance* guidance has been organized in a format conforming to Module 3 of  
117 the CTD, and it provides CMC content recommendations specific to drug substance,  
118 including recommendations for the Appendices, Regional Information, and Literature  
119 References sections. Alphanumeric designations in parentheses corresponding to the  
120 CTD format follow relevant headings and text to show where information is to be placed  
121 in the CTD.<sup>7</sup> Recommendations specific to drug product, including recommendations for  
122 the Appendices, Regional Information and Literature References sections, will be  
123 provided in the *Drug Product* guidance.  
124

- 125 • **Multiple Drug Substances in an Application**

126  
127 When an application is submitted for a drug product involving two or more drug  
128 substances (e.g., combination drug product, copackaged drug products), information for  
129 each drug substance should be presented separately in the application. Information  
130 presented separately means one complete S section for one drug substance followed by  
131 other complete S sections for additional drug substances. All of the information pertinent  
132 to each one of the drug substances (general information, manufacture, characterization,  
133 control, standards, container closure system, and stability) should be provided in a single  
134 section.  
135

### **B. Content of an Application**

136  
137 The application should include information in every S subsection for each of the drug  
138 substances and manufacturing schemes (e.g., alternative processes, manufacturing site)  
139 intended for approval under the application. Information should be provided in the  
140 Appendices, Regional Information, and Literature References sections for each of the  
141 drug substances and manufacturing schemes, as appropriate. If an Appendices or  
142 Regional Information subsection or the Literature References section is not applicable,  
143 this should be stated in the application.  
144  
145

### **C. Additional Guidance**

146  
147 This *Drug Substance* guidance and the *Drug Product* guidance, when finalized, will be  
148 the primary *content* guidances for NDA and ANDA applicants. For quality, the general  
149 *format* guidance is *M4Q: The CTD — Quality*. These are the first guidances an applicant  
150 should consider when preparing the quality section (i.e., chemistry, manufacturing, and  
151 controls) of an NDA or ANDA (Module 3).  
152  
153

154 This guidance references ICH guidance documents cited in the CTD-Q and FDA's  
155 guidances on general technical topics (i.e., stability, container closure systems, analytical  
156 procedures and methods validation, sterilization process validation, drug master files, and

---

<sup>7</sup> Arabic numbers have been assigned to specific sections of the CTD. For example, the designation 3.2 before S, P, A, and R indicates Module 3, Body of Data section 2. Where this guidance discusses Module 3, Body of Data section 2, for brevity, the initial designation 3.2 is not repeated throughout the rest of the guidance (e.g., 3.2.S.1.3 reads S.1.3).



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157 environmental assessments) rather than incorporating this detailed information. These  
158 guidances are referenced in the text and/or listed at the end of a section. An applicant  
159 should refer to these guidances for recommendations on the detailed information that  
160 should be included in the application to address the general technical topic.

161  
162 Finally, an applicant should consider guidances that are available for specific technical  
163 issues or type (e.g., synthetic peptides) of drug substance when preparing its application.  
164 These guidances provide additional recommendations on unique scientific and technical  
165 aspects of the topic. Some references to these types of guidances are included in this  
166 guidance. However, the references are given only as examples, and the list is not meant  
167 to be all-inclusive. Some examples of these types of guidance include the following:  
168

- 169 • *Submission of Chemistry, Manufacturing, and Controls Information for Synthetic*  
170 *Peptide Substances*
- 171 • *Submission of Chemistry, Manufacturing and Controls Information for a*  
172 *Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody*  
173 *Product for In Vivo Use, CBER/CDER (under development)*
- 174 • *Botanical Drug Products (under development)*
- 175 • *Fermentation Derived Drug Substances and Intermediates and Associated Drug*  
176 *Products (under development)*
- 177 • *Synthetic Oligonucleotides; Submission of Chemistry, Manufacturing, and*  
178 *Controls Information (under development)*
- 179 • *Radiopharmaceutical Drug Products: Chemistry, Manufacturing and Controls*  
180 *Information (under development)*

181  
182 FDA continues to update existing and publish new guidance documents. An applicant  
183 should use current guidance when preparing an NDA, ANDA, NADA or ANADA  
184 submission.<sup>8</sup>

### **D. References to Other Applications or Master Files (MFs)**

#### ***1. Other Applications***

189  
190 In some cases, chemistry, manufacturing, and controls information about drug substances  
191 is provided in one application by reference to pertinent information in another  
192 application. This situation is less common than inclusion of information by reference to a  
193 MF and usually occurs when the same firm submits both applications.

194 An applicant must identify in the application all other referenced applications, and each  
195 reference to information submitted in another application must identify where the  
196 information can be found in the referenced application (21 CFR 314.50(a)(1) and  
197 514.1(a)). If the referenced application was submitted by a firm other than the applicant,  
198 the referencing application must contain a written statement that authorizes the reference,

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<sup>8</sup> Current guidance documents are available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>,  
<http://www.fda.gov/cber/guidelines.htm>, and <http://www.fda.gov/cvm/guidance/published.htm>.

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199 signed by the holder of the referenced application (21 CFR 314.50(g)(1), 314.420(b), and  
200 514.1(a)).<sup>9</sup> Copies of letters of authorization (LOAs) should be submitted in Module 1 of  
201 the NDA or ANDA or in the appropriate section of an NADA or ANADA.  
202

### 203 2. *Master Files (MFs)*

204  
205 This guidance describes chemistry, manufacturing, and controls information for drug  
206 substances that should be submitted to the Agency as part of the process of seeking the  
207 approval of an NDA, ANDA, NADA, or ANADA. When a drug substance is  
208 manufactured by a firm other than the applicant, much of this information is frequently  
209 provided by reference to one or more Type II MFs rather than directly in an application.  
210 The CMC information in a Type II MF can be organized in CTD-Q format. Under FDA's  
211 regulations, an application can incorporate by reference all or part of the contents of any  
212 MF to address particular drug substance issues if the MF holder provides written  
213 authorization (i.e., LOA) to the applicant and the authorization is included in the  
214 application (Module 1 for an NDA or ANDA or in the appropriate section of an NADA  
215 or ANADA). The authorization must specifically identify the material being  
216 incorporated by reference (21 CFR 314.420 and 514.1(a)). The incorporated material  
217 should be identified by name, reference number, volume and page number of the MF, and  
218 date of submission. See 21 CFR 314.420, CDER's guidance on *Drug Master Files*, and  
219 CVM's guidance on *Preparation and Submission of Veterinary Master Files* for more  
220 information.  
221

222 Both the applicant and the drug substance manufacturer (MF holder) contribute to  
223 establishing and maintaining the identity, strength, quality, purity, and potency of the  
224 applicant's drug products by manufacturing and controlling the drug substance in  
225 accordance with the information submitted in the application and, by reference, in the  
226 MF. The following recommendations pertain to location of information in the MF and/or  
227 application when an applicant and Type II MF holder are different firms.  
228

- 229 • **General Information (S.1<sup>10</sup>):** Both the MF and the application should include this  
230 information. These sections should contain similar, though not necessarily identical,  
231 information. For example, if an applicant performed screening studies and  
232 established the existence of multiple polymorphs, information concerning these  
233 polymorphs might be present in the application but not in the MF.  
234
- 235 • **Manufacture (S.2):** The application should identify in S.2.1 the manufacturers of  
236 each drug substance with appropriate administrative information (see section IV.A).  
237 The MF should include this information for its manufacturing operations and any

---

<sup>9</sup> CVM discourages the reference of NDAs or ANDAs for drug substance information. In these instances, CVM recommends that the drug substance information be included in a master file or incorporated in the applicant's NADA or ANADA.

<sup>10</sup> Alphanumeric designations in parentheses that follow headings show where information should be placed in applications that are submitted in Common Technical Document (CTD) format.

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238 contract facilities that are used (e.g., intermediate manufacturers, laboratories). In  
239 general, a MF can be referenced for the information recommended in S.2.2 through  
240 S.2.6. However, the information should be augmented by the applicant, as  
241 appropriate. For example, if the applicant micronizes drug substance purchased from  
242 a MF holder the information on the micronization process should be included in the  
243 application.  
244

245 • **Characterization (S.3):** In general, a MF can be referenced for this information.  
246 However, the information should be augmented by the applicant, as appropriate. For  
247 example, characterization information on physical properties critical to the applicant's  
248 product, such as solid state form or particle size distribution, should be included in  
249 S.3.1 by the applicant under certain circumstances (e.g., applicant manipulates the  
250 physical property (micronizes), the MF holder has not characterized the physical  
251 property). Furthermore, information on an applicant's studies to characterize  
252 impurities (S.3.2) can be warranted to support the applicant's drug substance controls.  
253

254 • **Control of Drug Substance (S.4):** In general, information recommended in S.4  
255 should be provided in both the MF and the application. However, reference to an MF  
256 can be appropriate for some of the information in S.4.2 through S.4.5 if the MF  
257 holder and applicant are working together to develop the drug substance controls.  
258 Both the MF and the application should include a drug substance specification  
259 (S.4.1). The MF could include more than one drug substance specification if the  
260 holder sells different technical grades of the drug substance (e.g., micronized and  
261 nonmicronized).  
262

263 • **Reference Standards (S.5):** In general, information should be provided in both the  
264 MF and the application. However, reference to a MF can be appropriate for some of  
265 the information if the MF holder and applicant are working together to develop the  
266 reference standard.  
267

268 • **Container Closure System (S.6):** In general, MFs can be referenced for this  
269 information. However, the information should be augmented by the applicant, as  
270 appropriate.  
271

272 • **Stability (S.7):** In general, MFs can be referenced for this information. However,  
273 the information should be augmented by the applicant, as appropriate. For example,  
274 an applicant might perform stress studies to support the analytical procedures it used  
275 to control the drug substance.  
276

277 • **Appendices (A):** In general, MFs can be referenced for this information. However,  
278 the information should be augmented by the applicant, as appropriate.  
279

280 • **Regional Information (R):** Comparability protocols can be included in both the MF  
281 and application (R.2.S). A methods validation package should be included in the  
282 application (R.3.S).

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- **Literature References (3.3):** Both the MF and the application should include literature references as warranted.

Type II MFs for drug substance intermediates can also be submitted in the CTD-Q format. However, not all sections of the CTD-Q format would apply (e.g., S.4). The CMC information provided to support an intermediate should be appropriate for the particular situation (e.g., process, complexity of the molecule).

### **III. GENERAL INFORMATION (S.1)**

General information on the nomenclature, structure, and general properties of the drug substance, should be provided in S.1.

#### **A. Nomenclature (S.1.1)**

All appropriate names or designations for the drug substance should be provided in S.1.1. Any codes, abbreviations, or nicknames used in the application to identify the drug substance should also be listed, including the following, if they exist or have been proposed. A name that has not yet been finalized should be identified as proposed in the list.

- United States Adopted Name (USAN)
- Compendial name<sup>11</sup>
- Chemical names (e.g., Chemical Abstracts Service (CAS), International Union of Pure and Applied Chemistry (IUPAC))
- Company names or laboratory codes
- Other nonproprietary names (e.g., International Nonproprietary Name (INN), British Approved Name (BAN), Japanese Accepted Name (JAN))
- Chemical Abstracts Service (CAS) Registry Number

#### **B. Structure (S.1.2)**

Information on the chemical structure of the drug substance should be provided in S.1.2. This information should include:

- one or more drawings to show the overall chemical structure of the drug substance, including stereochemistry
- molecular formula
- molecular weight

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<sup>11</sup> A compendial name is a name that appears in an official compendium as defined in the Federal Food, Drug, and Cosmetic Act (e.g., United States Pharmacopeia (USP)) (§ 201(j) (21 U.S.C. 32(i))).

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325 For a naturally derived protein drug substance, the information should include:  
326

- 327 • the schematic amino acid sequence indicating glycosylation sites or other  
328 posttranslational modifications
- 329 • a general description of the molecule (e.g., shape, disulfide bonds, subunit  
330 composition)
- 331 • number of amino acid residues
- 332 • molecular weight

### 333 **C. General Properties (S.1.3)**

334 A list should be provided of the general physicochemical properties of the drug  
335 substance. Other relevant properties of the drug substance should also be listed.  
336 Relevant properties are those physical, chemical, biological and microbiological  
337 attributes relating to the identity, strength, quality, purity, and/or potency of the drug  
338 substance and, as appropriate, drug product. The information should include, as  
339 appropriate:  
340  
341

- 342 • A general description (e.g., appearance, color, physical state)
- 343 • Melting or boiling points
- 344 • Optical rotation
- 345 • Solubility profile (aqueous and nonaqueous, as applicable)
- 346 • Solution pH
- 347 • Partition coefficients
- 348 • Dissociation constants
- 349 • Identification of the physical form (e.g., polymorph, solvate, or hydrate) that will  
350 be used in the manufacture of the drug product
- 351 • Biological activities

352 For a naturally derived protein drug substance, additional information should be included,  
353 such as:  
354

- 355 • Isoelectric point
- 356 • Extinction coefficient
- 357 • Any unique spectral characteristics

358 If the drug substance can exist in more than one physical form, the information included  
359 in S.1.3 should be for the form (or forms) of the drug substance that will be used in the  
360 manufacture of the drug product. Detailed information on the characterization (e.g., X-  
361 ray powder diffraction data, thermal analysis curves) of these and other physical forms  
362 and conditions required to produce one form or another should be provided in S.3.1.  
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Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

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369

### 370 **IV. MANUFACTURE (S.2)**

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372 Information concerning the manufacture of the drug substance, as described below, should be  
373 provided in S.2.

374

375

#### **A. Manufacturers (S.2.1)**

376

377 The name, address, and manufacturing responsibility should be provided for each firm  
378 (including contract manufacturers and testing laboratories) and each site (i.e., facility)  
379 that will be involved in the manufacturing or testing of the drug substance. Each site  
380 should be identified by the street address, city, state, and, when available, the drug  
381 establishment registration number.<sup>12</sup> The addresses should be for the location where the  
382 relevant manufacturing or testing operation will be performed. Addresses for corporate  
383 headquarters or offices need not be provided. Building numbers or other specific  
384 identifying information should be provided for multifacility campuses. For sites  
385 processing sterile drug substances, the sterile processing area (e.g., room) should also be  
386 included. Addresses for foreign sites should be provided in comparable detail, and the  
387 name, address, and phone number of the U.S. agent for each foreign drug establishment,  
388 as required under 21 CFR 207.40(c), should be included.

389

390 To facilitate preapproval inspection related activities, it is recommended that the name,  
391 telephone number, fax number and e-mail address of a contact person be provided for  
392 each site listed in the application. Facilities should be ready for inspection when the  
393 application is submitted to FDA.

394

#### **B. Description of Manufacturing Process and Process Controls (S.2.2)**

395

396 The description of the drug substance manufacturing process represents the applicant's  
397 commitment for the manufacture of the drug substance. A flow diagram and a complete  
398 description of the processes and process controls that will be used to manufacture the  
399 drug substance or derive it from a biological source should be provided in S.2.2. If  
400

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<sup>12</sup> See 21 CFR part 207 for registration requirements for producers of drugs. The registration number is the seven-digit central file number (CFN) or ten-digit FDA Establishment Identifier (FEI).

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401 alternative processes are to be used, the information should be provided for each  
402 alternative. If justification for an alternative process is warranted, the information should  
403 be included in S.2.2 (e.g., comparative impurity data on intermediates) or can be cross-  
404 referenced if provided elsewhere in the application (e.g., S.4.4).

405

### 406 1. *Flow Diagram*<sup>13</sup>

407

408 A flow diagram that gives the steps of the process and shows where materials enter the  
409 process should be provided. The entire manufacturing process should be depicted (i.e.,  
410 starting materials through drug substance release testing). See Attachments 1 and 2 for  
411 information on starting materials. The flow diagram can be supplemented with  
412 information presented in tabular form, if appropriate. The flow diagram should include:

413

414 • Each manufacturing step with identification of those steps that are critical. These  
415 manufacturing steps can include reaction, workup (e.g., extraction), isolation (e.g.,  
416 centrifugation, distillation), purification (e.g., chromatography, electrophoresis),  
417 processing (e.g., micronization), drug substance release testing.

418 • The name or code number of the material being processed in each manufacturing  
419 step, as appropriate

420 • Chemical structure (including stereochemical configuration where applicable) or  
421 biological identification of starting materials, intermediates, structurally complex  
422 reagents, postsynthesis materials, and the drug substance

423 • Molecular formula and molecular weight of chemical starting materials,  
424 intermediates, postsynthesis materials, and drug substance

425 • Solvents, reagents, and auxiliary materials used in each manufacturing step

426 • Critical process controls and the points at which they are conducted

427 • Operating parameters (e.g., temperature, pH, pressure) for each manufacturing step

428 • An indication of whether intermediates are used in situ or isolated before being used  
429 in the next reaction step and which intermediates are considered the final  
430 intermediates

431 • Expected yield (percent) for each reaction step

432

433 Reagents and other materials should not be identified using only trade (i.e., proprietary)  
434 names. If a reaction results in a mixture of products (e.g., two or more isomers), each

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<sup>13</sup> Headings that are not followed by alphanumeric designations (i.e., non-CTD-Q headings) are included in this document for ease of providing recommendations on the information that should be included under a CTD-Q heading (in this instance *Description of Manufacturing Process and Process Controls (S.2.2)*). An application submitted in CTD-Q format need not include these non-CTD-Q headings. An applicant can physically or electronically separate information under a CTD-Q heading as it chooses. However, once a particular approach is adopted, the same approach should be used throughout the life of the application.

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435 component of the mixture should be indicated in the flow diagram. However,  
436 information on side products and impurities should be provided in S.3.2 (see section V.B).

437

### 438 2. *Description of the Manufacturing Process and Process Controls*

439

440 A narrative description of the manufacturing process that represents the sequence of  
441 manufacturing steps undertaken and the scale of production should be provided. This  
442 description should provide more detail than that given in the flow diagram. The  
443 description should identify all process controls and the associated numeric ranges, limits,  
444 or acceptance criteria. Furthermore, any process controls that are considered critical  
445 process controls should be highlighted. See below for additional information on process  
446 controls. The detailed description of the manufacturing process and process controls  
447 should include:

448

- 449 • A detailed description of each manufacturing step
- 450 • Starting materials or intermediate used in each step, with chemical or biological  
451 names and quantities specified
- 452 • Solvents, reagents, and auxiliary materials used in each step, with chemical or  
453 biological names and quantities specified
- 454 • Type of equipment (e.g., Centrifuge) used, including materials of construction  
455 when critical
- 456 • Identification of the manufacturing steps that are considered critical
- 457 • All process controls and their associated numeric ranges, limits, or acceptance  
458 criteria, with critical process controls highlighted
- 459 • Type of analytical procedure (e.g., HPLC) used for each process test
- 460 • Identification of intermediates, postsynthesis materials, and unfinished drug  
461 substance that are tested (details should be provided in S.2.4)
- 462 • Identification of manufacturing steps that involve recycling of filtrates (mother  
463 liquors) to recover reactants, intermediates, or drug substance, including for the  
464 purpose of producing or isolating additional crystals (i.e., Second crops) and the  
465 process controls on such operation (see section IV.B.3.c)
- 466 • Identification of manufacturing steps that use recovered solvents or auxiliary  
467 materials (see section IV.B.3.c)
- 468 • Identification of manufacturing steps that involve fraction collection (e.g.,  
469 Chromatographic purification), the process controls on such operations, and the  
470 disposition of unused fractions (e.g., Recycling)
- 471 • Identification of processes that involve combining intermediate or drug substance  
472 batches, drug substance and a diluent, or two or more drug substances
- 473 • Yield ranges (weight and percent) for each manufacturing step



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474  
475 Moreover for drug substance derived from a biological source or a semisynthetic drug  
476 substance, the description should include information on the processing operations  
477 conducted on the biological starting material and other procedures such as:  
478

- 479 • Storage and transportation conditions for biological starting materials
- 480 • Preparation procedures (e.g., cleaning, drying)
- 481 • Isolation processes (e.g., grinding, cell lysis, extraction from biomass)
- 482 • Holding times and storage conditions during manufacture
- 483 • Procedures used to maintain traceability of all intermediate and drug substance  
484 batches back to the batches of the starting material

485  
486 Information assessing the risk with respect to potential contamination with adventitious  
487 agents should be provided in Appendix A.2 of the application when appropriate (see  
488 section X.B of this guidance). A statement should be provided that bovine-derived  
489 materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S.  
490 Department of Agriculture (9 CFR 94.11) are not used or manipulated in the same  
491 facility. Submission of additional facility information could be warranted for multi-use  
492 facilities where there is a potential for cross-contamination with adventitious agents (see  
493 sections X.A and X.B). Additional facilities information for drug substances derived  
494 from biological sources should be included in A.1, when appropriate.  
495

496 Differences between the manufacturing process described in S.2.2 and the manufacturing  
497 process used to produce the primary stability batches should be discussed in S.2.6. (see  
498 section IV.F).  
499

### 500 • **Process Controls**

501  
502 *Process controls* is an all-inclusive term used to describe the controls used during  
503 production to monitor and, if appropriate, adjust the process and/or to ensure that an  
504 intermediate, postsynthesis material, or unfinished drug substance with an established  
505 specification or the drug substance will conform to its respective specification. The term  
506 includes:  
507

- 508 • Operating parameters — conditions that can be adjusted to control the manufacturing  
509 process (e.g., temperature, pH, time, mixing speed)
- 510 • Environmental controls — conditions associated with the manufacturing facility (e.g.,  
511 temperature, humidity, clean room classification)
- 512 • Process tests — measures used to monitor and assess the performance of an on-going  
513 manufacturing operation (e.g., analysis to determine concentration of reactant or  
514 product, measuring hydrogen gas uptake during hydrogenation)

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- 515 • In-process material tests — measures used to assess the quality attributes and/or the  
516 suitability for use in the manufacturing process of an isolated intermediate,  
517 postsynthesis material, or unfinished drug substance

518  
519 Steps in the process should have the appropriate process controls identified. Associated  
520 numeric values can be presented as an expected range. Process tests and in-process  
521 material tests can be performed on-line, at-line, or off-line. All process controls, critical  
522 or otherwise, should be included in the description of the manufacturing process.  
523

524 Depending on the drug substance and the manufacturing process, a particular process  
525 control may or may not be critical as illustrated in the following examples:  
526

- 527 • A mixing speed or temperature can be critical for manufacturing steps for protein  
528 drug substances, but may not be critical for similar operations performed on a  
529 synthetic chemical
- 530 • The humidity to which a powder is exposed during processing can be critical, but  
531 may not be critical if the powder is nonhygroscopic
- 532 • The clean room classification can be critical for certain steps in the manufacture of a  
533 sterile drug substance, but may not be critical for steps before the drug substance is  
534 rendered sterile or for a nonsterile drug substance.
- 535 • An end-of-reaction test used to determine impurity levels can be critical, but an end-  
536 of reaction test to maximize yield may not be critical

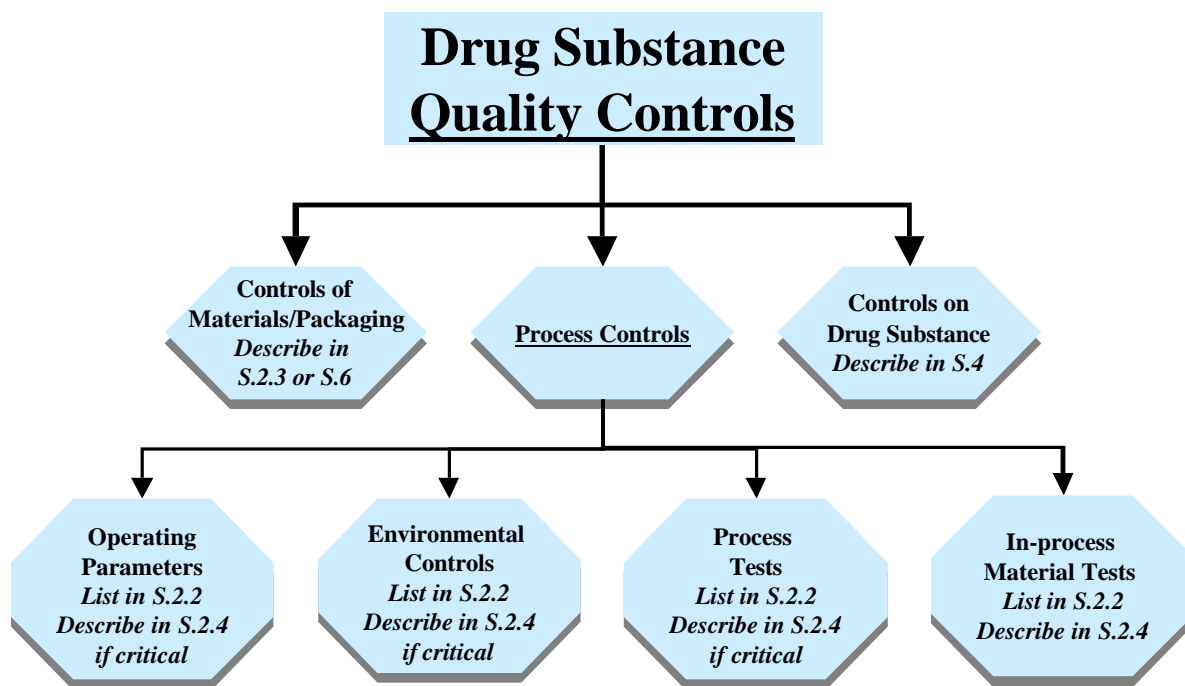
537  
538 All of the operating parameters, environmental conditions, and process tests that ensure  
539 each critical manufacturing step is properly controlled should be specifically identified as  
540 critical in the flow diagram and description of the manufacturing process in this section  
541 of the application (S.2.2) and in S.2.4. All tests on intermediates, postsynthesis materials,  
542 and unfinished drug substance should be listed in the description of the manufacturing  
543 process in S.2.2 and described in S.2.4. A summary of where information on drug  
544 substance quality controls should be located in applications submitted in CTD-Q format  
545 is provided in Figure 1.

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Figure 1



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### 3. *Reprocessing, Reworking, Recycling, Regeneration, and Other Operations*

552 Reprocessing should be described in S.2.2, when appropriate. When used, reworking,  
553 recycling, regeneration, and salvaging operations should be described in S.2.2. These  
554 operations should be adequately controlled to ensure that there is no adverse effect on the  
555 identity, quality, purity, or potency of the drug substance. Moreover, reprocessing and  
556 reworking operations should be capable of producing an improvement in one or more  
557 quality attributes without having an adverse effect on others. Information (e.g.,  
558 comparative analytical data) to support the appropriateness of these operations should be  
559 included in S.2.2 or can be cross-referenced in S.2.2 if information is provided elsewhere  
560 in the application. If the operation involves critical manufacturing steps or intermediates,  
561 information should also be provided in S.2.4. However, validation data, when warranted  
562 to support the operation, should be provided in S.2.5. (see section IV.E for possible  
563 situations when process validation information is warranted.)

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566

#### a. *Reprocessing*

567 Reprocessing is the introduction of an intermediate or drug substance, including  
568 one that does not conform to a standard or specification, back into the process and  
569 repeating a crystallization or other appropriate chemical or physical manipulations  
570 (e.g., distillation, filtration, chromatography, milling) that are part of the approved  
571 manufacturing process. See section IV.B.3.e for recommendations on chemical or  
572 physical manipulations performed after quality control release of the material.

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573  
574 Continuation of a manufacturing step after a process test has shown that the step  
575 is incomplete is considered to be part of the normal process and is not  
576 reprocessing. Repetition of a single reaction step should be carefully evaluated  
577 with respect to the potential formation of by-products and over-reacted materials.  
578 Repetition of multiple reaction steps is considered to be reworking, rather than  
579 reprocessing (see section IV.B.3.b).  
580

581 For most intermediates and drug substances, reprocessing need not be described  
582 in the application. In general, the documentation of and data to support the  
583 reprocessing of a production batch should be retained by the manufacturer and be  
584 available for review by FDA upon request. However, if there is a significant  
585 potential for the reprocessing operation to adversely affect the identity, strength,  
586 quality, purity, or potency of the drug substance, the reprocessing operations  
587 should be described and justified in this section (S.2.2) of the application. For  
588 example, CDER would consider reprocessing proteins to be reprocessing  
589 operations that should be described in the application.  
590

591 Reprocessing is considered a nonroutine event. If frequent reprocessing is  
592 expected, the procedures should be included as part of the manufacturing process  
593 described in the application. Depending on the frequency and type of  
594 reprocessing, a reprocessing operation that is included in the application can be  
595 (1) specified for use under certain circumstances (e.g., repetition of a purification  
596 step when impurities are found at or above a designated level) or (2) incorporated  
597 into the existing manufacturing process and performed on each batch when  
598 reprocessing occurs for the majority of batches.  
599

### b. Reworking

601  
602 Reworking is subjecting an intermediate or drug substance that does not conform  
603 to a standard or specification to one or more manufacturing steps that are different  
604 from the manufacturing process described in the application to obtain acceptable  
605 quality intermediate or drug substance. Repetition of multiple reaction steps is  
606 considered to be reworking because the material to be reintroduced into the  
607 process is not similar to the original reactant. Repetition of multiple reaction  
608 steps is discouraged because of concerns relating to unexpected impurities and  
609 degradants.  
610

611 Reworking is considered a nonroutine event. In general, reworking operations are  
612 developed postapproval, and the application is updated through submission of a  
613 prior approval supplement that provides test results and, if appropriate,  
614 new or updated analytical procedures that are demonstrated to be appropriate to  
615 evaluate the effect of the reworking procedure on the identity, quality, purity, or  
616 potency of the drug substance. However, if reworking operations are anticipated  
617 at the time of the original submission, they should be described in this section of  
618 the application (S.2.2) with justification for the reworking operation.

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### **c. Recovery**

The use of recovered solvents and recycling of filtrates (mother liquors) to recover reactants, intermediates, or drugs substance, including for the purpose of producing or isolating additional crystals (i.e., second crops), should be described in S.2.2. Recovery operations should be adequately controlled so impurity levels do not increase over time.

Recovered solvents can be used with or without further processing to improve the quality of the solvent as long as the quality of the recovered solvent is appropriate for its intended use. The use of recovered solvents, including the point at which they might be used in the process, should be included in the description of the manufacturing process. The solvent recovery operation itself need not be described in detail. However, information should be provided on whether (1) any processing is done to improve the quality of the recovered solvent with a brief description of the process (e.g., distillation) and (2) the recovered solvent comes only from the manufacture of this drug substance or can come from other sources. Appropriate specifications for recovered solvents should be included in S.2.3.

Recycling of filtrates should be included in the description of the manufacturing process if these operations are performed. Information should be provided on the maximum number of times material will be recycled and for the process controls for such operations. Data on impurity levels should be provided to justify recycling of filtrates.

### **d. Regeneration**

The regeneration of materials such as column resins and catalysts should be described in S.2.2 if these operations are performed. The process controls for regeneration operations should be provided. Controls on regenerated material can include, for example, a maximum number of times the material will be regenerated and/or tests to determine the continued suitability (e.g., column efficiency) of the material. When appropriate, specifications for regenerated materials should be included in S.2.3

### **e. Other Operations**

The recommendations for reworking apply to (1) recovery of drug substance from drug product or drug product in-process materials or (2) a drug substance, after it has been released by the quality control department, that undergoes processing to bring the material back into conformance with its specification (e.g., purification of aged material to decrease the level of degradation products to conform with the approved acceptance criteria). The recommendations for reworking operations apply irrespective of whether the operation repeats steps that are part of the approved manufacturing process (see section IV.B.3.b).

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Additional guidance is available in:

- ICH: *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

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### C. Control of Materials (S.2.3)

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Information on the materials (starting materials, reagents, solvents, auxiliary materials, and diluents) that will be used to manufacture the drug substance or derive it from a biological source, including purification, should be provided in S.2.3. Information indicating where each material is used in the manufacturing process should be provided in the flow diagram and in the narrative description of the manufacturing process (S.2.2).

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When appropriate, specific tests and acceptance criteria to control microbial contamination should be included in the specification for materials used to manufacture drug substances. For materials of biological origin, information assessing the risk with respect to potential contamination with adventitious agents should be provided in Appendix A.2 of the application when appropriate (see section X.B).

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#### 1. Starting Materials

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For application purposes, *starting materials* mark the beginning of the manufacturing process described in an application. The starting material for application purposes can differ from the *active pharmaceutical ingredient (API) starting material*, which marks the point in the manufacturing process from which appropriate GMP should be applied (as defined in ICH Q7A: *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*). In general, the starting material and API starting material should be the same for a synthetic drug substance. However for a drug substance derived from a biological source, the starting material (e.g., plant) and API starting material (e.g., extract) can be different. In this case, information on the biological source (e.g., potential pathogens, herbicides, pesticides) is warranted in the application so FDA can evaluate the suitability of the biological source as a starting material for drug manufacture (see Attachment 2). The recommendations for starting materials provided in this guidance are for application purposes. See ICH Q7A for recommendations on API starting materials.

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Starting materials for a synthetic drug substance are chemical compounds of defined molecular structure that contribute to the structure of the drug substance. A proposed starting material for a synthetic drug substance should be chosen so that sufficient information will be available to FDA on the manufacturing process to evaluate the safety and quality of the drug substance. The FDA considers (1) cells; (2) plants, plant parts,

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702 macroscopic fungi, or algae; or (3) animal tissues, organs, or body fluid from which the  
703 drug substance is derived to be the starting material for a drug substance derived from a  
704 biological source. For semisynthetic processes, information should be provided for the  
705 biological source starting material and starting materials of synthetic origin, if there are  
706 any.

707  
708 The following information should be included in the application to support the proposed  
709 starting materials:

- 710
- 711 • A list of proposed starting materials and/or information on plant or animal starting
  - 712 materials
  - 713 • A flow diagram
  - 714 • A specification for each starting material
  - 715 • Justification for the proposed starting materials, when appropriate
- 716

717 More detailed information and recommendations on the information to support proposed  
718 starting materials for synthetic drug substances and starting materials of plant or animal  
719 origin are included in Attachment 1 and 2, respectively.

720

### 721 2. *Reagents, Solvents, and Auxiliary Materials*

722

723 The following information should be submitted in S.2.3 for reagents, solvents, and other  
724 auxiliary materials (e.g., filter aids, decolorizing agents) used in the manufacture of a  
725 drug substance. When contamination with viral adventitious agents or transmissible  
726 spongiform encephalopathy (TSE) agents is a concern, additional information may be  
727 warranted (see section X.A and X.B). Information on the manufacture of certain reagents  
728 (e.g., those produced by rDNA technology) may be warranted and when warranted, this  
729 information should be included in S.2.3.

730

#### 731 a. List of Reagents, Solvents, and Auxiliary Materials

732

733 A list of reagents, solvents, and other auxiliary materials used in the manufacture  
734 of a drug substance should be provided.

735

#### 736 b. Specification

737

738 A specification should be provided for each material. The specification sheet  
739 should list all tests to which the material will conform and the associated  
740 acceptance criteria and should also include a reference to the analytical  
741 procedures that will be used to perform each test. At a minimum, the reference  
742 should identify the type of analytical procedure used (e.g., GC, HPLC).

743

744 The tests and acceptance criteria in each specification should be appropriate for  
745 the kind of material and its intended use, and should be consistent with the quality  
746 of the material used to manufacture the batches of drug substance used to

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747 establish the specification for the drug substance (see sections VI.A, VI.D, and  
748 V.I.E). For example, extensive purity testing of an inorganic base used to adjust  
749 pH would not normally be warranted, but testing of enantiomeric purity might be  
750 appropriate for an optically active organic acid used in a resolution step.

751  
752 Water used in the manufacture of drug substances should be of appropriate quality  
753 for its intended use.

### 754 3. *Diluents*

755  
756 Occasionally the drug substance used to manufacture a drug product is dispersed in a  
757 diluent (e.g., conjugated estrogens, nitroglycerin). Information on the controls for the  
758 diluent (e.g., lactose, dextrose) should be included in S.2.3. The information should be  
759 provided at the same level of detail as for a drug product excipient. Recommendations on  
760 control of excipients will be provided in section VI of the *Drug Product* guidance, when  
761 finalized.  
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Additional guidance is available in:

- ICH: *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*
- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL17 Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products*

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### D. **Controls of Critical Steps and Intermediates (S.2.4)**

In this section of the application, all critical operating parameters, environmental controls, process tests and all tests performed on intermediates, postsynthesis materials, and unfinished drug substance should be listed and their associated numeric ranges, limits, or acceptance criteria should be identified. Any of the tests and associated numeric ranges, limits, or acceptance criteria for intermediates, postsynthesis materials, or unfinished drug substance that are judged to be non-critical can be indicated as such. FDA recommends that the noncritical be listed separately from the critical tests to distinguish them from the critical tests that constitute the specification for the intermediate, postsynthesis material, or unfinished drug substance.



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778  
779 For all critical process controls, the associated numeric ranges, limits, or acceptance  
780 criteria should be justified and a brief description of the test provided. Any experimental  
781 data to support the justification should be included in this section (S.2.4) as well. For  
782 critical operating parameters and environmental conditions, numeric ranges, limits, or  
783 acceptance criteria typically can be based on the experience gained during the  
784 development of the manufacturing process. (See section IV.E for possible exceptions  
785 when process validation information is warranted.) Critical process control values from  
786 relevant batches (i.e., those for which batch analyses have been provided in S.4.4) should  
787 be provided as part of the justification. Additional information should be provided in this  
788 section (S.2.4) under the following circumstances.

789  
790 • **Biological Tests**

791  
792 Analytical procedures and associated validation information should be provided for  
793 biological tests.<sup>14</sup>  
794

795 • **Tests Used In Lieu of Drug Substance Tests**

796  
797 In some cases, results from tests performed during the manufacturing process (e.g.,  
798 process tests, tests on intermediates, postsynthesis materials, or unfinished drug  
799 substance) can be used in lieu of testing the drug substance to satisfy a test listed in the  
800 drug substance specification. For example, testing to determine the level of a residual  
801 solvent on an isolated intermediate may be sufficient to satisfy a test listed in the drug  
802 substance specification provided in S.4.1. This approach, however, should be supported  
803 with data that demonstrate that test results or drug substance performance characteristics  
804 do not undergo an adverse change from the in-process stage to drug substance. These  
805 data, along with the analytical procedure and associated validation information, should be  
806 provided in S.2.4. Information should be included in the method validation package  
807 (R.3.S), as appropriate. When the same analytical procedure is used for both the in-  
808 process test and the drug substance test, the acceptance criterion for the in-process test  
809 should be identical to or tighter than the acceptance criterion in the drug substance  
810 specification. Tests performed in-process in lieu of testing the drug substance should be  
811 included in the drug substance specification (S.4.1) and the results of such tests should be  
812 included in the batch analysis report (e.g., certificate of analysis)).  
813

814 • **Intermediates**

815  
816 When warranted, a specification should be established for an isolated intermediate to  
817 ensure that it has appropriate quality attributes for further downstream processing. A  
818 specification for an intermediate should usually include testing for assay and impurities.  
819 The specification should be provided in S.2.4.

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<sup>14</sup> The term *biological tests* includes biological (e.g., animal, cells), biochemical (e.g., enzyme reaction rates), and immunochemical procedures. In this circumstance, procedures from an official compendium to assess pyrogen, bacterial endotoxin, sterility, and microbial levels are excluded from this definition.

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820  
821 For a semisynthetic drug substance, FDA recommends that the following information be  
822 provided in S.2.4 for the intermediate used at the beginning of the synthetic operations:  
823

- 824 • The chemical name, CAS Registry Number, structure (including amino acid  
825 sequence, if appropriate), molecular formula, and molecular weight
- 826 • Evidence supporting the chemical structure
- 827 • Information concerning impurities
- 828 • The proposed specification for the intermediate  
829

830 Because the intermediate is obtained from a plant or animal, the evaluation of potential  
831 impurities should not be limited to structurally related organic compounds, residual  
832 solvents, and inorganic impurities. Other potential sources of impurities (e.g., pesticide  
833 or herbicide residues in plant-sourced intermediates) should also be considered and  
834 discussed. Information concerning the removal or inactivation of adventitious agents in  
835 intermediates obtained from animal sources should be provided in Appendix A.2 as  
836 appropriate. The need for heavy metals testing should be considered due to the  
837 concentration of metals by some plant species.  
838

- 839 • **Postsynthesis Materials**  
840

841 For synthetic or semisynthetic drug substances, a postsynthesis material is a material that  
842 appears in the process after the final intermediate and before the drug substance  
843 (unfinished drug substance or form of drug substance used to produce the drug product).  
844 Postsynthesis materials can differ from the drug substance, for example, in  
845 stereochemical identity, solid state form, or either the absence of a counterion or the  
846 presence of a counterion different from that in the drug substance. Although firms have  
847 sometimes referred to such materials as *intermediates*, these materials do not meet the  
848 definition of intermediate and final intermediate provided in this guidance for synthetic or  
849 semisynthetic drug substances. If a specification for a postsynthesis material is  
850 established, this specification should be included in S.2.4.  
851

852 There is no distinction between intermediates, final intermediate, and postsynthesis  
853 materials for drug substances derived from biological sources. The in-process materials  
854 are referred to as intermediates (see discussion above on *intermediates* for guidance).  
855

- 856 • **Unfinished drug substance**  
857

858 Multiple forms (i.e., *technical grades*) of the drug substance may be part of the  
859 manufacturing process described in the application. For example, an applicant might  
860 purchase a drug substance from an MF holder and then micronize or further purify the  
861 drug substance for use in its drug product. If a specification for an unfinished drug  
862 substance is established, this specification should be included in S.2.4. The specification  
863 for the form of the drug substance used to produce the drug product should be included in  
864 S.4.1.

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Additional guidance is available in:

- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL17 Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products*

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### **E. Process Validation and/or Evaluation (S.2.5)**

Validation information relating to the adequacy and efficacy of any sterilization process (e.g., drug substance, packaging components) should be submitted in this section of the application for sterile drug substances. Furthermore, if a step in the manufacturing process is designed to reduce the amount of microbial contamination, such as for certain drug substances derived from biological sources, information to support the appropriateness of the step should be included. Submission of other manufacturing process validation information in the application is not necessary for most drug substances.<sup>15</sup> However, for naturally derived protein drug substances, information concerning the evaluation of purification processes related to the removal of impurities should be provided in this section. When applicable, validation information should be provided for processes used to control adventitious agents. This information should be included in A.2.

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Submission of validation information for reprocessing and reworking operations usually is not warranted. However, it can be warranted when the reprocessing or reworking operation is of the type for which process validation information is submitted when routinely performed or when the reprocessing or reworking operations have a significant potential to affect the identity, strength, quality, purity, or potency of the product (e.g., naturally derived protein drug substances).

### **F. Manufacturing Process Development (S.2.6)**

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A description of the manufacturing process for the drug substance throughout the various development phases should be provided in S.2.6. The primary focus of this description

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<sup>15</sup> All manufacturing processes should be validated. However, in most cases, the validation information is reviewed during facility audits.

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894 should be the relationship between changes in the manufacturing process or  
895 manufacturing site and any associated changes in the chemical or physical properties of  
896 the drug substance. Manufacturing changes associated with changes in the impurity  
897 profiles of intermediates should also be described. Information for early manufacturing  
898 processes (i.e., those used prior to the manufacture of drug substance batches for which  
899 chemistry, clinical, or toxicity data will be submitted in the application) need not be  
900 provided. If in vitro studies (e.g., dissolution) or in vivo studies (e.g., bioequivalence) on  
901 the drug product were warranted because of a change in the drug substance  
902 manufacturing process, the study results should be summarized,<sup>16</sup> and a cross-reference  
903 to the studies (with study numbers) should be provided in S.2.6.

904  
905 The primary stability batches should be manufactured using the same manufacturing  
906 processes (e.g., synthetic route) and procedures and a method of manufacture that  
907 simulate the process intended for production batches as described in S.2.2. Section 2.6 of  
908 the application should contain a description of any significant differences between the  
909 process used to produce the primary stability batches and the process described in S.2.2  
910 (see section IV.B). The description should include an explanation for the differences.  
911

Additional guidance is available in:

- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL10 Impurities in New Veterinary Drug Substances*

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## 914 V. CHARACTERIZATION (S.3)

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### 916 A. Elucidation of Structure and Other Characteristics (S.3.1)

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918 Data and analysis to support the elucidation of the structure and other characteristics of  
919 the drug substance should be provided in S.3.1. Summary information relating to these  
920 characteristics should be included in S.1.2 and S.1.3. Key physicochemical  
921 characteristics of the drug substance that can influence the performance or  
922 manufacturability of the drug product should be discussed in P.2.1.1 for NDAs and  
923 ANDAs or the appropriate section of the NADA or ANADA.

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#### 925 1. *Elucidation of Structure*

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<sup>16</sup> Here and elsewhere in the guidance when a summary of clinical or nonclinical information is recommended, the summary information or a cross-reference to the appropriate summary information in Module 2 of a CTD formatted NDA or ANDA can be provided in the specified Module 3 section.

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927 The chemical structure of the drug substance should be confirmed using physical and  
928 chemical techniques such as elemental analysis, mass spectrometry (MS), nuclear  
929 magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, infrared (IR)  
930 spectroscopy, X-ray crystallography, and other tests (e.g., functional group analysis,  
931 derivatization, complex formation). Issues such as counterion stoichiometry,  
932 regiochemistry, geometric and configurational isomerism, and absolute stereochemistry  
933 should be addressed. When the drug substance consists of more than one molecular  
934 species, information confirming the structure of each should be provided. The  
935 elucidation of structure of synthetic and semisynthetic drug substances, including  
936 stereochemistry, can be supported by the chemical structures of synthetic precursors. The  
937 amount of data warranted to support the elucidation of structure can vary depending on  
938 the complexity of the molecule.

939

940 For naturally derived proteins, the primary, secondary, tertiary and, if applicable,  
941 quaternary structures should be confirmed using appropriate techniques such as amino  
942 acid compositional analysis, full amino acid sequencing, peptide mapping, and mass  
943 spectrometry. Additional tests (e.g., isoforms analysis, carbohydrate composition or  
944 sequence) may be warranted for glycoproteins. For naturally derived protein drug  
945 substances, additional information on structural characterization can be found in ICH  
946 *Q6B Specifications: Test Procedures and Acceptance Criteria for*  
947 *Biotechnological/Biological Products.*

948

### 949 2. *Physicochemical Characterization*

950

951 Detailed information on and data to support the physicochemical characterization of the  
952 drug substance should be provided in S.3.1. This information should include data to  
953 support the general properties listed in S.1.3 (e.g., optical rotation, solubility profile,  
954 dissociation constant) as well as information and data on more complex physicochemical  
955 properties that are not included in the list of general properties (e.g., heterogeneity of  
956 naturally derived proteins). Information can include data from various analytical  
957 procedures such as X-ray diffraction (single crystal or powder), thermal analysis (e.g.,  
958 differential scanning calorimetry, thermal gravimetric analysis, hot-stage microscopy),  
959 particle size analysis, or other spectroscopic techniques (e.g. IR, Raman, solid-state  
960 NMR, mass). Moreover, for proteins information can include data from techniques such  
961 as electrophoresis (e.g., sodium dodecyl sulfate (SDS)-polyacrylamide gel, capillary),  
962 isoelectric focusing, optical analysis (e.g., circular dichroism), column chromatography  
963 (e.g., size exclusion, reverse phase-HPLC, ion exchange), and Western-blot.

964

965 The kind and extent of the physicochemical characterization information that should be  
966 provided depends on (1) the type of drug substance (e.g., synthetic molecule, protein), (2)  
967 the type of dosage form in which the drug substance will be used, (3) the ability or  
968 tendency of the drug substance to occur in one or more solid state forms, and (4) the  
969 importance of the differences in physical characteristics of the different forms to the  
970 stability, dissolution, or bioavailability of the drug product. The information in S.3.1 can  
971 be cited elsewhere in the application, for example, to justify proposed process controls or  
972 lack thereof (see section IV.D), or the presence or absence of tests for physical

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973 characterization in the proposed drug substance specification (see sections VI.A and  
974 V.I.E).<sup>17</sup>

975  
976 Based on the above stated considerations, an applicant or drug substance manufacturer  
977 should investigate whether a drug substance is capable of existing in different solid state  
978 forms. Solid state form in this context refers to amorphous and crystalline forms,  
979 hydrates, and solvates. The information can include studies of (1) the conditions that lead  
980 to the formation of one or another solid state form or (2) the conditions under which one  
981 solid state form can be converted or equilibrated with another. Applicants do not need to  
982 investigate the occurrence of different forms under conditions that deviate significantly  
983 from the conditions used in the manufacturing processes for the drug substance and drug  
984 product. However, screening a variety of solvents with different polarities and hydrogen-  
985 bonding properties can be valuable for early detection of other polymorphs.  
986 At an appropriate stage of development, the potential for interconversion of solid state  
987 forms should usually be investigated in stability studies. A summary of these  
988 investigations should be included in S.3.1 of the application even if no other forms were  
989 found. Information on differences in particle size distribution or crystal habit (shape) can  
990 also be important in some circumstances.

991  
992 In some cases, characterization of the drug substance will be insufficient to conclude  
993 whether the physical properties of the drug substance will have an impact on the  
994 dissolution or bioavailability of the drug product, and further studies on the drug product  
995 itself should be conducted. A summary of these studies should be provided in section  
996 P.2.1.1 of the NDA or ANDA or the appropriate section of the NADA or ANADA.

997  
998 **3. *Biological and Other Relevant Characteristics***

999  
1000 Information on the elucidation of other relevant characteristics should be provided as  
1001 appropriate. For example, information on biological activity, purity (e.g., product-related  
1002 substances), and when appropriate, immunochemical properties should be provided for  
1003 naturally derived protein drug substances.

1004

Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

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<sup>17</sup> ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* provides guidance on how to decide what controls on solid state form or particle size are appropriate. Although this guidance applies only to new drug substances of synthetic chemical origin, the same principles for evaluating solid state form can be used, when appropriate, for other types of drug substances.

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### 1006 **B. Impurities (S.3.2)**

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1008 Information on drug substance impurities should be provided in S.3.2. The applicant  
1009 should summarize the actual and potential impurities most likely to arise during  
1010 manufacture, purification, and storage of the drug substance. Impurities of all kinds (e.g.,  
1011 organic, inorganic, residual solvents) should be discussed. For drug substances of  
1012 biological origin and semisynthetic drug substances, the description of impurities should  
1013 include, if appropriate, those related to the natural origin of the material (e.g., pesticide  
1014 residues, heavy metals due to the concentration of metals by certain plant species, related  
1015 substances whose concentrations vary with changes in harvesting conditions (species,  
1016 location, season, organ)). The discussion should identify organic impurities as:

- 1017
- 1018 • Impurities observed in the drug substance (both identified and unidentified)
- 1019 • Substances that are considered potential impurities but that have not been
- 1020 observed in the batches of drug substance manufactured
- 1021 • Impurities that were once present in the drug substance but that have been
- 1022 eliminated by process modifications
- 1023 • Degradation products observed in stability and stress studies on the drug
- 1024 substance or following processing (e.g., micronization)
- 1025

1026 The type of information provided for each impurity can vary with the nature of the  
1027 impurity, the analytical procedure by which it is detected, whether it is actually present in  
1028 significant quantities in the drug substance, whether it has been identified, and the  
1029 methods used to identify the impurity.

1030  
1031 Evaluation of inorganic impurities and residual solvents should primarily be guided by  
1032 knowledge of the method of manufacture of the drug substance. Factors that should be  
1033 considered in evaluating potential sources of organic impurities include the route of  
1034 synthesis, impurities in the starting materials or biological source materials, possible side  
1035 reactions, and potential degradation pathways.

1036  
1037 Attempts should be made to identify all impurities found in significant quantities in the  
1038 drug substance. The studies to characterize these impurities should be described. FDA  
1039 regulates a variety of drug substances; no single recommendation applies to all drug  
1040 substances for the level of an impurity that would warrant identification.

1041 Recommendations on identification levels may be provided for specific situations. For  
1042 example, *ICH Q3A Impurities in New Drug Substances* recommends thresholds for the  
1043 identification and qualification of organic impurities for synthetic new drug substances.  
1044 As discussed in the guidance, however, those thresholds are not necessarily appropriate  
1045 for potential impurities that are expected to be unusually potent. An applicant is  
1046 encouraged to discuss any questions about the identification of impurities with the  
1047 appropriate review divisions.  
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1049 The following are typical of the information that should be provided for impurities:  
1050

- 1051 • Identity of the impurity or potential impurity (chemical name and structure)
- 1052 • Analytical procedure used to detect or search for the impurity or potential  
1053 impurity
- 1054 • An indication as to whether a potential impurity was actually detected in  
1055 significant quantities in the drug substance (a detailed accounting of the  
1056 impurities found in various batches should be provided in S.4.4)
- 1057 • Structural characterization data and/or other data on the physical or chemical  
1058 properties of the impurity or potential impurity
- 1059 • Summary of the route of synthesis or method of preparation if the impurity or  
1060 potential impurity was independently prepared
- 1061 • A summary of the attempts made to identify an impurity if it has not been  
1062 possible to identify it
- 1063 • A table listing the qualified level of expected impurities with a cross-reference to  
1064 the appropriate studies (including study numbers and batch numbers). A similar  
1065 table should be provided in section 3.4 of module 4.  
1066

1067 For naturally derived protein drug substances, additional information on product-related  
1068 and process-related impurities should be provided as recommended in the ICH *Q6B*  
1069 *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological*  
1070 *Products*.

1071  
1072 Information concerning the removal or inactivation of adventitious agents in drug  
1073 substances obtained from animal sources (including semisynthetics that originate from an  
1074 animal source) should be provided in Appendix A.2 of the application (see section X.B).  
1075

Additional guidance is available in:

- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL10 Impurities in New Veterinary Drug Substances*
- VICH: *GL17 Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products*
- VICH: *GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances, and Excipients*



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### VI. CONTROL OF DRUG SUBSTANCE (S.4)

#### A. Specification (S.4.1)

The proposed specification for the drug substance should be provided. The drug substance specification of the drug substance manufacturer, drug product manufacturer, and/or applicant should be included in this section, as appropriate. The specification included in this section (S.4.1) should be for the drug substance used to produce the drug product. If the drug substance is processed (e.g., micronized) before it is used to manufacture the drug product, the specification for the unfinished drug substance, if there is one, should be included in section in S.2.4. If a physical mixture of two or more drug substances is used to produce the drug product, the specifications for the individual drug substances should be included in S.4.1 of the application. The specification for the mixture should be include in P.3.4 of the application.

The specification establishes criteria to which each batch of drug substance should conform to be considered acceptable for its intended use. *Conformance to specification* means that the drug substance, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. A specification is one part of the strategy to control drug substance quality. The specification is proposed and justified by the drug substance manufacturer and applicant. Drug substance specifications are part of the approved application. Specifications are established to confirm the quality of drug substances rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring the quality of the drug substance as it relates to safety and efficacy of the drug product. Information on periodic quality indicator tests is provided below.

The specification sheet should list all tests to which each batch of a drug substance will conform and the associated acceptance criteria and should also include a reference to the analytical procedures that will be used to perform each test. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. If an analytical procedure will be used only to generate stability data the analytical procedure should be described in S.7.3. Justified interim acceptance criteria and tests with sunset provisions should be included in the specification (see section VI.E). The specification from the applicant and/or drug product manufacturer should identify the tests that it will routinely perform and the test results that will be accepted from the drug substance manufacturer's certificate of analysis (COA).<sup>18</sup> Presentation of information in a tabular format is suggested. The specification sheet should also identify:

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<sup>18</sup> The applicant and/or drug product manufacturer must establish the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(2)). The reliability of the analyses need not be established at the time the application is submitted. However, the specification should indicate the tests that will be performed once the reliability of the supplier's results has been established in accordance with current good manufacturing practices.

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- Tests that can be performed in-process (e.g., Process tests, intermediate tests, postsynthesis material tests, unfinished drug substance tests) in lieu of testing the drug substance (the results of such tests should be included in the batch analysis report (e.g., Certificate of analysis))
  - All analytical procedures that will be used for a test; identifying which are regulatory and which are alternative analytical procedures when multiple analytical procedures can be used for a test<sup>19</sup>
  - Acceptance criteria for the test using the regulatory analytical procedure and acceptance criteria for any alternative analytical procedures
  - Release and shelf-life acceptance criteria when both are used

An illustrative example of a specification sheet is provided in tables 1 and 2, below.

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<b>Table 1: Specification for Synthesized Drug Substance X</b>			
Tests	Acceptance Criteria	Regulatory Analytical Procedure	Alternative Analytical Procedure
Appearance	White crystalline powder	Visual	
Identification Tests	Regulatory Analytical Procedure: (1) Retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation obtained as specified in the assay. (2) Spectra is similar to that of corresponding preparation of the reference standard (3) Responds to the tests for sulfate  Alternative Analytical Procedure: Conforms to established spectral library	(All performed)  (1) HPLC, AP <sup>1</sup> # EFG (2) Infrared Absorption, USP <197M> (3) Sulfate, USP <191>	Near Infrared Analysis <sup>2</sup> , AP # ABC
Melting Range	100° to 102°C	AP #BCD	USP <741>, Class Ib
Residue on Ignition	NMT <sup>3</sup> 0.1%	USP <281>, ignition temp. 225°C	
Heavy Metals	0.001%	USP <231>, Method II	
Loss on Drying	NMT 1.0%	USP <731>, dry at 45°C to a constant weight	
Assay	NLT <sup>4</sup> 98.0% and NMT 102.0% of	HPLC, AP # EFG	

<sup>19</sup> Certain *General Chapters* in the USP contain a statement that the text of the USP is harmonized with the corresponding texts of the *European Pharmacopoeia* (EP) and the *Japanese Pharmacopoeia* (JP). However, where a difference appears, or in the event of dispute, the result obtained from the USP procedure is conclusive.

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Tests	Acceptance Criteria	Regulatory Analytical Procedure	Alternative Analytical Procedure
	$C_xH_xN_xO_x$ , calculated on the dried basis		
Organic Impurities Specified Impurities <ul style="list-style-type: none"> <li>• Impurity A</li> <li>• Impurity B</li> <li>• Impurity at RRT<sup>5</sup> <del>XX</del></li> </ul> Unspecified Impurities <ul style="list-style-type: none"> <li>• Any Unspecified</li> </ul> Total Organic Impurities	NMT 0.3% NMT 0.4% NMT 0.3%  NMT 0.1% NMT 1.0%	HPLC; AP # EFG	
Residual Solvent A	NMT 200 ppm in Drug Substance X or NMT 200 ppm in Intermediate C	GC, AP # XYZ	
Particle Size Distribution (D)  <ul style="list-style-type: none"> <li>• D (10%)</li> <li>• D (50%)</li> <li>• D (90%)</li> </ul>	NMT 5 microns NMT 10 microns NMT 30 microns	Brand X Particle Size Analyzer AP # LMN	
<sup>1</sup> AP = Analytical Procedure <sup>2</sup> Test will be performed on-line during final drying operation. <sup>3</sup> NMT = not more than <sup>4</sup> NLT = not less than <sup>5</sup> RRT = relative retention time			

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Tests	Acceptance criteria	Regulatory Analytical Procedure (AP) <sup>2</sup>
Appearance	White lyophilized powder	Visual
Identification Tests:		
Identification Test #1	Retention time of the major peak corresponds to that of the reference standard	RP-HPLC <sup>3</sup> , AP # A123
Identification Test #2	Retention time of the major peak corresponds to that of the reference standard	SE-HPLC <sup>4</sup> , AP # B345
Identification Test #3	Major bands of sample correspond to major bands of the reference standard and account for NLT <sup>5</sup> 85% of total signal	Isoform pattern by isoelectric focusing/Coomassie Blue staining and scanning, AP # C678
Assays:		
Monomer	NLT 95%	SE-HPLC, AP # B345
Specific Biological Activity	20,000-30,000 International Units (IU)/mg	Mouse Bioassay, AP # D901 and Lowry, AP# D902
Purity Tests:		
Dimers and aggregates	NMT <sup>6</sup> 2%	SE-HPLC, AP # B345
Oxidized Forms	Area of the peaks corresponding to oxidized forms is NMT 3% of the sum of peak areas of intact and oxidized products	RP-HPLC, AP # E234
Electrophoretic purity	No additional significant band (NMT 2%) when	SDS-PAGE <sup>7</sup> dissociated and

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Tests	Acceptance criteria	Regulatory Analytical Procedure (AP) <sup>2</sup>
	compared to the profile of the reference	non-dissociated/silver stain, AP # F567
Bacterial endotoxins	NMT 100 Endotoxin Units (EU)/mg	USP <85>, Gel-Clot Techniques
Microbial Limits	NMT 10 Colony Forming Units (CFU)/10 mg Absence of specified indicator organisms	USP <61>, Plate Method
Water Content	NMT 5% (w/w)	USP <921>, Method Ia
pH	7.0-8.0 in a solution containing 10 mg of Drug Substance Y/mL	USP<791>

<sup>1</sup>This is an example specification and is not intended to imply that these are the typical tests and acceptance criteria for a naturally derived protein drug substance. The tests and acceptance criteria appropriate for a particular naturally derived protein drug substance depend on the biological source, manufacturing process, and its intended use. For example, (1) residual monoclonal antibody (mAbs) should be monitored for drug substances purified by affinity chromatography using mAbs; (2) for proteins that are not as highly purified, less vigorous acceptance criteria for purity tests may be appropriate; and (3) the need for bacterial endotoxins and microbial limits testing and the associated acceptance criteria depend on the route of administration of the drug product and the controls used during the manufacture of the drug product.

<sup>2</sup>There are no alternative analytical procedures specified for Drug Substance Y

<sup>3</sup>RP-HPLC = reverse phase high-pressure liquid chromatography

<sup>4</sup>SE-HPLC = size exclusion high-pressure liquid chromatography

<sup>5</sup>NLT = not less than

<sup>6</sup>NMT = not more than

<sup>7</sup>SDS-PAGE = Sodium dodecyl sulfate polyacrylamide gel electrophoresis

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- **Periodic Quality Indicator Tests**

The CGMP regulations require that each batch of drug substance will be tested for conformity with the appropriate written specification; a batch that does not meet the specification must not be used to manufacture the drug product (21 CFR 211.84). Occasionally and when justified, other tests and associated acceptance criteria and analytical procedures that assess drug substance quality can be included in the application and not be listed in the drug substance specification. These tests, referred to as periodic quality indicator tests (PQITs), augment the drug substance specification. A PQIT is performed at release on preselected batches and/or at predetermined intervals, rather than on a batch-to-batch basis. A PQIT can be warranted when a test, performed and reported as part of the batch analysis, has value as an indicator of drug substance quality, but information indicates that the test need not to be performed on each batch of drug substance considering the specific drug products in which the drug substance is used. Designation of certain tests such as for description, identification, assay, or impurities as PQITs would not be considered appropriate. PQITs, along with the drug substance

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1151 specification, form a basis for approving the application (see, for example, section  
1152 505(b)(1)(D) and 505(d)(3) of the Federal Food, Drug, and Cosmetic Act).<sup>20</sup>

1153  
1154 Sufficient data should be available to support a proposal to designate a test as a PQIT. If  
1155 sufficient data (e.g., data from multiple batches, all proposed manufacturing sites and  
1156 processes) are available, a PQIT proposal can be included in the original application. A  
1157 proposal for a PQIT should include:

- 1158
- 1159 • The reason the PQIT is being proposed
  - 1160 • Justification and data to support the periodic testing
  - 1161 • The protocol (e.g., Frequency) for performing the test, including when
  - 1162 postapproval changes are implemented
  - 1163 • A commitment
- 1164

1165 The commitment should state that:

- 1166
- 1167 • The PQIT will be performed according to the protocol approved in the  
1168 application.
  - 1169 • Failure to meet the acceptance criteria for the PQIT will be handled (e.g.,  
1170 Investigation, batch rejection decision) in the same manner as a failure of a test  
1171 included in the drug substance specification and the PQIT will be performed on  
1172 each subsequent batch until the failure is resolved.
  - 1173 • Any investigation will assess the effect on all batches produced, in particular, the  
1174 batches between the last batch tested with a passing test result and the batch that  
1175 failed.
  - 1176 • If the result of the investigation confirms a batch failure or is inconclusive, a  
1177 changes- being-effected supplement will be submitted to include the test in the  
1178 drug substance specification.

1179  
1180 A list of PQITs, with associated acceptance criteria and reference to analytical  
1181 procedures, should be included in S.4.1 of the application. The protocol and commitment  
1182 should also be included in S.4.1. Data and justification to support the designation of a  
1183 PQIT should be included in S.4.4 and S.4.5, as appropriate. The recommendations on  
1184 CMC information that should be provided in S.4.2 and S.4.3 also apply to PQITs.

1185  
1186 It is recognized that only limited data may be available at the time of submission of an  
1187 application. Therefore, this concept would generally be implemented postapproval once  
1188 sufficient data are available and after approval of a prior approval supplement.

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<sup>20</sup> 21 U.S.C. 355 (b)(1) and 355 (d)(3).

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Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

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### B. Analytical Procedures (S.4.2)

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The analytical procedures used for testing a drug substance should be provided.

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Recommendations on the content and format of analytical procedures submitted in NDAs

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and ANDAs will be provided in a forthcoming CDER/CBER guidance on *Analytical*

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*Procedures and Methods Validation: Chemistry, Manufacturing, and Controls*

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*Documentation*. Information should be provided for all analytical procedures listed in the

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specification (S.4.1). The following additional guidance is provided on submitting

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analytical procedure information from published sources.

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- **Analytical Procedures from an Official Compendium or Another FDA-Recognized Standard Reference**

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If the analytical procedure used is in the current revision of an official compendium or

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another FDA-recognized standard reference (e.g., AOAC International Book of Methods)

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and the referenced analytical procedure is not modified, the analytical procedure need not

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be provided. A specific citation to the analytical procedure is sufficient.<sup>21</sup> When a

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general chapter or monograph included in an official compendium or other FDA

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recognized standard reference allows for the use of more than one analytical procedure

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for a test, the specific analytical procedure that will be used should be cited here (S.4.2)

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and in the specification (S.4.1). For example, when using USP <921> *Water*

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*Determination*, the method should be specified (e.g., Method Ia). If an analytical

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procedure is based on one of these sources but has been modified, the analytical

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procedure should be provided.

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- **Analytical Procedures from Other Published Sources**

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Analytical procedures from any other published source (e.g., another country's

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compendium, scientific journal) should be provided.

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<sup>21</sup> The current revision of an analytical procedure in a compendial monograph or general chapter should be used. Therefore, when citing an official compendium, the version of the compendium should not be included in the citation. For example, the *USP* should be cited rather than *USP 25*.

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Additional guidance is available in:

- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL1 Validation of Analytical Procedures: Definition and Terminology*

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### C. Validation of Analytical Procedures (S.4.3)

Analytical validation information, including experimental data (e.g., representative chromatograms with peak identification), for the analytical procedures used for testing the drug substance should be provided. Validation of an analytical procedure is the process of demonstrating that analytical procedures are suitable for their intended use. This information should be provided for all analytical procedures listed in the specification (S.4.1). Stability data (S.7.3), including data from stress studies, should be used to support the validation of the analytical procedures. Recommendations on the analytical validation information that should be submitted in NDAs and ANDAs will be provided in a forthcoming CDER/CBER guidance on *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*. The methods validation package should be provided in R.3.S.

Additional guidance is available in:

- FDA: *Submitting Samples and Analytical Data for Methods Validation*
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL1 Validation of Analytical Procedures: Definition and Terminology*
- VICH: *GL2 Validation of Analytical Procedures: Methodology*

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### D. Batch Analyses (S.4.4)

A description of relevant batches and results of batch analyses should be provided. Batch analysis reports (e.g., certificates of analysis (COAs)) should be provided for all drug substance batches used for (1) nonclinical studies (i.e., pharmacology and/or toxicology), (2) drug product clinical efficacy and safety, bioavailability, bioequivalence, and (3) primary stability studies. Batch analysis data should also be provided for any other batches that are being used to establish or justify specifications and/or evaluate consistency in manufacturing. The batch analysis reports and collated batch analyses

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1247 data should include a description of the batches. This information can be presented (1)  
1248 with the batch data as space permits or (2) in a separate table with only the batch identity  
1249 being included with the batch data. The description should include:

1250

- 1251 • Batch identity (i.e., batch number) and size
- 1252 • Date of manufacture
- 1253 • Site of manufacture
- 1254 • Manufacturing process (e.g., synthetic route A), where applicable
- 1255 • Use of batch (e.g., bioavailability, stability)

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1257 Test results should be expressed numerically or qualitatively (e.g., white crystalline  
1258 powder), as appropriate. We discourage the use of terms such as *conforms* or *meets*  
1259 *specification*.

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### 1. *Batch Analysis Reports*

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1263 The batch analysis reports should include results from all tests performed on the batch,  
1264 including tests that are not part of the proposed specification. References to analytical  
1265 procedures should be provided.

1266

1267 A summary of any changes in the analytical procedures should be provided if the  
1268 analytical procedures (1) changed over the course of generating the batch analyses data  
1269 and/or (2) are different from the analytical procedure included in S.4.2. The summary  
1270 should identify when an analytical procedure changed, the differences between the  
1271 analytical procedures, and the impact of the differences with respect to the data being  
1272 reported. For example, a summary could state that the solvent system for the assay was  
1273 changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute  
1274 using System A could be quantitated separately. If there are significant differences in the  
1275 analytical procedures (e.g., different fundamental principles such as titration and HPLC),  
1276 a more detailed summary describing the changes may be warranted.

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### 2. *Collated Batch Analyses Data*

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1280 Presentation of results from all batches for a particular test in tabular and/or graphical  
1281 format is often helpful in justifying the acceptance criteria. Collated batch analyses data  
1282 are not warranted for all tests. However, collated data should be provided for assay and  
1283 impurities (e.g., degradation products, residual solvents) and should be considered for  
1284 other tests such as water content.

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Additional guidance is available in:

- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL10 Impurities in New Veterinary Drug Substances*
- VICH: *GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances, and Excipients*

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### **E. Justification of Specification (S.4.5)**

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Justification for the proposed drug substance specifications should be provided. The justification should be based on relevant development data (S.2.6), information on impurities (S.3.2), standards in an official compendium, batch analyses data (S.4.1), stability studies (S.7), toxicology data, and any other relevant data. The discussion in this section should unify data and information that are located in other sections of the application, either by reference or in summary. When justifying the specification, an applicant should consider data from (1) drug substance batches used in evaluating clinical efficacy and safety, bioavailability, and/or bioequivalence, (2) primary stability batches, and (3) relevant development and process validation batches, when available. If multiple drug substance manufacturing sites or processes are planned, it can be valuable to consider data from these sites and processes in establishing the tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug substance at any particular site or by any particular method. Justification for an in-process test that is used in lieu of a drug substance test should be included in S.2.4.

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#### **• Tests**

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Inclusion of a test in the drug substance specification need not be justified. However, exclusion of a test that is normally performed on a type of drug substance, one that is recommended in a relevant FDA guidance, or one that was reported in the batch analyses (S.4.4) should be justified. Justification for the designation of a test as a periodic quality indicator test also should be provided (see section VI.A).

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Occasionally, it may appear that a test performed and reported as part of the batch analyses may not be necessary or that a drug substance characteristic may not be critical to the quality of the specific drug products in which the drug substance is used. For example, the available test results for heavy metals may be very low or below the limit of

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1318 detection of the analytical procedure for the batches produced in support of the  
1319 application indicating that there may be no need to perform the test. However, it is not  
1320 certain if the same type of results will continue to be observed for production batches  
1321 because (1) limited data are available at the time the application is submitted and/or (2)  
1322 the manufacturing process for production batches will be different (e.g., scale,  
1323 equipment) from that used to produce the batches used to support the application and the  
1324 effect, if any, of the differences has yet to be characterized. In these or similar  
1325 circumstances, an applicant could propose a *sunset test protocol* for a test, which would  
1326 provide for the test to be dropped from the specification after an agreed number of  
1327 production batches have met certain criteria.<sup>22</sup> The proposal should include the (1)  
1328 reason why the sunset provision is being proposed; (2) number of consecutive production  
1329 batches that will be tested before inclusion of the test in the drug substance specification  
1330 is reevaluated; (3) criteria that would be achieved, including data analysis plan, for the  
1331 test to be dropped; and (4) postapproval reporting mechanism for notifying FDA of the  
1332 test results when the criteria have been achieved. A *sunset test protocol* could also be  
1333 considered when FDA requests that a test be added to the specification.  
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- **Acceptance Criteria**

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1337 Justification should be provided for all proposed acceptance criteria included in the drug  
1338 substance specification. Results from nonclinical (pharmacology and/or toxicology),  
1339 clinical, and stability studies and manufacturing and analytical capability should be  
1340 considered when proposing acceptance criteria. Proposed acceptance criteria can include  
1341 a reasonable allowance for analytical and manufacturing variability. The justification  
1342 should discuss the basis of the proposed acceptance criteria from the perspectives of  
1343 available data and analytical and manufacturing capability and variability. Furthermore,  
1344 any statistical approaches that are used to establish the acceptance criteria should be  
1345 described.  
1346

1347 Occasionally, an applicant may wish to propose *interim acceptance criteria* for a specific  
1348 test because there is some uncertainty whether the same type of results will continue to be  
1349 observed for subsequent drug substance batches. This uncertainty often occurs when (1)  
1350 there are limited data available at the time the application is submitted and/or (2) the  
1351 manufacturing process for production batches will be different (e.g., scale, equipment)  
1352 from that used to produce the batches used to support the application and the effect, if  
1353 any, of the differences has yet to be characterized. The proposal should include the (1)  
1354 reason why the interim acceptance criteria are being proposed, (2) number of consecutive  
1355 batches from each process (if alternative processes are used) that will be tested and/or the  
1356 time frame before the acceptance criteria will be finalized, (3) data analysis plan, and (4)  
1357 proposed reporting mechanisms for finalizing the acceptance criteria when the proposed  
1358 final acceptance criteria are tighter, broader, or the same as the interim acceptance  
1359 criteria. An applicant should not propose using interim acceptance criteria as a substitute  
1360 for providing recommended or agreed upon (e.g., at pre-NDA meetings) information in

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<sup>22</sup> A proposal to drop a test, based on historical data, can also be submitted postapproval in a prior approval supplement.

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1361 an application. For example, proposing interim acceptance criteria would not be  
1362 appropriate when the stability data package recommended in the ICH guidance *Q1A*  
1363 *Stability Testing of New Drug Substances and Products* or VICH guidance *GL3 Stability*  
1364 *Testing of New Veterinary Drug Substance and Medicinal Products* has not been  
1365 provided.<sup>23</sup> For NDAs, finalization of interim acceptance criteria will be a phase 4  
1366 commitment.

1367  
1368 The proposed acceptance criteria for impurities should not be greater than the levels  
1369 qualified through nonclinical or clinical studies presented in the NDA. The qualified  
1370 level of each impurity that is individually listed in the drug substance specification should  
1371 be provided in S.3.2. Appropriate qualified levels can be obtained from published  
1372 toxicology studies or guidance documents. Acceptance criteria for residual solvents  
1373 should generally be based upon manufacturing capability. An applicant should consider  
1374 the contribution of residual solvents in its drug product excipients when proposing  
1375 acceptance criteria for residual solvents in the drug substance. See ICH *Q3C Impurities:*  
1376 *Residual Solvents* or VICH *GL18 Impurities: Residual Solvents in New Veterinary*  
1377 *Medicinal Products, Active Substances, and Excipients*.

### 1378 1379 • Analytical Procedures

1380  
1381 The analytical procedures listed in the drug substance specification normally need not be  
1382 justified because the appropriateness of the procedure is supported by information in  
1383 S.4.2, S.4.3, and R.3.S. In some instances, however, justification for the type of  
1384 analytical procedure used would be warranted. For example, justification should be  
1385 provided for the use of a nonstability-indicating assay procedure. The justification  
1386 should explain the scientific reasons why a stability indicating procedure is not viable or  
1387 warranted (e.g., inorganic salts) and, when appropriate, which analytical procedures  
1388 complement the assay procedure by qualitatively and/or quantitatively monitoring  
1389 impurities, including degradants.  
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Additional guidance is available in:

- ICH: *Q3A Impurities in New Drug Substances*
- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*
- VICH: *GL10 Impurities in New Veterinary Drug Substances*
- VICH: *GL18 Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances, and Excipients*

<sup>23</sup> For those applications that fall within the scope of these guidances.

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### VII. REFERENCE STANDARDS OR MATERIALS (S.5)

Information on the reference standards or reference materials used for testing of the drug substance (active moiety) should be provided. If the reference standard is obtained from an official source, this should be stated. When the reference standard is not from an official source, it should be fully characterized. Recommendations on the information that should be provided for reference standards will be provided in a forthcoming CDER/CBER guidance for industry on *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*. A list of any available reference standards for impurities and intermediates should be included in S.5.<sup>24</sup>

Additional guidance is available in:

- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

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### VIII. CONTAINER CLOSURE SYSTEM (S.6)

A description of the container closure system for the drug substance should be provided, including the identity of materials of construction of each primary packaging component and its specification. The same type of information should be provided for functional secondary packaging components as is provided for primary packaging components. For nonfunctional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light,<sup>25</sup> compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction. Stability data used to support the suitability of the container closure systems should be provided in S.7.3 and referenced in S.6.

<sup>24</sup> Whether or not information is included in the application, complete records must be maintained of any testing and standardization of laboratory reference standards (21 CFR 211.194(c)).

<sup>25</sup> Data, such as light transmission data, would be provided in S.6. Results from photostability studies, when warranted, should be provided in S.7.3 and cross-referenced in this section (S.6).

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Additional guidance is available in:

- FDA: *Container Closure Systems for Packaging Human Drugs and Biologics*

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### 1423 **IX. STABILITY (S.7)**

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1425 Information relating to the stability of the drug substance should be provided in S.7.

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#### 1427 **A. Stability Summary and Conclusions (S.7.1)**

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1429 The types of studies conducted, protocols used, and the results of the studies should be  
1430 summarized. The discussion should include for example (1) a summary of stability  
1431 batches tested, storage conditions used, attributes tested, shelf-life acceptance criteria, test  
1432 schedule, amount of data available, and analysis of data (including a summary of the  
1433 statistical analysis if performed) and (2) conclusions regarding the label storage  
1434 conditions and retest or expiration dating period, as appropriate.

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#### 1436 **B. Postapproval Stability Protocol and Stability Commitment (S.7.2)**

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1438 A postapproval stability protocol and stability commitment should be provided.

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#### 1440 **C. Stability Data (S.7.3)**

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1442 Results of stability studies, including statistical analysis if performed, should be  
1443 presented in an appropriate format (e.g. tabular, graphical, narrative). An applicant  
1444 should propose a retest or expiration dating period and appropriate label storage  
1445 conditions for the drug substance. There should be a direct link between the proposed,  
1446 retest or expiration dating period and proposed label storage conditions and the  
1447 demonstrated stability characteristics of the drug substance.

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##### 1449 *1. Primary Stability Studies*

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1451 The results from long-term, accelerated and, when performed, intermediate studies  
1452 undertaken on primary batches should be provided. Stability study reports should also be  
1453 included.

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1455 The analytical procedures used to generate the data should be identified. Information on  
1456 the analytical procedures used to generate the data should be included in this section of  
1457 the application as follows:

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- The analytical procedure, validation of analytical procedures and justification of acceptance criteria, as appropriate, should be included if the analytical procedure listed in the stability protocol is different from the analytical procedure described in S.4 for the corresponding test (i.e., batch release versus stability analytical procedure), or if a test included in the stability protocol is not described in S.4.
  - A summary of any changes in the analytical procedures should be provided if the analytical procedure was changed over the course of generating the stability data. The summary should identify when an analytical procedure changed, the differences between the analytical procedures, and the impact of the differences with respect to the data being reported. For example, a summary could state that the solvent system for the assay was changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute using System A could be quantitated separately. If there are significant differences in the analytical procedures (e.g., different fundamental principles such as titration and HPLC) a more detailed summary describing the changes may be warranted.

### 2. *Supporting Stability Studies*

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Data, other than those from primary stability studies, that support the analytical procedures, the proposed retest date or shelf life, and label storage statements can be provided. Such data can include, for example, stability data on small-scale batches of drug substance or manufacturing processes not proposed for production batches. Stability data to support holding times for intermediates or during processing should also be provided in this section when warranted (e.g. certain proteins). The analytical procedures should be identified, and when analytical procedures are different from those described elsewhere in the application, information should be provided on the analytical procedures to the extent warranted to support the use of the data.

### 3. *Stress Studies*

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Any results from drug substance stress testing should be provided in this section of the application. The design of the stress studies should be discussed briefly. The information should be used, as appropriate, to support the validation of analytical procedures (S.4.3), the impurities acceptance criteria and/or characterization of expected impurities (S.3.2, S.4.1), justification of the drug product specification (S.4.5), and stability summary and conclusions (S.7.1 and S.7.3).

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Additional guidance is available in:

- FDA: *Submitting Documentation for the Stability of Human Drugs and Biologics*<sup>26</sup>
- ICH: *Q1A Stability Testing of New Drug Substances and Products*
- ICH: *Q1B Photostability Testing of New Drug Substances and Products*
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- ICH: *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*
- VICH: *GL1 Validation of Analytical Procedures: Definition and Terminology*
- VICH: *GL2 Validation of Analytical Procedures: Methodology*
- VICH: *GL3 Stability Testing of New Veterinary Drug Substance and Medicinal Products*
- VICH: *GL5 Stability Testing: Photostability Testing of New Veterinary Drug Substance and Medicinal Products*
- VICH: *GL17 Stability Testing of New Biotechnological/Biological Veterinary Medicinal Products*

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## 1500 X. APPENDICES (A)

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1502 When warranted, information relating to both drug substances and drug products should be  
1503 included in the Appendices (section A) of the NDA or ANDA or appropriate section of the  
1504 NADA or ANADA. If drug substance and drug product information is provided in an appendix,  
1505 the preferred presentation is drug substance information followed by drug product information  
1506 (e.g., A.1 drug substance then drug product, followed by A.2). The recommendations provided  
1507 below relate to drug substances. Recommendations on the information to include in the  
1508 Appendices for drug products will be provided in the forthcoming drug product guidance.  
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### A. Facilities and Equipment (A.1)

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1512 Information on facilities and equipment, in addition to the information provided in other  
1513 sections of the application (e.g., S.2.1, S.2.2), is usually not needed. However, for  
1514 naturally derived protein drug substances, or when contamination with viral adventitious  
1515 agents or transmissible spongiform encephalopathy (TSE) agents is a concern, additional  
1516 information can be warranted and should be included in this section of the application.  
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#### • Viral Adventitious Agents and TSE Agents

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<sup>26</sup> In June 1998 (63 FR 31224), the Agency made available a draft revision of this guidance entitled *Stability Testing of Drug Substances and Drug Products*. When finalized, this revision will be the primary reference source on stability testing of drug substances and drug products.

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1520 All developmental or marketed drug substances manufactured or processed in the same  
1521 areas as the applicant's drug substance should be identified when there is potential for  
1522 cross-contamination with TSE agents or viral adventitious agents. Information should be  
1523 included on the design features of the facility and procedures to prevent cross-  
1524 contamination of areas and equipment.

1525  
1526 If bovine-derived materials from BSE countries as defined by the U.S. Department of  
1527 Agriculture (9 CFR 94.11) are used or manipulated in the same facility, additional  
1528 information should be provided, such as whether dedicated equipment is used.

1529  
1530 • **For Naturally Derived Protein Drug Substances**

1531  
1532 A diagram should be provided illustrating the manufacturing flow, including movement  
1533 of raw materials, personnel, waste, and intermediates in and out of the manufacturing  
1534 areas. Information should be presented with respect to adjacent areas or rooms that may  
1535 be of concern for maintaining integrity of the drug substance (e.g., cross contamination).

1536  
1537 Information on all development or marketed drug substances manufactured or  
1538 manipulated in the same areas as the applicant's drug substance should be included.

1539  
1540 A summary description of the product-contact equipment and its use (dedicated or multi-  
1541 use) should be provided. Information on preparation, cleaning, sterilization, and storage  
1542 of specified equipment and materials should be included, as appropriate.

1543  
1544 Information should be included on procedures (e.g., cleaning and production scheduling)  
1545 and design features of the facility (e.g., area classifications) to prevent contamination or  
1546 cross-contamination of areas and equipment where drug substance manufacturing is  
1547 performed.

1548  
1549 For biotechnology-derived protein drug substances, additional recommendations will be  
1550 provided in the forthcoming guidance on the submission of CMC information for a  
1551 therapeutic recombinant DNA-derived product or a monoclonal antibody for in vivo use.

1552  
1553 **B. Adventitious Agents Safety Evaluation (A.2)**

1554  
1555 Information assessing the risk with respect to potential contamination with adventitious  
1556 agents should be provided. The recommendations provided below relate to the drug  
1557 substance. Recommendations on the information to include in A.2 for drug product will  
1558 be provided in the forthcoming drug product guidance. For example, if viral safety  
1559 evaluation studies are performed as part of the drug substance manufacturing (e.g.,  
1560 assessment of a starting material from an animal source), the applicant should refer to the  
1561 drug substance guidance. However, an applicant should refer to the forthcoming drug  
1562 product guidance for recommendations when the studies are performed as part of the  
1563 drug product manufacturing (e.g., assessment of a biotechnology-derived excipient).

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1565 For synthetic or semisynthetic drug substances, reduced testing of materials or drug  
1566 substance and/or validation of removal and/or inactivation of adventitious agents can be  
1567 appropriate in certain instances, with justification. Such instances can include synthetic  
1568 steps that inactivate adventitious agents. Early dialog with FDA is encouraged in these  
1569 circumstances.

1570  
1571 Furthermore, for biotechnology-derived protein drug substances, additional  
1572 recommendations will be provided in the forthcoming guidance on the submission of  
1573 CMC information for a therapeutic recombinant DNA-derived product or a monoclonal  
1574 antibody for in vivo use.

### *1. Nonviral Adventitious Agents*

1575  
1576  
1577  
1578 The detailed information regarding the routine manufacturing control of adventitious  
1579 agents, such as bacteria, mycoplasma, and fungi, typically using well-established (e.g.,  
1580 pharmacopoeial) analytical procedures, should be provided in the appropriate sections  
1581 within Module 3.2.S. If well-established (e.g., pharmacopoeial) analytical procedures are  
1582 not used, more detailed information regarding the analytical procedures used should also  
1583 be included in 3.2.S.

1584  
1585 With respect to other nonviral adventitious agents, such as transmissible spongiform  
1586 encephalopathy agents and prions, the detailed information should be placed in 3.2.A.2.

1587  
1588 Certifications and/or certificates relating to the use of bovine-derived materials and  
1589 sourcing of materials from BSE countries as defined by the U.S. Department of  
1590 Agriculture (9 CFR 94.11) should be provided, as appropriate.

### *2. Viral Adventitious Agents*

1591  
1592  
1593  
1594 Detailed information from viral safety evaluation studies should be provided in this  
1595 section. Viral evaluation studies should demonstrate that the materials used in production  
1596 are considered safe and that the approaches used to test, evaluate, and eliminate the  
1597 potential risks during manufacturing are suitable.

1598  
1599 Information essential to evaluate the virological safety of materials of animal or human  
1600 origin (e.g., biological fluid, tissue, organ) should be provided. See related information  
1601 in section IV.C.

1602  
1603 The selection of virological tests that are conducted during manufacturing (e.g.,  
1604 unprocessed bulk, post viral clearance testing) should be justified. The type of test,  
1605 sensitivity and specificity of the test, if applicable, and frequency of testing should be  
1606 included. Test results to confirm, at an appropriate stage of manufacture (including drug  
1607 substance release if possible), that the product is free from viral contamination should be  
1608 provided. (See related information in section.) Results for viral testing of unprocessed  
1609 bulk should be included.

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1611 The rationale and action plan for assessing viral clearance and the results and evaluation  
1612 of the viral clearance studies should be provided. Data can include those that  
1613 demonstrate the validity of the scaled-down model compared to the commercial scale  
1614 process; the adequacy of viral inactivation or removal procedures for manufacturing  
1615 equipment and materials; and manufacturing steps that are capable of removing or  
1616 inactivating viruses (see related information in section IV.E).  
1617

Additional guidance is available in:

- ICH: *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

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1619

### **XI. REGIONAL INFORMATION (R)**

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1622 When warranted, information relating to both drug substances and drug products should be  
1623 included in the Regional Information section (section R) of the NDA or ANDA or appropriate  
1624 section of the NADA or ANADA. The recommendations provided below relate to drug  
1625 substances. Recommendations on the information to include in the Regional Information section  
1626 for drug products will be provided in the forthcoming drug product guidance.

1627

#### **A. Executed Production Records (R.1.S)**

1629

An executed batch record is not required, but if an executed production record is provided for illustrative purposes, it should be included in R.1.S.

1631

1632

#### **B. Comparability Protocols (R.2.S)**

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1634

A comparability protocol is a protocol describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of postapproval manufacturing changes on the identity, quality, purity, and potency of the drug substance as these factors may relate to the safety and effectiveness of the drug product. Comparability protocols are optional. If a comparability protocol is proposed, it should be included in this section (R.2.S). Approval of a comparability protocol can justify a reduced reporting category for the particular postapproval change described in the protocol.

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#### **C. Methods Validation Package (R.3.S)**

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1645

Methods validation is the process of demonstrating that analytical procedures are suitable for their intended use. Part of the methods validation process can include FDA

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1648 laboratory analysis to demonstrate that an analytical procedure is reproducible by  
1649 laboratory testing. A methods validation package (multiple copies for paper applications)  
1650 must be submitted in the application (21 CFR 314.50(e)(2) and 314.94(a)(10)) and should  
1651 be included in this section (R.3.S).  
1652  
1653

### 1654 **XII. LITERATURE REFERENCES (3.3)** 1655

1656 When warranted, references to the scientific literature relating to both drug substances and drug  
1657 products should be included in the Literature References (3.3) section of the NDA or ANDA or  
1658 appropriate section of the NADA or ANADA.  
1659

1660 The full bibliographic reference should be cited close to where the reference appears in the text  
1661 of the application (e.g., in a footnote or section endnote). The full text of the literature cited  
1662 (e.g., journal article) should be included in the Literature References section, except when  
1663 otherwise indicated. For example, as previously stated in this guidance, monographs from an  
1664 official compendium need not be included in the application.  
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### **ATTACHMENT 1:**

#### **STARTING MATERIALS FOR SYNTHETIC DRUG SUBSTANCES**

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A starting material for a synthetic drug substance is a chemical compound of defined molecular structure that contributes to the structure of the drug substance. A reagent that contributes a minor structural element to the drug substance (e.g., hydride ion) is not considered to fall within the meaning of *starting material*. A synthesis can be linear or convergent. Therefore, an applicant should propose one or more starting materials to mark the beginning of each synthesis branch.

The description of the manufacturing process in an application begins with the starting material or materials. Appropriate GMPs, as defined in ICH Q7A, can apply to the manufacturing steps after introduction of the starting material. Because there is limited FDA oversight of the manufacturing of the starting material, the starting material should be selected and controlled so that the risk from future changes in the quality of the starting material affecting the identity, quality, purity, or potency of the drug substance is minimized. A proposed starting material should be chosen so that sufficient information will be available to the FDA on the manufacturing process to evaluate the safety and quality of the drug substance. A drug substance that is used to synthesize another drug substance is not an appropriate candidate for designation as a starting material. An applicant can discuss the selection of proposed starting materials prior to submitting its application. For NDAs, FDA recommends that the choice of starting material be discussed during the investigational period (e.g., at end-of-phase 2 (EOP-2) meeting).

The extent of information that should be submitted in the application to justify the proposed starting materials depends on whether or not the chemical has a significant nonpharmaceutical market. FDA will consider the justification provided to support a proposed starting material as well as other relevant information such as the proposed starting material specification and controls on manufacturing steps downstream from the proposed starting material when evaluating the appropriateness of a proposal to designate a chemical as a starting material.

- **Starting Materials with a Significant Nonpharmaceutical Market**

A significant nonpharmaceutical market is considered to exist if the quantity of the chemical needed for the production of the drug substance represents only a small fraction of the chemical's total market. This is true whether the chemical is made by the drug substance manufacturer for its own use or is obtained from another firm. If the quantity of the chemical made for the nonpharmaceutical market is insufficient to ensure consistent quality of the drug substance and the chemical is further processed to produce material of higher quality, the purification operations should be described as part of the manufacturing process of the drug substance (S.2.2). See section II of this attachment for recommendations on the documentation that should be provided for these starting materials.

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### **1708 • Starting Materials without a Significant Nonpharmaceutical Market**

1709  
1710 A chemical should not be considered to have a significant nonpharmaceutical market if (1) the  
1711 only market for the chemical is to manufacture drug substance; (2) the drug substance  
1712 manufacturer had to synthesize the chemical, or arrange for another firm to synthesize it, to  
1713 produce drug substance for clinical trials (phase 1 and phase 2 clinical trials for human drug  
1714 products); (3) an existing manufacturer of the chemical had to scale up its process to produce  
1715 sufficient quantities of drug substance for clinical trials (phase 1 and phase 2 clinical trials for  
1716 human drug products); or (4) the method of manufacture was provided by the drug substance  
1717 manufacturer to the other firms that manufacture the chemical. See sections I and II of this  
1718 attachment, respectively, for selection principles and recommendations on the documentation  
1719 that should be provided for these starting materials.

1720  
1721

### **1722 I. SELECTION PRINCIPLES FOR STARTING MATERIALS WITHOUT A** **1723 SIGNIFICANT NONPHARMACEUTICAL MARKET**

1724  
1725 Each proposed starting material without a significant nonpharmaceutical market should be  
1726 evaluated with respect to the selection principles described in sections I.A through I.D. These  
1727 principles are intended to assist an applicant in proposing starting materials at a point in the  
1728 process that ensures the following:

- 1729
- 1730 • Sufficient information is submitted in the application for FDA to evaluate the safety and  
1731 quality of the drug substance.
  - 1732 • Future changes in the manufacture of the starting material are unlikely to affect the safety or  
1733 quality of the drug substance.

1734  
1735 The selection principles should be discussed when justifying proposed starting materials (see  
1736 II.D.2 of this attachment). If a proposed starting material is inconsistent with a selection  
1737 principle, this should be justified or the applicant should consider proposing as a starting material  
1738 a chemical earlier in the manufacturing process that is consistent with the selection principles.

1739  
1740

#### **A. Propinquity**

1741  
1742 A chemical proposed as a starting material should be separated from the final  
1743 intermediate by several reaction steps that result in isolated and purified intermediates.  
1744 Having several reaction steps and associated purification and isolation steps separating  
1745 the starting material and the final intermediate reduces the risk that changes in the  
1746 manufacturing steps prior to the starting material would adversely affect the identity,  
1747 quality, purity, or potency of the drug substance as these factors relate to the safety and  
1748 efficacy of the drug product. For example, the risk of a new starting material impurity  
1749 (e.g., from a new source or different manufacturing process) being carried over to the  
1750 drug substance decreases as the number of manufacturing steps between the starting  
1751 material and the final intermediate increase.

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1753 A reaction followed by multiple purifications should be counted as a single reaction step.  
1754 The reaction step that produces the final intermediate can be counted as a reaction step  
1755 for purposes of evaluating propinquity if the final intermediate is isolated and purified.  
1756 An interconversion of a salt to or from its free acid or base form should not be counted as  
1757 a reaction step for the purpose of evaluating propinquity.  
1758

1759 Isolated and purified intermediates are typically obtained by filtration or centrifugation,  
1760 fractional distillation from a mixture, or chromatographic procedures. A key element in  
1761 each of these examples is that some removal of organic impurities usually results from  
1762 the isolation operation. An operation should not be considered to produce an isolated and  
1763 purified intermediate if some purification of this nature does not simultaneously take  
1764 place. For example, evaporating solvent from a reaction mixture or the extraction work  
1765 up of a reaction mixture is not considered to produce an isolated and purified  
1766 intermediate.  
1767

### **B. Isolated and Purified**

1768  
1769  
1770 A chemical proposed as a starting material should be an isolated and purified substance.  
1771 Identification of an isolated and purified substance as the starting material, as opposed to  
1772 an in situ and/or crude substance reduces the risk of degradants and/or impurities  
1773 affecting the identity, quality, purity, or potency of the drug substance.  
1774

### **C. Carryover of Impurities**

1775  
1776  
1777 A chemical proposed as a starting material should not be the source of significant levels  
1778 of impurities in the drug substance. Robust acceptance criteria for starting material  
1779 impurities reduces the risk of a new starting material impurity (e.g., from a new source or  
1780 different manufacturing process) and/or its associated reaction by-products being carried  
1781 over to the drug substance in levels that warrant identification and qualification from a  
1782 safety perspective.  
1783

1784 For purposes of selecting proposed starting materials, a significant level is considered to  
1785 be greater than 0.10 percent in the drug substance (0.20 percent for veterinary drug  
1786 substances not used in human drug products) of any of the following impurities:  
1787

- 1788 • The proposed starting material
  - 1789 • Impurities in the proposed starting material
  - 1790 • Synthetic derivatives of impurities in the proposed starting material
- 1791

1792 Moreover, a proposed starting material should be at or before the point in the  
1793 manufacturing process where transmissible spongiform encephalopathy (TSE) agents can  
1794 be introduced into the process. For example, if a chemical is produced using an enzyme  
1795 that can introduce TSE agents into the process, the proposed starting material should be  
1796 prior to the enzymatic step regardless of whether the chemical is consistent with all other  
1797 selection principles.

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### **D. Complexity of Structure**

A chemical proposed as a starting material should be readily distinguishable from potential isomers and analogs so that adequate controls can be established for the starting materials. There is increased risk to the identity, quality, purity, or potency of the drug substance if a chemical cannot be readily distinguished from its potential isomers and analogs. Moreover, a chemical with a complex molecular structure (e.g., multiple chiral centers) are usually produced through complex synthetic pathways, which can also increase the risk. A proposed starting material typically should possess only a limited number of functional groups and structural features that can result in geometric or stereoisomerism for it to be considered readily distinguishable. It is impossible to set meaningful limits on the maximum number of such elements that a starting material can possess to be considered readily distinguishable. However, data demonstrating that instrumental techniques commonly used for identification tests (e.g., ultraviolet-visible spectrophotometry, infrared spectroscopy) are specific can be provided to justify proposed starting materials that the Agency might otherwise consider to be too complex. If advanced techniques suitable for complex structures (<sup>1</sup>H-NMR, <sup>13</sup>C-NMR, 2D NMR, mass spectrometry, elemental analysis, X-ray crystallography, chiral HPLC) are needed to distinguish the proposed starting material from potential isomers and analogs, the chemical is not an appropriate candidate for designation as a starting material.

## **II. DOCUMENTATION**

Applicants should provide the following information in S.2.3:

### **A. List of Proposed Starting Materials**

The chemical name, CAS Registry Number, structure, molecular formula, molecular weight, and relevant physical characteristics (e.g., appearance, physical state, melting or boiling range) should be provided for each proposed starting material.

### **B. Flow Diagram of the Complete Synthesis**

A flow diagram should be provided showing the complete route of synthesis of the drug substance. Each synthesis branch should begin with chemicals that have a significant nonpharmaceutical market, regardless of whether these chemicals are being proposed as starting materials. The proposed starting materials should be highlighted in the flow diagram.

If all of the proposed starting materials have significant nonpharmaceutical markets, this flow diagram should be the same as the flow diagram provided in S.2.2. The flow diagram in S.2.2 can be cross-referenced.

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### 1843 **C. Specifications**

1844  
1845 A specification for each proposed starting material should be provided. Each  
1846 specification should be based on the quality of the material used to prepare the batches of  
1847 drug substance used to establish the specification for the drug substance (see sections  
1848 VI.A, VI.D, and VI.E of this guidance).

1849  
1850 Identification tests for a proposed starting material should be specific and should be able  
1851 to discriminate between it and any related compounds that are likely to be present. More  
1852 than one identification test may be appropriate. Tests to confirm the presence of a  
1853 counter ion (e.g., sodium, chloride) should be included in addition to other identity tests.

1854  
1855 The specification for a proposed starting material generally should include individual  
1856 limits on impurities and a limit on total impurities. A limit on unspecified impurities  
1857 should also be considered. Acceptance criteria for residual solvents and inorganic  
1858 impurities should also be considered, taking into account the potential for carryover.  
1859 Moreover, FDA recommends that acceptance criteria be established for all organic  
1860 impurities that occur above 0.10 percent and that a limit of NMT 0.10 percent be  
1861 established for unspecified organic impurities when there is greater potential for  
1862 impurities originating from the starting material to carryover to the drug substance (0.20  
1863 percent for a veterinary drug substance not used in human drug products). There can be a  
1864 greater potential for carryover (1) when the proposed starting material is the first isolated  
1865 and purified chemical (counting backwards from the drug substance) consistent with the  
1866 selection principle concerned with the carryover of impurities or (2) based on the  
1867 proximity of the starting materials to the drug substance.

### 1868 **D. Justification**

#### 1869 *1. Starting Materials with a Significant Nonpharmaceutical Market*

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1871  
1872  
1873 When a significant nonpharmaceutical market exists for a proposed starting material, the  
1874 discussion of the relationship between the proposed starting materials and the selection  
1875 principles described in section I of this attachment need not be provided. However, an  
1876 applicant should be prepared to provide documentation demonstrating that a significant  
1877 nonpharmaceutical market exists for a proposed starting material. Documentation is  
1878 more likely to be requested for proposed starting materials with complex molecular  
1879 structures within a few steps of the drug substance and/or where the extent of use in  
1880 nonpharmaceutical markets is less obvious. When warranted, this documentation should  
1881 typically consist of the following:

- 1882  
1883
- A description of the uses other than for drug substance production
  - Examples of manufacturers who are able to provide quantities suitable for both  
1884 drug substance production and other markets
  - Confirmation that (1) the drug substance manufacturer did not synthesize the  
1885 chemical, or arrange for another firm to synthesize it, to produce drug substance  
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1888 for clinical trials (phase 1 and phase 2 clinical trials for human drug products); (2)  
1889 an existing manufacturer of the chemical did not scale up its process to produce  
1890 sufficient quantities of drug substance for clinical trials (phase 1 and phase 2  
1891 clinical trials for human drug products); and (3) the method of manufacture was  
1892 not provided by the drug substance manufacturer to the other firms that  
1893 manufacture the chemical (i.e., no technology transfer occurred).

1894  
1895 2. *Starting Materials without a Significant Nonpharmaceutical Market*  
1896

1897 The justification for starting materials without a significant nonpharmaceutical market  
1898 should discuss the relationship between each proposed starting material and the selection  
1899 principles.

1900  
1901 Data (e.g., carryover of impurities) used to justify the proposed starting material should  
1902 be from batches manufactured by the proposed manufacturing process. If data from  
1903 batches produced by other manufacturing processes are also used, the data should be  
1904 clearly identified as supporting data and the differences in these manufacturing processes  
1905 and the proposed manufacturing process should be described.

1906  
1907 a. Propinquity  
1908

1909 The flow diagram provided in S.2.3 will indicate the separation between the final  
1910 intermediate and the proposed starting material. A cross-reference to the flow  
1911 diagram in S.2.3 is sufficient.

1912  
1913 b. Isolated and Purified Substances  
1914

1915 The starting material specification and the flow diagrams provided in S.2.3 should  
1916 indicate whether a proposed starting material is an isolated and purified substance.  
1917 Therefore, cross-reference to this information is sufficient.

1918  
1919 c. Carryover of Impurities  
1920

1921 Impurities reported in S.3.2 that are found in the drug substance at levels greater  
1922 than 0.10 percent (0.20 percent for a veterinary drug substance not used in human  
1923 drug products) should be listed in S.2.3, or a cross-reference should be provided  
1924 to the information in S.3.2. For each of the listed impurities, information should  
1925 be provided to demonstrate that the impurity did not originate from the proposed  
1926 starting material. Such information should consist of, for example:

- 1927  
1928
- 1929 • Analytical data demonstrating that the impurity is not present in the proposed starting material
  - 1930 • Data indicating that the impurity originates as part of the synthetic process
  - 1931 after the introduction of the proposed starting material

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- Analytical data to show that the bulk of the impurity found in the drug substance originates from sources other than the proposed starting material, when the assignment of the source of an impurity in the drug substance is uncertain (e.g., An impurity might logically result from the degradation of the proposed starting material, the drug substance, or any of the intermediates in between)

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If changes were made in the manufacturing process that follows the introduction of the starting material (e.g., by the addition of a purification procedure or by the repetition of an existing procedure on a routine basis) so that the proposed starting material is not a significant source of impurities in the drug substance, this should be clearly stated in the discussion.

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If a firm is not able to identify one or more of the impurities present above 0.10 percent in the synthetic drug substance (0.20 percent for a veterinary drug substance not used in human drug products), an empirical approach can be attempted provided that the proposed starting material can be demonstratively purified by recrystallization or some other technique. Two samples of the proposed starting material, one the quality of the material used to prepare the batches of drug substance used to establish the specification for the drug substance (see sections VI.A, VI.D, and VI.E of this guidance) and one highly purified, can be converted under identical conditions at bench scale to drug substance. If the unidentified impurities are present in both samples of drug substance, this would indicate that they do not originate from impurities in the proposed starting material. If this approach is used, applicants should provide a report documenting all salient aspects of the experiment.

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d. Complexity of Structure

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Information on the complexity of the structure of the starting material need not be provided for proposed starting materials that possess only a limited number of functional groups and structural features that can result in geometric or stereoisomerism. However, if the chemical structure of the proposed starting material is sufficiently complex, information should be provided to support that the starting material is readily distinguishable from potential isomers and analogs using common instrumental techniques (e.g., ultraviolet-visible spectrophotometry, infrared spectroscopy). Applicants should provide data (e.g., analytical, spectra) comparing the proposed starting material to a reasonable selection of isomers and analogs to demonstrate that the identification tests for the proposed starting material are sufficiently specific.

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### 1974 **III. POST APPROVAL ISSUES**

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1976 When a starting material has been designated in and approved as part of an application,  
1977 postapproval changes to the manufacturing process of the approved starting materials, including  
1978 changes in the route of its synthesis, need not be reported to the Agency unless a commitment to  
1979 report such changes was included in the approved application. Changes in the specification of an  
1980 approved starting material and changes to the manufacturing process of the drug substance  
1981 following the introduction of the starting material should be reported to the Agency in  
1982 accordance with applicable regulations and guidances.

1983

1984 It is valuable for drug substance manufacturers to maintain close communication with  
1985 manufacturers of starting materials. The quality of a starting material can be affected by changes  
1986 in manufacturing process (e.g., changes in solvents, purification, catalysts, route of synthesis),  
1987 and knowledge that a change has taken place can assist a drug substance manufacturer in  
1988 maintaining a valid starting material specification.

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### **ATTACHMENT 2:**

#### **STARTING MATERIALS OF PLANT OR ANIMAL ORIGIN**

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The FDA considers (1) cells; (2) plants, plant parts, macroscopic fungi, or algae; or (3) animal tissues, organs, or body fluid from which the drug substance is derived to be starting material for a drug substance derived from a biological source. Identification of the biological source is warranted to ensure the identity, quality, and purity of the drug substance and to address critical safety issues (e.g., viruses, residual pesticides). The term *drug substance derived from a biological source* includes drug substances that are the chemical obtained directly from the biological source and semisynthetic drug substances that are produced by modification of a chemical (i.e., intermediate) obtained from the biological source. A semisynthetic drug substance can have more than one starting material, depending on the number of branches in the synthetic portion of the manufacturing process. A drug substance is considered semisynthetic when at least one of the starting materials is of biological origin.

The recommendations in Attachment 2 do not pertain to:

- Starting materials that are highly purified chemicals obtained from biological sources that had significant nonpharmaceutical markets before they were used in the drug substance synthesis (e.g., Sucrose, tartaric acid).
- Starting materials of synthetic origin for semisynthetic drug substances
- Cells used in fermentation processes
- Cells or tissue used in cell culture processes
- Transgenic plants or animals

The recommendations in Attachment 1 apply to starting materials of biological origin that have significant nonpharmaceutical markets and starting materials of synthetic origin for semisynthetic drug substances. Starting materials for antibiotics and other cellular metabolites produced by microorganisms using conventional fermentation processes will be covered by a forthcoming guidance.

#### **I. DOCUMENTATION**

Applicants should provide the following information in S.2.3 for plant or animal starting materials. For semisynthetic drug substances the information recommended in Attachment 1 should be provided for the starting materials of synthetic origin, if there are any, in addition to the information provided for the plant or animal starting materials.

##### **A. Information on Plant or Animal Starting Materials**

The following should be provided for plant starting materials:

- Biological identification (i.e., Family, genus, species, variety) and the process for confirming taxonomic authenticity

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- 2035 • Part of the plant used (e.g., Seed, flower, roots, all)
- 2036 • Geographic areas of harvesting (e.g., Countries, provinces, states)
- 2037 • Growing season and harvest time
- 2038 • List of pesticides and herbicides that may be used in the geographic areas of
- 2039 harvesting
- 2040 • Supplier (i.e., Company with overall responsibility for collecting biomass, not
- 2041 individual harvesters, plantation owners, or subcontractors)
- 2042

2043 The following should be provided for animal starting materials:

- 2044
- 2045 • Biological identification (i.e., Species)
- 2046 • Specific part of animal used (e.g., Pancreas, bone, urine)
- 2047 • Country of origin<sup>27</sup>
- 2048 • A list of known diseases or pathogens associated with the type of animal
- 2049 • Criteria for ensuring animal health
- 2050 • For animals that are consumed for food, a statement of compliance with USDA or
- 2051 equivalent requirements
- 2052 • Supplier (i.e., Company with overall responsibility for collecting biomass, not
- 2053 individual farmers or subcontractors)
- 2054

### **B. Flow Diagram of the Manufacturing Process**

2055 When the drug substance is the chemical obtained directly from the biological source this

2056 flow diagram should be the same as the flow diagram in S.2.2. The flow diagram in S.2.2

2057 can be cross-referenced.

2058 For semisynthetic drug substances, the flow diagram should depict the manufacturing

2059 process that results in the chemical (i.e., intermediate) from the biological source and the

2060 synthetic part of the manufacturing process. See Attachment 1, Section II. B for

2061 recommendations on the flow diagram for the synthetic part of the manufacturing

2062 process.

### **C. Specifications for Plant or Animal Starting Materials**

2063 The specification for the starting material should be based on the quality of the material

2064 used to prepare the batches of drug substance used to establish the specification for the

2065 drug substance (see sections V.A, V.D, and V.E of this guidance). The specification for

2066 plant starting materials should include identity tests for determining taxonomic

2067 authenticity and, when appropriate, screening for pesticides and herbicides. The

2068 specification for the animal starting material should include screening for adventitious

2069 agents, when appropriate.

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<sup>27</sup> Bovine-derived materials should not be from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) unless otherwise exempted by the Agency.

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2076  
2077 A chemical substance (e.g., plant extract) used to produce a semisynthetic drug substance  
2078 or a crude drug substance derived from a plant or animal starting material is considered  
2079 an intermediate. Information on the intermediate, including the specification, should be  
2080 provided in S.2.4.  
2081

2082

### **II. ENVIRONMENTAL ASSESSMENT**

2084  
2085 All NDAs, ANDAs, NADAs, and ANADAs must include either an environmental assessment  
2086 (EA) or claim of categorical exclusion from the requirement to provide an environmental  
2087 assessment (21 CFR 25.15(a)). Environmental information should be included in Module 1 of an  
2088 NDA or ANDA submitted in the CTD format or the Environmental Impact section of an NADA  
2089 or ANADA. CDER's position on when an EA should be submitted in the NDA or ANDA to  
2090 support the use of a drug substance derived from a plant or animal is described in the guidance  
2091 *Environmental Assessment of Human Drug and Biologics Applications*. Applicants should refer  
2092 to this guidance, the VICH guidance *GL6 Environmental Impact Assessments (EIAs) for*  
2093 *Veterinary Medicinal Products (VMPs)*, and 21 CFR part 25 for additional information on  
2094 environmental assessments.

2095

### **III. POSTAPPROVAL ISSUES**

2098  
2099 Changes in the information on plant or animal starting materials (see section I.A of this  
2100 attachment) should be reported to the Agency in a prior approval supplement. The supplement  
2101 should include a new or revised environmental assessment or claim of categorical exclusion from  
2102 the requirement to provide an environmental assessment, as appropriate. Information should also  
2103 be provided concerning the potential for the change to result in new impurities or higher levels of  
2104 known impurities. A change that is merely editorial or administrative (e.g., a change in  
2105 ownership of the supplier with no change in the process for overseeing collection of biomass)  
2106 can be submitted in an annual report.

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### GLOSSARY

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**Adventitious Agents:** For the purpose of this guidance, pathogenic viruses and non-viral agents (e.g., transmissible spongiform encephalopathy agents, pathogenic bacteria, mycoplasma) in plants, animals, or cells or any materials derived therefrom, used in the manufacture of human drug substances or products

**Alternative Processes:** Two or more manufacturing processes described in an application that can be used to prepare the same intermediate or drug substance

**Auxiliary Materials:** Substances (e.g., charcoal, filter aid) used during the manufacturing process of a drug substance that are not normally considered to be starting materials, intermediates, reagents, solvents, catalysts, or diluents

**Critical:** Describes a process step or process control (e.g., process condition, test requirement, or other relevant parameter or item) that must be controlled within predetermined criteria to ensure that the drug substance meets its specification

**Crystal Shape (Habit):** Crystals with the same internal structure but different external shape because different crystal faces have developed during growth

**Degradation Product:** A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of, for example, light, temperature, pH, water, and/or by reaction with an excipient (or diluent), another drug substance, and/or the immediate container closure system. Also called decomposition product.

**Drug Substance:** An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)). The term *drug substance* can also be used to refer to a physical mixture of two or more drug substances used to produce a fixed-combination drug product.

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

**Identification Threshold:** A limit above (>) which an impurity should be identified (ICH Q3A or VICH GL10)

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2151 **In-process Material Tests:** Measures used to assess the quality attributes of an intermediate,  
2152 postsynthesis material, or unfinished drug substance and/or their suitability for use in the  
2153 manufacturing process

2154  
2155 **In Situ Intermediate:** An intermediate that is not isolated. It is normally, but not necessarily, in  
2156 solution

2157  
2158 **Intermediate:**

2159  
2160 • For synthetic drug substances, a material produced during steps of the synthesis of a drug  
2161 substance that undergoes further molecular change before it becomes a drug substance.  
2162 Intermediates may or may not be isolated (ICH Q3A and Q7A or VICH GL10)

2163  
2164 • For drug substances derived from a biological source, a material produced during the  
2165 manufacturing process of a drug substance that undergoes further purification or molecular  
2166 modification before it becomes a drug substance

2167  
2168 **Intermediate Tests:** Measures used to assess the quality attributes of an intermediate and/or its  
2169 suitability for use in the manufacturing process

2170  
2171 **Operating Parameters:** Conditions that can be adjusted to control the manufacturing process  
2172 (e.g., temperature, pressure, pH, time, mixing speed)

2173  
2174 **Particle Size Distribution:** A measurement of the relative proportion of particles in a sample as  
2175 a function of size

2176  
2177 **Physical Properties:** Attributes such as physical state, melting point, boiling point, solubility,  
2178 hygroscopicity, color, density, refractive index, partition coefficient, crystal shape, solid state  
2179 form, and particle size distribution

2180  
2181 **Polymorphic Forms:** Different crystalline forms of the same drug substance. These can  
2182 include solvation or hydration products (also known as pseudo-polymorphs) and amorphous  
2183 forms (ICH Q6A, Q3A)

2184 **Postsynthesis Material:** For synthetic or semisynthetic drug substances, a postsynthesis  
2185 material is a material that appears in the process after the final intermediate and before the drug  
2186 substance (unfinished drug substance or form of drug substance used to produce the drug  
2187 product). Postsynthesis materials can differ from the drug substance, for example, in  
2188 stereochemical identity, solid state form, or either the absence of a counterion or the presence of  
2189 a counterion different from that in the drug substance. Although firms have sometimes referred  
2190 to such materials as *intermediates*, these materials do not meet the definition of intermediate and  
2191 final intermediate provided in this guidance for synthetic or semisynthetic drug substances.

2192 **Postsynthesis Material Tests:** Measures used to assess the quality attributes of a postsynthesis  
2193 material and/or its suitability for use in the manufacturing process

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2195 **Process Controls:** An all-inclusive term used to describe the controls used during production to  
2196 monitor and, if appropriate, adjust the process and/or to ensure an intermediate with an  
2197 established specification or the drug substance will conform to its respective specification. The  
2198 term includes operating parameters, environmental controls, process tests, intermediate tests,  
2199 postsynthesis materials tests, and unfinished drug substance tests.

2200 **Process Tests:** Measures used to monitor and assess the performance of the process (e.g., a test  
2201 to evaluate reaction progress)  
2202

2203 **Reaction Step:** A unit operation or number of unit operations that effect a change in the  
2204 molecular structure of a starting material or intermediate. More than one reaction step can take  
2205 place sequentially in a single reaction vessel.  
2206

2207 **Residual Solvents:** Organic volatile chemicals that are used or produced in the manufacture of  
2208 drug substances or excipients, or in the preparation of drug products, that are not completely  
2209 removed by practical manufacturing techniques (ICH Q3C or VICH GL18)  
2210

2211 **Retest Period:** The period of time during which the drug substance is expected to remain within  
2212 its specification and, therefore, can be used in the manufacture of a given drug product, provided  
2213 that the drug substance has been stored under the defined conditions. After this period, a batch of  
2214 drug substance destined for use in the manufacture of a drug product should be retested for  
2215 compliance with the specification and then used immediately. A batch of drug substance can be  
2216 retested multiple times and a different portion of the batch used after each retest, as long as it  
2217 continues to comply with the specification. For most biotechnological/biological substances  
2218 known to be labile, it is more appropriate to establish a shelf life than a retest period. The same  
2219 may be true for certain antibiotics (ICH Q1A or VICH GL3).  
2220

2221 **Semisynthetic Drug Substance:** A drug substance where structural elements have been  
2222 introduced by a combination of chemical synthesis and elements of biological origin  
2223

2224 **Solid State Form:** A particular crystalline or noncrystalline structure of a solvated or  
2225 nonsolvated drug substance. This can include polymorphs, pseudopolymorphs (hydrates or  
2226 solvates), and amorphous forms.  
2227

2228 **Specification:** The quality standard (i.e., tests, analytical procedures, and acceptance criteria)  
2229 provided in an application to confirm the quality of drug substances, drug products,  
2230 intermediates, raw materials, reagents and other components including container closure system  
2231 and in-process materials. A specification sheet includes the list of tests, reference to analytical  
2232 procedures, and acceptance criteria.  
2233

2234 **Starting Material:** Materials that mark the beginning of the manufacturing process as described  
2235 in an application. A starting material for a synthetic drug substance is a chemical compound of  
2236 defined molecular structure that contributes to the structure of the drug substance. The starting  
2237 material for a drug substance obtained from a biological source is considered to consist of the (1)  
2238 cells; (2) plants, plant parts, macroscopic fungi, or algae; or (3) animal tissues, organs, or body  
2239 fluid from which the drug substance is derived.

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2241 **Synthesis Branch:** A portion of a convergent synthesis that ends with an intermediate that is to  
2242 be covalently joined with another intermediate or starting material in the next step of the  
2243 synthesis

2244

2245 **Unfinished Drug Substance:** A form of the drug substance that is further processed to produce  
2246 the form of the drug substance used to manufacture the drug product

2247

2248 **Unfinished Drug Substance Tests:** Measures used to assess the quality attributes of an  
2249 unfinished drug substance and/or its suitability for use in the manufacturing process

2250

2251 **Validation:** A documented program that provides a high degree of assurance that a specific  
2252 process, method, or system will consistently produce a result meeting predetermined acceptance  
2253 criteria (ICH Q7A)

2254