

---

# Guidance for Industry

## Drug Product

**Chemistry, Manufacturing, and Controls Information**

### ***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 150 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Upinder Atwal 301-827-5848 or (CBER) Christopher Joneckis 301-435-5681.

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

**January 2003  
CMC**

# Guidance for Industry

## Drug Product

### Chemistry, Manufacturing, and Controls Information

*Additional copies are available from:*

*Office of Training and Communication  
Division of Drug Information, HFD-240  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
(Tel) 301-827-4573  
<http://www.fda.gov/cder/guidance/index.htm>*

*and/or*

*Office of Communication, Training and  
Manufacturers Assistance, HFM-40  
Center for Biologics Evaluation and Research*

*Food and Drug Administration  
1401 Rockville Pike, Rockville, MD 20852-1448  
<http://www.fda.gov/cber/guidelines.htm>.  
(Tel) Voice Information System at 800-835-4709 or 301-827-1800*

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

**January 2003  
CMC**

## TABLE OF CONTENTS<sup>1</sup>

<b>I. INTRODUCTION .....</b>	<b>1</b>
<b>II. BACKGROUND.....</b>	<b>2</b>
<b>A. The Common Technical Document — Quality (CTD-Q) Format.....</b>	<b>2</b>
1. <i>Format of Drug Product Information in Multiple Related Applications.....</i>	<i>3</i>
2. <i>Format of Drug Product Information for Multiple Product Presentations and/or Manufacturing Schemes in One Application.....</i>	<i>3</i>
<b>B. Content Information Included in an Application.....</b>	<b>4</b>
<b>C. Additional Guidance.....</b>	<b>5</b>
<b>D. Drug Master Files.....</b>	<b>6</b>
<b>E. Environmental Assessments.....</b>	<b>6</b>
<b>III. DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (P.1).....</b>	<b>6</b>
<b>A. Description of Dosage Form.....</b>	<b>6</b>
<b>B. Container Closure System.....</b>	<b>7</b>
<b>C. Composition Statement.....</b>	<b>7</b>
<b>IV. PHARMACEUTICAL DEVELOPMENT (P.2).....</b>	<b>10</b>
<b>A. Components of the Drug Product (P.2.1).....</b>	<b>11</b>
1. <i>Drug Substance (P.2.1.1).....</i>	<i>11</i>
2. <i>Excipients (P.2.1.2).....</i>	<i>12</i>
<b>B. Drug Product (P.2.2) .....</b>	<b>13</b>
1. <i>Formulation Development (P.2.2.1).....</i>	<i>13</i>
2. <i>Overages (P.2.2.2) .....</i>	<i>14</i>
3. <i>Physicochemical and Biological Properties (P.2.2.3) .....</i>	<i>14</i>
<b>C. Manufacturing Process Development (P.2.3) .....</b>	<b>15</b>
<b>D. Container Closure System (P.2.4).....</b>	<b>16</b>
<b>E. Microbiological Attributes (P.2.5).....</b>	<b>16</b>
<b>F. Compatibility (P.2.6) .....</b>	<b>17</b>
<b>V. MANUFACTURE (P.3) .....</b>	<b>18</b>
<b>A. Manufacturer(s) (P.3.1) .....</b>	<b>18</b>
<b>B. Batch Formula (P.3.2) .....</b>	<b>19</b>
<b>C. Description of Manufacturing Process and Process Controls (P.3.3) .....</b>	<b>21</b>
1. <i>Flow Diagram.....</i>	<i>21</i>
2. <i>Description of Manufacturing Process and Process Controls .....</i>	<i>22</i>

---

<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.

3. <i>Reprocessing and Reworking</i> .....	24
<b>D. Controls of Critical Steps and Intermediates (P.3.4)</b> .....	<b>25</b>
<b>E. Process Validation and/or Evaluation (P.3.5)</b> .....	<b>26</b>
<b>VI. CONTROL OF EXCIPIENTS (P.4)</b> .....	<b>27</b>
<b>A. Specifications (P.4.1)</b> .....	<b>28</b>
<b>B. Analytical Procedures (P.4.2)</b> .....	<b>29</b>
<b>C. Validation of Analytical Procedures (P.4.3)</b> .....	<b>29</b>
<b>D. Justification of Specifications (P.4.4)</b> .....	<b>30</b>
<b>E. Excipients of Human or Animal Origin (P.4.5)</b> .....	<b>31</b>
<b>F. Novel Excipients (P.4.6)</b> .....	<b>31</b>
<b>VII. CONTROL OF DRUG PRODUCT (P.5)</b> .....	<b>31</b>
<b>A. Specification(s) (P.5.1)</b> .....	<b>31</b>
<b>B. Analytical Procedures (P.5.2)</b> .....	<b>35</b>
<b>C. Validation of Analytical Procedures (P.5.3)</b> .....	<b>36</b>
<b>D. Batch Analyses (P.5.4)</b> .....	<b>36</b>
1. <i>Batch Analysis Reports</i> .....	37
2. <i>Collated Batch Analyses Data</i> .....	37
<b>E. Characterization of Impurities (P.5.5)</b> .....	<b>38</b>
1. <i>List of Expected Impurities</i> .....	38
2. <i>Identification of Impurities</i> .....	38
<b>F. Justification of Specification(s) (P.5.6)</b> .....	<b>40</b>
<b>VIII. REFERENCE STANDARDS OR MATERIALS (P.6)</b> .....	<b>42</b>
<b>IX. CONTAINER CLOSURE SYSTEM (P.7)</b> .....	<b>43</b>
<b>X. STABILITY (P.8)</b> .....	<b>44</b>
<b>A. Stability Summary and Conclusion (P.8.1)</b> .....	<b>44</b>
<b>B. Postapproval Stability Protocol and Stability Commitment (P.8.2)</b> .....	<b>44</b>
<b>C. Stability Data (P.8.3)</b> .....	<b>44</b>
1. <i>Formal Stability Studies</i> .....	44
2. <i>Supporting Stability Studies</i> .....	45
3. <i>Stress Studies</i> .....	45
<b>XI. APPENDICES (A)</b> .....	<b>46</b>
<b>A. Facilities and Equipment (A.1)</b> .....	<b>46</b>
<b>B. Adventitious Agents Safety Evaluation (A.2)</b> .....	<b>47</b>
1. <i>Nonviral Adventitious Agents</i> .....	48
2. <i>Viral Adventitious Agents</i> .....	48
<b>C. Excipients (A.3)</b> .....	<b>49</b>
<b>XII. REGIONAL INFORMATION (R)</b> .....	<b>50</b>

**A. Executed Production Records (R.1.P)..... 50**  
    1. Executed Production Records..... 50  
    2. Information on Components..... 50  
**B. Comparability Protocols (R.2.P)..... 51**  
**C. Methods Validation Package (R.3.P) ..... 51**  
**XIII. LITERATURE REFERENCES (3.3) .....51**  
**ATTACHMENT 1 .....52**  
**GLOSSARY .....58**

# Guidance for Industry<sup>2</sup>

## Drug Product

### 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. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

*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 [cunninghamp@cder.fda.gov](mailto:cunninghamp@cder.fda.gov).*

#### I. INTRODUCTION

This guidance provides recommendations on the chemistry, manufacturing, and controls (CMC) information for drug products that should be submitted in original new drug applications (NDAs) and abbreviated new drug applications (ANDAs). The guidance addresses the content of original NDAs and ANDAs. The guidance is structured to facilitate the preparation of applications submitted in Common Technical Document (CTD) format (see section II.A and B). The recommendations apply to all NDAs and ANDAs, although more detailed guidance on the content of an application may be available in separate guidance documents for specific types of drug products or dosage forms (see section II.C).

This guidance addresses the information to be submitted for marketing approval of drug products to ensure continued product quality (i.e., the identity, strength, quality, purity, and potency). Recommendations are provided on the information that should be included for (1) description and composition of the drug product, (2) manufacture, (3) control of excipients, (4) control of drug products, (5) reference standards or materials, (6) container closure systems, and (7)

<sup>2</sup> This guidance has been prepared by the Drug Product Technical Committee of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration in collaboration with the Center for Biologics Evaluations and Research (CBER).

40 stability. Information is also provided on the type of pharmaceutical development information  
41 that should be included in an NDA or ANDA.

42  
43 This guidance, when finalized, will replace the guidance entitled *Submitting Documentation for*  
44 *the Manufacture of and Controls for Drug Products* (February 1987).

45  
46

## 47 **II. BACKGROUND**

48

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

50

51 In November 2000, the International Conference on Harmonisation of Technical  
52 Requirements for Registration of Pharmaceuticals for Human Use issued harmonized  
53 guidance for the format of drug product applications (i.e., Common Technical Document  
54 (CTD)). The CTD describes a format for applications that (supplemented with regional  
55 information) can be used for submission to the regulatory authorities in the United States,  
56 European Union, and Japan. One focus of this effort was harmonizing the format for  
57 quality information (i.e., chemistry, manufacturing, and controls) that will be submitted  
58 in an application. FDA's guidance on *M4Q: The CTD — Quality* describes the format  
59 for the quality information submitted in Module 3 of an application and provides  
60 additional information on formatting aspects of an application. Applicants can submit  
61 NDAs and ANDAs using the CTD-Q format. Applicants should review FDA's guidance  
62 on *M4Q: The CTD — Quality* and other related CTD guidance documents for detailed  
63 formatting recommendations on preparing an application in CTD format.

64

65 Module 3 of each application should include the specified CTD sections: Drug Substance  
66 (3.2.S), Drug Product (3.2.P), Appendices (3.2.A), Regional Information (3.2.R) and  
67 Literature References (3.3). In some cases, the majority of information to address the  
68 drug substance sections will be incorporated by reference from a drug master file (DMF).  
69 However, an applicant should still provide information to address some of the drug  
70 substance subsections. The content of the drug substance section (3.2.S) of Module 3  
71 will be the subject of a forthcoming guidance addressing CMC information for drug  
72 substances (drug substance guidance). The Appendices, Regional Information, and  
73 Literature References sections include information for both drug substance and drug  
74 product, as appropriate.

75

76 This *Drug Product* guidance has been organized in a format conforming to Module 3 of  
77 the CTD, and it provides CMC content recommendations specific to drug product,  
78 including recommendations for the Appendices, Regional Information, and Literature  
79 References sections. Alphanumeric designations in parentheses corresponding to the  
80 CTD format follow relevant headings and text to show where information is to be placed  
81 in the CTD.<sup>3</sup> Recommendations specific to drug substance, including recommendations

---

<sup>3</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.P.3.1 reads P.3.1).

82 for the Appendices, Regional Information and Literature References sections, will be  
83 provided in the drug substance guidance.

84  
85 *1. Format of Drug Product Information in Multiple Related Applications*

86  
87 In general, when separate applications are submitted for drug products, each application  
88 should contain stand-alone drug product information even when the applications are  
89 related (e.g., tablet and oral solution with the same active ingredient submitted at the  
90 same time). In some rare cases, quality information can be incorporated by reference  
91 from a related application (e.g., co-marketing agreements). It is recommended that an  
92 applicant discuss cross-referencing of drug product quality information with the  
93 appropriate review division before submitting an application that uses cross-references.  
94 Information on when separate applications should be submitted is available in the  
95 following guidances:

- 96  
97 • *Submitting Separate Marketing Applications and Clinical Data for Purposes of*  
98 *Assessing User Fees*<sup>4</sup>
- 99  
100 • *Variations in Drug Products that May Be Included in a Single ANDA*

101  
102 *2. Format of Drug Product Information for Multiple Product Presentations and/or*  
103 *Manufacturing Schemes in One Application*

104  
105 Under certain circumstances (see guidances cited in II.A.1), different product  
106 presentations (e.g., strengths, container closure configurations, formulations) and/or  
107 manufacturing schemes (e.g., aseptic and terminal sterilization) can be submitted in the  
108 same application. In general, when a single application can be submitted, information for  
109 each of the product presentations and manufacturing schemes should be combined and  
110 presented together in one Drug Product (P) section with information provided in the  
111 Appendices, Regional Information, and Literature References sections for each of the  
112 product presentations and manufacturing schemes, as warranted. For example, if 100  
113 milligram (mg) tablets will be marketed in a bottle and a unit-dose blister package, the  
114 information should be presented in one P section. The majority of the CMC information  
115 would be identical for the two products. The information that differs between the two  
116 would be presented together in the appropriate subsections (e.g., P.7 — Container  
117 Closure System, P.8 — Stability), but would be physically or electronically separated  
118 within the subsection.

119  
120 However, there are cases when it is more appropriate and logical to have information  
121 presented separately for product presentations or manufacturing schemes that can be  
122 included in a single application. Information presented separately means one complete P

---

<sup>4</sup> In February 2001 (66 FR 11175), the Agency made available a draft version of this guidance.



123 section followed by other complete P sections.<sup>5</sup> Information should be presented  
124 separately when a single application can be and is submitted for:<sup>6</sup>  
125

- 126 • A drug product that consists of two different formulated products. Separate P  
127 sections for each of the formulated products should be provided. For example,  
128 information on the drug product and reconstitution diluent should be presented in  
129 separate P sections for a drug product supplied with a reconstitution diluent.<sup>7</sup>  
130 Similarly, separate P sections should be provided for an oral contraceptive with active  
131 and placebo tablets.  
132
- 133 • Parenteral drug products with different formulations (e.g., lyophilized, liquid,  
134 preserved, nonpreserved). Each formulation should be presented in a separate  
135 section. However, different strengths, fills, and container closure configurations can  
136 be included in the same P sections. For example, if an application includes a  
137 nonpreserved formulation packaged in two sizes of unit dose vials and a prefilled  
138 syringe and a preserved formulation packaged in a multidose vial, two separate P  
139 sections should be provided. One P section will include the information on the  
140 nonpreserved formulation and the other P section would include the information on  
141 the preserved product.  
142
- 143 • Modified release products with different release mechanisms or release rates (e.g., 1-  
144 day and 7-day transdermal drug delivery system). Each release mechanism or release  
145 rate should be presented separately.  
146

## 147 **B. Content Information Included in an Application**

148

149 The application should include information in every P subsection for each of the product  
150 presentations (e.g., strengths, container closure configurations, formulations) and  
151 manufacturing schemes (e.g., alternative processes, drug substance source, manufacturing  
152 site) intended for approval under the application. There may be circumstances in which  
153 specific documentation (e.g., batch release data or certificate of analysis, executed  
154 production record, stability data) on a presentation or manufacturing scheme need not be  
155 included, such as when the intermediate strengths or container sizes are omitted in a  
156 bracketed stability study or when site specific stability studies are not needed  
157 preapproval. Although specific documentation might not be needed in some  
158 circumstances, the application should still include the remaining information on the  
159 product presentation or manufacturing scheme.  
160

---

<sup>5</sup> See FDA's guidance on *M4Q: The CTD — Quality* for additional guidance on formatting separate P sections.

<sup>6</sup> An applicant should refer to the guidances cited in section II.A.1 for information on when a single application can be submitted. For NDAs, the Agency may, for administrative reasons, choose to file separate NDAs for a submission that is eligible to be filed in a single NDA. When separate NDAs are filed, the recommendations in II.A.1 apply.

<sup>7</sup> If the diluent is the subject of a Center for Devices and Radiological Health (CDRH) 510k application or premarket approval application (PMA), only a citation to that application need be provided. Citations can be provided to approved applications in other situations when appropriate (e.g., devices).

161 If information is not provided in a P subsection at all or for a particular product  
162 presentation or manufacturing scheme, this should be stated in the application and a  
163 reason given. Information should be provided in the Appendices, Regional Information,  
164 and Literature References sections for each of the product presentations and  
165 manufacturing schemes, as appropriate. If an Appendices or Regional Information  
166 subsection or the Literature References section is not applicable, this should be stated in  
167 the application.  
168

169 Before preparing an application, an applicant can discuss with CDER or CBER questions  
170 about providing less than full information on each of the product presentation and  
171 manufacturing schemes included in an application. This advance discussion can preclude  
172 expending time and effort in preparing an application that CDER or CBER might later  
173 determine to be incomplete.  
174

### 175 **C. Additional Guidance**

176  
177 This *Drug Product* guidance and the forthcoming drug substance guidance, when  
178 finalized, will be the primary *content* guidances for NDA and ANDA applicants. For  
179 quality, the general *format* guidance is *M4Q: The CTD — Quality*. These are the first  
180 guidances an applicant should consider when preparing the quality section (i.e.,  
181 chemistry, manufacturing, and controls) of an NDA or ANDA (Module 3).  
182

183 This guidance references ICH guidance documents cited in the CTD-Q and FDA's  
184 guidances on general technical topics (i.e., stability, container closure systems, analytical  
185 procedures and methods validation, sterilization process validation, drug master files, and  
186 environmental assessments) rather than incorporating this detailed information. These  
187 guidances are referenced in the text and/or listed at the end of a section. An applicant  
188 should refer to these guidances for recommendations on the detailed information that  
189 should be included in the application to address the general technical topic.  
190

191 Finally, an applicant should consider guidances that are available for specific technical  
192 issues, dosage forms, or drug product types when preparing its NDA or ANDA. These  
193 guidances provide additional recommendations on unique scientific and technical aspects  
194 of the topic. Some references to these types of guidances are included in this guidance.  
195 However, the references are given only as examples, and the list is not meant to be all-  
196 inclusive. Some examples of these types of guidance are:  
197

- 198 • *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products*
- 199
- 200 • *The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by*  
201 *Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human*  
202 *Use*
- 203
- 204 • *ANDAs: Impurities in Drug Products* (under development)
- 205

- *Submission of Chemistry, Manufacturing and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use*, CBER/CDER (under development)

CDER and CBER continue to update existing and publish new guidance documents. An applicant should use current guidance when preparing an NDA or ANDA submission. Current guidance documents are available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> and <http://www.fda.gov/cber/guidelines.htm>.

#### **D. Drug Master Files**

Under FDA's regulations, an application may incorporate by reference all or part of the contents of any drug master file (DMF) to address particular drug product issues if the DMF holder provides written authorization to the applicant and the authorization is included in the application (Module 1). The authorization must describe the incorporated material by name, reference number, volume and page number of the DMF (21 CFR 314.420). See CDER's *Drug Master Files* guidance for more information.

#### **E. Environmental Assessments**

All NDAs and ANDAs must include either an environmental assessment (EA) or claim of categorical exclusion from the requirement to provide an environmental assessment (21 CFR 25.15(a)). Although included in Module 1 of the CTD, this information is considered part of the chemistry, manufacturing, and controls documentation in the United States. Applicants should refer to 21 CFR part 25 and the guidance for industry *Environmental Assessment of Human Drug and Biologics Applications* for additional information on environmental assessments.

### **III. DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (P.1)**

A brief description of the dosage form and container closure system and a statement of the composition of the drug product should be provided.

#### **A. Description of Dosage Form<sup>8</sup>**

A brief description of the dosage form should be provided. For CDER products, the description should use standard dosage form terminology found in the CDER *Data Standards Manual* (<http://www.fda.gov/cder/dsm>).<sup>9</sup>

---

<sup>8</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 and Composition of the Drug Product (P.1)*). 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.

246 **B. Container Closure System**  
247

248 A brief description of the container closure systems proposed for marketing should be  
249 provided. If an overfill (see section IV.B.1) is used, the amount of overfill in each  
250 container should be identified. Information on the suitability of the container closure  
251 systems should be provided in P.2.4. A full description of the container closure systems  
252 and their specifications should be provided in P.7.  
253

254 **C. Composition Statement**  
255

256 The composition statement describes the qualitative and quantitative formulation of the  
257 drug product intended for commercial distribution. The composition statement must  
258 contain a list of all components used in the manufacture of the drug product regardless of  
259 whether or not they appear in the finished drug product (21 CFR 314.50(d)(1)(ii)(a)).  
260 Furthermore, the statement should include: (1) reference to the quality standards used, (2)  
261 the function of the component, (3) the amount of the component on a per unit basis, (4)  
262 the total weight, volume or other appropriate measure of the unit, and (5) any explanatory  
263 notes.  
264

265 In some instances, the composition of distinct subformulations (e.g., cores, coating) of  
266 the drug product should be listed separately in the composition statement. For example,  
267 some modified release products (1) contain a mixture of immediate release and extended  
268 release beads within a capsule shell or (2) are formulated with the drug substance  
269 apportioned between a modified release core and an immediate release coating. In these  
270 cases, the composition of the immediate release and extended release portions of the drug  
271 product should be listed separately.  
272

273 Additional guidance on each element of the composition statement is provided below.  
274 An illustrative example of a composition statement is provided in Table 1.  
275

276 • Components  
277

278 Components used in the manufacture of the drug product, regardless of whether or not  
279 they appear in the finished drug product, should be identified by the established name. If  
280 an established name does not exist for a component, a complete chemical name (i.e., the  
281 current Chemical Abstracts Service (CAS) index name) should be used.  
282

283 Trace amounts of harmless substances added solely as tracers or markers for individual  
284 product identification should be included in the composition statement and the batch  
285 formula (P.3.2). Suitability of the proposed tracer or marker should be discussed in

---

<sup>9</sup> CDER's *Data Standards Manual* (DSM) provides standard nomenclature for use in various FDA databases. For the list of dosage form terminology used for approved drug products (e.g., on label), applicants should refer to Appendix C of FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (i.e., the Orange Book). An applicant proposing to use different terminology should contact the appropriate chemistry review team.

286 P.2.1.2. Tracers and markers need not be disclosed in the drug product labeling except  
287 for those used in parenteral drug products (21 CFR 201.100(b)).  
288

289 For drug product components that are mixtures (e.g., colorants, coatings, flavors, inks),  
290 proprietary names can be used in the drug product composition statement if the  
291 quantitative and qualitative composition of the mixture is provided or referenced. For  
292 ease of review, CDER and CBER prefer that the quantitative and qualitative composition  
293 of mixtures be included in the application in a separate table. If it is not possible to  
294 include this information in the application, the information can be provided in a drug  
295 master file (DMF) when an appropriate letter of authorization from the DMF holder is  
296 included in the application (21 CFR 314.420(b)).  
297

298 Capsule shells should be listed as a component and descriptive information provided in  
299 the composition statement (e.g., size, shape, color). The quantitative and qualitative  
300 composition of the capsule shell should be provided or referenced.  
301

302 • References to Quality Standards  
303

304 For compendial components, the appropriate official compendium should be cited.<sup>10</sup>  
305 Compendial components should comply with the monograph standard included in the  
306 official compendium, and citation of the official compendium confirms compliance with  
307 this standard. The compendium should be cited even if an in-house specification that  
308 provides for more testing than that of the compendial monograph is used to evaluate the  
309 component. For noncompendial components, the type of standard used to evaluate the  
310 component should be listed (e.g., in-house standard, *Code of Federal Regulations* (CFR)  
311 citation, DMF holder's standard). The applicant specific numeric code (e.g., SPEC  
312 101.2b) of the specification used to evaluate the quality of the component should not be  
313 listed in the composition statement. The actual specification used for the drug substance  
314 should be provided in S.4.1. For the excipients, the actual specification should be  
315 provided in P.4.1 or P.4.6 and A.3 as appropriate.  
316

317 • Function(s)  
318

319 The function (i.e., role) of each component in the formulation should be stated.  
320 Components that are used in the manufacture of the drug product and do not appear in the  
321 finished drug product except at residual levels (e.g., some solvents) should be identified  
322 as processing agents.  
323

324 • Amount  
325

326 The target amount of each component by definite weight or other measure should be  
327 provided on a per unit basis. The amount of weight per unit volume should be on the  
328 per milliliter (mL) basis regardless of the size of the container. The metric system  
329 should be used whenever possible.

---

<sup>10</sup> A compendial component is a component that has a monograph in an official compendium as defined in section 201(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(j)).

330  
331 In general, a fixed amount for each component should be stated. A quantity sufficient  
332 (q.s.) designation can be used when appropriate (e.g., q.s. to pH 5.5, q.s. to 1 mL). For  
333 excipients (e.g., coatings, lubricants) where a range has been justified (see section  
334 IV.A.2), the target amount should be listed in composition statement. However, the  
335 target and range should be included in the batch formula (P.3.2). The following  
336 components should be listed in the composition statement, but the amount of each  
337 component on a per unit basis need not be provided: (1) processing agents, (2)  
338 purposefully added gases that are intended to remain as part of the finished drug product  
339 (e.g., nitrogen added to head space), and (3) imprinting inks.

340  
341 The amount of drug substance in the specified unit, including any overages, should be  
342 listed. An explanatory note should identify any justified overages (see section IV.B.2).  
343 If the amount of the drug substance in the composition statement and the strength listed  
344 in the labeling on the specified unit basis differ (e.g., when label strength is based on  
345 active ingredient rather than the salt or hydrate), an explanatory note should be included.

- 346  
347 • Total weight, volume, or other appropriate measure

348  
349 The total weight, volume, or other appropriate measure (e.g., one transdermal patch) of  
350 the unit being described should be specified.

- 351  
352 • Notes

353  
354 Explanatory notes should be included as appropriate. For example, explanatory notes  
355 should be used to identify drug substance overages, differences in the amount of drug  
356 substance on the per unit basis and labeled strength, and the location of the qualitative  
357 and quantitative composition statements for mixtures listed in the composition statement.

358

<b>Table 1: Example Target Composition Statement</b>					
Component	Reference to Quality Standard	Function	50 mg tablet	100 mg tablet	150 mg tablet
<b>Core Tablet</b>					
Drug substance	In-house standard	Drug Substance	55 mg <sup>1</sup>	110 mg <sup>1</sup>	165 mg <sup>1</sup>
Excipient X	NF	Diluent	30 mg	60 mg	90 mg
Excipient Y	NF	Disintegrant	22 mg	44 mg	66 mg
Excipient Z	In-house standard	Binding Agent	5 mg	10 mg	15 mg
Magnesium Stearate	NF	Lubricant	1.5 mg	3 mg	4.5 mg
Core Tablet Weight			113.5 mg	227.0 mg	340.5 mg
<b>Film Coat Solution</b>					
Purified Water	USP	Processing Agent	—	—	—
Hydroxypropyl Methylcellulose	USP	Film Coat	4.5 mg	9 mg	13.5 mg
Color Red <sup>TM2</sup>	DMF Holder Y standard	Film Coat Color	—	0.2 mg	—
Color Blue <sup>TM2</sup>	DMF Holder Y Standard	Film Coat Color	0.05 mg	—	0.45 mg
Titanium Dioxide	USP	Opacifier	0.1 mg	0.1 mg	—
Total Tablet Weight			118.15 mg	236.30 mg	354.45 mg
<b>Print Ink Solution</b>					
Printing Ink Solution <sup>3</sup>	DMF Holder Z Standard	Identification	—	—	—
<sup>1</sup> Equivalent to 50, 100, and 150 mg, respectively, on the anhydrous basis <sup>2</sup> The qualitative and quantitative composition statements for the two colors are incorporated by reference from DMF 99999. The information is located in the January 21, 2001 amendment to the DMF, Volume 2, page 104 and 105. See the letter of authorization from DMF Holder Y in Module 1. <sup>3</sup> The qualitative and quantitative composition of the ink is provided in Table XYZ in the application.					

359

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*

360

361

#### 362 IV. PHARMACEUTICAL DEVELOPMENT (P.2)

363

364 The Pharmaceutical Development section should contain information on the development studies  
 365 conducted to establish that the dosage form, formulation, manufacturing process, container  
 366 closure system, microbiological attributes, and usage instructions are appropriate for the purpose  
 367 specified in the application. The studies included in this section are distinguished from routine  
 368 control tests conducted according to specifications (e.g., release testing, stability testing).

369 Additionally, this section should identify and describe the formulation and process attributes,  
370 including critical parameters, that can influence batch reproducibility, product performance, and  
371 drug product quality.

372  
373 Supportive data and results from specific studies or published literature can be included within or  
374 attached to the Pharmaceutical Development section. Additional supportive data can be  
375 referenced to the relevant nonclinical or clinical sections of the application.

376  
377 **A. Components of the Drug Product (P.2.1)**

378  
379 *1. Drug Substance (P.2.1.1)*

380  
381 a. Key Physicochemical Characteristics

382  
383 Key physicochemical characteristics (e.g., water content, solubility, particle size  
384 distribution, polymorphic form, solvation or hydration state, pH, dissociation  
385 constant (pKa)) of the drug substance identified in S.3.1 that can influence the  
386 performance or manufacturability of the drug product should be discussed. If the  
387 drug substance is structurally modified from an active moiety (e.g., salt,  
388 endogenous protein) and the modification affects a key physicochemical (e.g.,  
389 solubility) and/or biological characteristic, this should be discussed. These  
390 discussions should cross-reference any relevant stability data in S.7.3.

391  
392 To evaluate the potential effect of key drug substance physicochemical  
393 characteristics on the performance of the drug product, studies on drug product  
394 are sometimes warranted. For example, if particle size is expected to influence  
395 the dissolution rate, drug product testing should be conducted to support the  
396 appropriateness of the test and acceptance criteria for the drug substance particle  
397 size distribution. Data from drug product studies to investigate the potential  
398 effect of and the appropriateness of the acceptance criteria for drug substance  
399 physicochemical characteristics should be provided in this section of the  
400 application. For example, the ICH *Q6A Specifications: Test Procedures and*  
401 *Acceptance Criteria for New Drug Substances and New Drug Products: Chemical*  
402 *Substances* describes some of the circumstances in which drug product studies are  
403 recommended (e.g., Decision Tree #3 and #4 (Part 2)). The data from these  
404 studies should be used, as appropriate, to justify the drug substance specification  
405 (S.4.5).

406  
407 b. Compatibility

408  
409 The compatibility of the drug substance with the excipients used in the drug  
410 product should be discussed. For combination drug products, the compatibility of  
411 the drug substances with each other should also be discussed.

412  
413 If there is evidence of chemical or physical incompatibility, justification for using  
414 the component should be provided. This justification can include, for example,



415 stability data to demonstrate that changes observed in development studies do not  
416 occur at significant levels in the drug product through shelf life or qualification of  
417 impurities that result from an interaction between the drug substance and an  
418 excipient or between drug substances.

419  
420 2. *Excipients (P.2.1.2)*  
421

422 The choice of excipients, their concentration, and the characteristics that can influence  
423 the drug product performance or manufacturability should be discussed relative to the  
424 respective role of each excipient. Any excipient ranges included in the batch formula  
425 (P.3.2) should be justified in this section of the application (P.2.1.2). Excipient ranges  
426 can often be justified based on the experience gained during the development of the  
427 formulation and manufacturing process. The ability of functional excipients (e.g.,  
428 antioxidants, penetration enhancers) to perform throughout the intended drug product  
429 shelf life should also be discussed. The information provided should be used, as  
430 appropriate, to justify the excipient (P.4.4) and drug product (P.5.6) specifications.  
431

432 Additional information should be provided for certain types of excipients, as discussed  
433 below. Applicants can refer to the forthcoming guidance on nonclinical studies for  
434 development of pharmaceutical excipients, for recommendations on the development of  
435 safety profiles that may be warranted for an excipient.  
436

437 • Novel Excipients  
438

439 Novel excipients are those that are used in the United States for the first time in a human  
440 drug product or by a new route of administration. The manufacturing, chemistry, and  
441 controls (CMC) information for a novel excipient should be provided in the same level of  
442 detail as that provided for a drug substance. The CMC information or a cross-reference  
443 to a DMF that provides the CMC information should be included in A.3. See sections VI  
444 and XI.C for additional guidance on the information that should be submitted to support  
445 the use of a novel excipient.  
446

447 • Noncompendial–Non-novel Excipients  
448

449 Depending on the functionality (e.g., complexing agent) and the route of administration  
450 of the drug product, additional information, up to and including the level of information  
451 recommended for novel excipients, can be warranted. An applicant is encouraged to  
452 discuss the use of noncompendial–non-novel excipients with the appropriate review  
453 division prior to submitting its application to ascertain the level of information that would  
454 be warranted to support the use of the excipient. The additional CMC information or a  
455 cross-reference to a DMF that provides the additional CMC information should be  
456 included in A.3. See sections VI and XI.C for additional guidance on the information  
457 that should be submitted to support the use of this type of excipient.  
458  
459

- 460
- Excipients used at higher levels than in previously approved products with the same
- 461 route of administration, or components used as tracers or markers
- 462

463 Information to support the safety of these materials should be referenced in this section of

464 the application. This information could include citations to FDA's regulations, Food

465 Chemical Codex citations, or citations to supporting toxicology data provided elsewhere

466 in the application (include study number).

467

- 468
- Excipients that can impart their own pharmacological activity
- 469

470 Information should be provided in this section of the application (P.2.1.2) when using any

471 excipient (e.g., docusate sodium, caffeine, methionine) that has the potential to impart its

472 own pharmacological effect. Data or cross-reference to data that support the lack of

473 pharmacological activity of the excipient at the levels used in the drug product should be

474 provided. If studies have been included elsewhere in the application, the study number

475 should be provided in the cross-reference.

476

477 When a component that is usually identified as an excipient contributes to the intrinsic

478 pharmacological activity of the drug substance (e.g., levonordefrin or epinephrine for

479 local anesthesia), CMC information for the component should be provided in the

480 application or incorporated by reference from a DMF. The information should be

481 provided in the same level of detail as that for a drug substance. The CMC information or

482 a cross-reference to a DMF that provides the CMC information should be included in

483 A.3.

484

485 **B. Drug Product (P.2.2)**

486

487 *1. Formulation Development (P.2.2.1)*

488

489 A brief summary describing the development of the drug product should be provided,

490 taking into consideration the proposed route of administration and usage. For modified

491 release drug products, a detailed description of the release mechanism (e.g., erodible

492 matrix system, barrier erosion, diffusion) and a summary of the development of the

493 release mechanism should be included.

494

495 A summary of all formulations used in clinical trials should be provided. The differences

496 between clinical formulations and the proposed commercial formulation described in P.1

497 (i.e., composition statement) should be discussed. Any changes between the proposed

498 commercial formulation and those formulations used in clinical batches and primary

499 stability batches should be clearly described and the rationale for the changes provided.

500 Results from comparative in vitro studies (e.g., dissolution), or comparative in vivo

501 studies (e.g., bioequivalence), that link clinical formulations to the proposed commercial

502 formulation described in P.1 should be summarized<sup>11</sup> and a cross-reference to the studies

---

<sup>11</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 application can be provided in the specified Module 3 section.

503 (with study numbers) should be provided. A summary of the development of an in  
504 vitro/in vivo correlation and a cross-reference to the studies (with study numbers) should  
505 be provided.

506  
507 Any special features of the drug product (e.g., scoring of immediate release tablets,  
508 multilayer tablet) should be identified and a rationale provided for their use. Data to  
509 support the appropriateness of such features should also be provided. For example, use  
510 of a tablet score could be justified if the product labeling indicates that the split tablet is a  
511 valid dose (i.e., efficacy established). Data to support scoring should include content  
512 uniformity and dissolution studies comparing split versus whole tablet.<sup>12</sup>

513  
514 Some dosage forms (e.g., liquids and semisolids) normally include an overfill of the  
515 formulation in the product container. Overfill is the volume or weight of the formulation  
516 filled in each container in slight excess of the labeled content. The amount of overfill is  
517 dependent on the physical properties of the finished dosage form (e.g., viscosity, surface  
518 tension) and the container closure system (e.g., design). In determining the amount of  
519 overfill, the applicant should consider the labeled dose to be delivered and how the dose  
520 will be administered (e.g., metered dose, syringe void volumes). The rationale for the  
521 amount of overfill should be provided. The amount of overfill should be sufficient to  
522 ensure that the finished dosage form meets appropriate pharmacopeial tests (e.g., *United*  
523 *States Pharmacopeia* (USP) *General Chapters* <1> *Injections*, <698> *Deliverable*  
524 *Volume*, <755> *Minimum Fill*).

525  
526 For drug products supplied with a reconstitution diluent, the development and choice of  
527 any co-packaged diluents should be discussed.

528

529 2. *Overages (P.2.2.2)*<sup>13</sup>

530

531 An overage is a fixed amount of the drug substance in the dosage form that is added in  
532 excess of the label claim. Any overages included in the formulations described in P.1  
533 should be justified. Information should be provided on the: (1) amount of overage, (2)  
534 reason for overage (e.g., compensate for expected and documented manufacturing losses,  
535 ensure proper dose delivery), and (3) justification for the amount of the overage. The  
536 overage should be included in the amount of drug substance listed in the composition  
537 statement (P.1) and the representative batch formula (P.3.2). In general, use of an  
538 overage of a drug substance to compensate for degradation during manufacture or a  
539 product's shelf life, or to extend the expiration dating period, is not appropriate.

540

541 3. *Physicochemical and Biological Properties (P.2.2.3)*

542

---

<sup>12</sup> CDER's Manual of Policies and Procedures (MAPP 5223.2) *Scoring Configuration of Generic Drug Products*. explains the Center's policy on this topic. CDER MAPPs are available at <http://www.fda.gov/cder/mapp.htm>.

<sup>13</sup> Justified ranges, rather than overages, can be used for excipients. The justification for a proposed excipient range should be included in section P.2.1.2.

543 Parameters relevant to the performance or manufacturability (e.g., powder flow  
544 characteristics) of the drug product should be addressed. Physicochemical and biological  
545 properties such as pH, osmolarity, dissolution, redispersion, reconstitution, particle size  
546 distribution, aggregation, polymorphism, rheological properties, biological activity or  
547 potency, and/or immunological activity can be relevant. The discussion should cross-  
548 reference any relevant stability data in P.8.3. A summary of the development of a  
549 dissolution or drug release test and a cross-reference to the studies (with study numbers)  
550 should be provided.

551  
552 For solutions, the concentration of the drug substance in the drug product should be  
553 compared to the solubility of the least soluble solid state form. When the drug load is  
554 close to saturation, the solid state forms of the drug substance that can crystallize from  
555 the drug product vehicle should be discussed. The discussion should cross-reference any  
556 relevant data in S.3.1.

557  
558 Development studies to investigate the potential effect of and the appropriateness of drug  
559 product acceptance criteria for physicochemical and biological properties of the drug  
560 product should be summarized in this section of the application (P.2.2.3). For example,  
561 information would be provided from studies to investigate whether acceptance criteria for  
562 polymorphism should be included in the drug product specification or to support the  
563 robustness of the formulation and manufacturing process with respect to the selection of  
564 dissolution versus disintegration testing (ICH *Q6A Specifications: Test Procedures And*  
565 *Acceptance Criteria For New Drug Substances And New Drug Products: Chemical*  
566 *Substances*; Decision Tree #4 (Part 3) and Decision Tree #7 (Part 1)). The data from  
567 these studies should be used, as appropriate, to justify the drug product specification  
568 (P.5.6).

### 569 **C. Manufacturing Process Development (P.2.3)**

570  
571  
572 The selection and optimization of the manufacturing process described in P.3.3 (i.e.,  
573 intended for production batches), in particular the critical aspects of the process, should  
574 be explained. During the development phase, the process should be well documented so  
575 differences between the manufacturing processes used to produce the clinical safety and  
576 efficacy, bioavailability, bioequivalence, or primary stability batches and the process  
577 described in P.3.3 can be identified. The differences that can influence the performance  
578 or manufacturability of the product should be discussed.

579  
580 A table should be provided that compares the equipment used to produce clinical batches  
581 that support efficacy or bioequivalence and primary stability batches to the equipment  
582 proposed for production batches. The information should be presented in a way that  
583 facilitates comparison of the processes and the corresponding batch analyses information  
584 (P.5.4). The table should identify (1) the identity (e.g., batch number) and use of the  
585 batches produced using the specified equipment (e.g., bioequivalence study batch #  
586 1234), (2) the manufacturing site, (3) the batch size, and (4) any significant equipment  
587 differences (e.g., different design, operating principle, size).

588

589 **D. Container Closure System (P.2.4)**  
590

591 *Container closure system* refers to the sum of packaging components that together  
592 contain and protect the dosage form. This includes primary packaging components and  
593 secondary packaging components, if the latter are intended to provide additional  
594 protection to the drug product.  
595

596 A brief description of the container closure systems listed in P.7 and the container closure  
597 system used for storage and transportation of protein drug products should be provided.  
598 The suitability of the container closure systems should be discussed. The discussion  
599 should consider, for example, choice of materials, protection from moisture and light,<sup>14</sup>  
600 compatibility of the materials of construction with the dosage form (including sorption to  
601 container and leaching),<sup>15</sup> safety of materials of construction, and performance (such as  
602 reproducibility of the dose delivery from the device when presented as part of the drug  
603 product). Other information to support the appropriateness of the container closure  
604 system or its use (e.g., cleaning instructions for a metered dose inhaler) should be  
605 provided as warranted. The studies performed to assess the suitability of the container  
606 closure system should be provided in this section of the application (P.2.4).  
607

608 If an NDA is submitted for a new plastic that will be used for blood component storage,  
609 adequate information on the plastic should be submitted, including the identification of  
610 the leachables such as plasticizers since plasticizers are more readily leached into a lipid  
611 such as blood than an aqueous solution.  
612

613 The results of suitability studies can form the basis for inclusion, or omission, of specific  
614 tests on the finished product, container closure system, or individual packaging  
615 components. For example, when suitability studies and stability data demonstrate that  
616 leachables from the container closure systems used for products such as ophthalmic  
617 solutions or large volume parenterals (LVPs) are consistently below agreed upon levels,  
618 routine testing of the finished product for leachables would not be necessary.  
619

Additional guidance is available in:

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

620  
621 **E. Microbiological Attributes (P.2.5)**  
622

623 Where appropriate, the microbiological attributes of the drug product, drug substance,  
624 and excipients should be discussed in this section (P.2.5). The discussion should include,  
625 for example:  
626

---

<sup>14</sup> Data, such as light transmission data, would be provided in P.2.4. Results from photostability studies, when warranted, should be provided in P.8.3 and cross-referenced in this section (P.2.4).

<sup>15</sup> The level of di-2-ethylhexyl phthalate (DEHP) leaching from polyvinyl chloride containers should be assessed, and appropriate reference to DEHP leaching should be included in the product labeling.

- 627
- 628
- 629
- the rationale for not performing microbial limits testing for nonsterile products (e.g., Decision Tree #8 in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*)
- 630
- 631
- 632
- 633
- the rationale for not performing microbial limits testing for nonsterile drug substances and excipients (e.g., Decision Tree #6 in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*)
- 634
- 635
- 636
- 637
- the selection and effectiveness of preservative systems in products containing antimicrobial preservative or the antimicrobial effectiveness of products that are inherently antimicrobial
- 638
- 639
- for sterile products, the integrity of the container closure system as it relates to preventing microbial contamination
- 640

641 Although chemical testing for preservative content is the attribute normally included in  
642 the drug product specification, antimicrobial preservative effectiveness should be  
643 demonstrated during development. The lowest specified concentration of antimicrobial  
644 preservative should be demonstrated to be effective in controlling microorganisms by  
645 using an antimicrobial preservative effectiveness test (e.g., USP <51> *Antimicrobial*  
646 *Effectiveness Testing*).

647

648 Tests and acceptance criteria for microbiological attributes should be included in the  
649 specifications, as appropriate (e.g., drug substance, S.4.1; excipients, P.4.1, P.4.6; drug  
650 product, P.5.1).

651

Additional guidance is available in:

- FDA: *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*
- ICH: *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

652

653

654

655

656

657

658

659

## F. Compatibility (P.2.6)

The compatibility of the drug product with any diluents (i.e., constitution, dilution of concentrates, admixing),<sup>16</sup> or dosage devices specified in the drug product labeling and the compatibility of the drug product with likely coadministered drug products should be addressed to provide appropriate and supportive information for the labeling. The information should be used to identify in the labeling diluents and other drug products

---

<sup>16</sup> *Admixing* refers to the removal of a parenteral drug product from its immediate container and its subsequent addition to IV fluids.

660 that are compatible with the drug product as well as those that are found to be  
661 incompatible. Compatibility studies should assess, for example, precipitation, sorption  
662 onto injection vessels or devices, leachables<sup>17</sup> from containers and administration sets,  
663 and stability. The design and extent of the compatibility studies depend on the type of  
664 drug product and its anticipated usage. Recommendations on stability studies to assess  
665 compatibility will be provided in the forthcoming guidance *Stability Testing of Drug*  
666 *Substances and Drug Products*.<sup>18</sup>

667 In addition to assessing the compatibility of drug products admixed with diluents  
668 identified in the labeling, compatibility studies should also be performed with commonly  
669 used diluents even if they are not identified in the drug product labeling. These studies  
670 should be performed because it is likely that the diluents will be used whether or not they  
671 are specifically discussed in the labeling. At a minimum, admixing with Lactated  
672 Ringer's Injection, 5% weight/volume (w/v) Dextrose Injection, and 0.9% w/v Sodium  
673 Chloride Injection should be studied.

674  
675 Constitution or dilution studies performed as part of formal stability studies to confirm  
676 product quality through shelf life should be reported in P.8.3.

677  
678

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*

679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689

## V. MANUFACTURE (P.3)

### A. Manufacturer(s) (P.3.1)

The name, address, and manufacturing responsibility should be provided for each firm (including contract manufacturers, packagers, and testing laboratories) and each site (i.e., facility) that will be involved in the manufacturing, packaging, or testing of the drug product. Each site should be identified by the street address, city, state, and, when available, the drug establishment registration number.<sup>19</sup> The addresses should be for the

<sup>17</sup> The level of di-2-ethylhexyl phthalate (DEHP) leaching from polyvinyl chloride containers should be assessed, and appropriate reference to DEHP leaching should be included in the product labeling.

<sup>18</sup> In June 1998 (63 FR 31224), the Agency made available a draft revision of this guidance. When finalized, this revision will be the primary reference source on stability testing of drug substances and drug products.

<sup>19</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).

690 location where the relevant manufacturing, packaging, or testing operation will be  
691 performed. Addresses for corporate headquarters or offices need not be provided.  
692 Building numbers or other specific identifying information should be provided for  
693 multifacility campuses. For sites processing sterile drug substances, drug products, or  
694 packaging components, the sterile processing area (e.g., room, filling line) should also be  
695 included. Addresses for foreign sites should be provided in comparable detail, and the  
696 name, address, and phone number of the U.S. agent for each foreign drug establishment,  
697 as required under 21 CFR 207.40(c), should be included.

698  
699 The information should be provided for:

- 700
- 701 • Manufacturers of the drug product and in-process materials (e.g., controlled release
  - 702 beads)
  - 703 • Packagers and labelers<sup>20</sup>
  - 704 • Laboratories that perform quality control tests on bulk drug substance(s),
  - 705 components, intermediates, container closure systems, and finished drug product,
  - 706 including stability testing
  - 707 • Facilities other than the drug product manufacturing site that perform sterilization
  - 708 operations (e.g., gamma irradiation of packaging components)
- 709

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

714  
715 **B. Batch Formula (P.3.2)**

716  
717 A batch formula should be provided that includes a list of all components used in the  
718 manufacturing process, their amounts on a per batch basis, including overages, a  
719 reference to their quality standards, and any explanatory notes. Batch formulas should  
720 be provided for the intended validation batch sizes of each formulation. If a common  
721 formulation is used to produce multiple products (e.g., strengths), a single batch formula  
722 can be provided.

723  
724 In some instances, separately blended or formulated materials that are later combined  
725 during manufacturing should be listed separately in the batch formula. For example,  
726 some modified release products contain a mixture of immediate release and extended  
727 release beads within a capsule shell. In this case, separate batch formulas for the  
728 individual subcomponents of the dosage unit should be provided.

729  
730 Additional guidance on each element of the batch formula is provided below. An  
731 illustrative example of a batch formula is provided in Table 2.

- 732  
733 • List of All Components

---

<sup>20</sup> Only those required to register under 21 CFR part 207.



734  
735 All components should be included in the batch formula. Processing agents (such as  
736 water, solvents, and nitrogen or other gases) that do not remain in the finished product  
737 should be included in the batch formula. Any gases used during manufacture should be  
738 listed and their purpose identified (e.g., blanket formulation, fill vial headspace) in an  
739 explanatory note.

- 740  
741 • Amounts

742  
743 The definite weight or measure for each component of the batch formula should be listed.  
744 The amount of drug substance listed should include any justified overage (see section  
745 IV.B.2). For excipients where a range has been justified (see section IV.A.2), the target  
746 amount and range should be included in the batch formula.

- 747  
748 • Reference to Quality Standards

749  
750 For compendial components, the appropriate official compendium should be cited.<sup>21</sup>  
751 Compendial components should comply with the monograph standard included in the  
752 official compendium, and citation of the official compendium confirms compliance with  
753 this standard. The compendium should be cited even if an in-house specification that  
754 provides for more testing than that of the compendial monograph is used to evaluate the  
755 component. For noncompendial components, the type of standard used to evaluate the  
756 component should be listed (e.g., in-house standard, CFR citation, DMF holder's  
757 standard). The applicant specific numeric code (e.g., SPEC 101.2b) of the specification  
758 used to evaluate the quality of the component should not be listed in the composition  
759 statement. The actual specification used for the drug substance should be provided in  
760 S.4.1. For the excipients, the actual specification should be provided in P.4.1 or P.4.6  
761 and A.3 as appropriate.

- 762  
763 • Notes

764  
765 Explanatory notes should be included as appropriate. For example, explanatory notes  
766 should be used to identify components that are removed during processing or the purpose  
767 of inert gases used during the manufacturing process.

---

<sup>21</sup> A compendial component is a component that has a monograph in an official compendium as defined in the Federal Food, Drug, and Cosmetic Act.

768  
769

<b>Table 2: Proposed Batch Formula<sup>1</sup> ¾ 250 mg Trademark™ Tablets</b>		
<b>Core Tablet</b>		
Component	Reference to Quality Standard	Amount (kg) per batch
Drug Substance	In-house Standard	500
Excipient X	NF	310
Excipient Y	NF	280
Excipient Z	In-house standard	50
Magnesium Stearate	NF	15 (range 14.5 to 15.5)
Purified Water	USP	(200) <sup>2</sup>
Total Batch Size		X
<b>Film Coat Solution<sup>3</sup></b>		
Component	Reference to Quality Standard	Amount (kg) per batch
Hydroxypropyl Methylcellulose	USP	10
Purified Water	USP	(200) <sup>2</sup>
Color Red™	DMF Holder Y Standard	10
Color White™	DMF Holder Y Standard	1.5
Total Batch Size		Y
<b>Print Ink Solution</b>		
Component	Reference to Quality Standard	Amount (kg) per batch
Colorant™	DMF Holder Z Standard	0.15
Solvent	NF	10
Total Batch Size		Z
<sup>1</sup> Theoretical yield is 2,000,000 tablets.		
<sup>2</sup> Water is removed during processing.		
<sup>3</sup> Film coat weight may vary between 80% – 120% of target coating weight.		

770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786

### C. Description of Manufacturing Process and Process Controls (P.3.3)

The description of the manufacturing process and process controls should include a flow diagram of the manufacturing process and a detailed description of the manufacturing process and process controls. If alternative processes are to be used, the information should be provided for each alternative. Differences in the manufacturing process described in this section and the manufacturing processes used to produce the batches used for clinical efficacy, bioavailability, bioequivalence, or primary stability studies that can influence the performance of the product should be discussed in P.2.3.

#### 1. Flow Diagram

A flow diagram should be provided giving the steps of the process and showing where materials enter the process. The entire manufacturing process should be depicted (e.g., weighing of components through finished product release). The flow diagram can be

787 supplemented with information presented in tabular form, if appropriate. The flow  
788 diagram should include:

- 789
- 790 • each manufacturing step with identification of the critical steps and any
  - 791 manufacturing step where, once the step is completed, the material might be held for
  - 792 a period of time (i.e., noncontinuous process ) before the next processing step is
  - 793 performed
  - 794 • the material being processed
  - 795 • critical process controls and the points at which they are conducted
  - 796 • the type of equipment used (equipment model number is not needed)
  - 797

798 2. *Description of Manufacturing Process and Process Controls*

799

800 A description of the manufacturing process, including packaging, that represents the  
801 sequence of steps undertaken and the scale of production should be provided. This  
802 description provides more detail than that provided in the flow diagram. The complete  
803 manufacturing process intended for the validation batches should be described for each  
804 drug product (e.g., strength, packaging configuration). However, segments of the  
805 manufacturing process common to multiple products need only be described once. For  
806 example, the formulation of a solution that is used to produce vials and prefilled syringes  
807 can be described once, but a separate description of the filling/packaging operations  
808 would be expected. Equipment should, at least, be identified by type (e.g., tumble  
809 blender, in line homogenizer) and working capacity where relevant. Novel processes or  
810 technologies and packaging operations that directly affect product quality should be  
811 described in greater detail. The description should identify all process controls and the  
812 associated numeric ranges, limits, or acceptance criteria. Furthermore, any process  
813 controls that are considered critical process controls should be highlighted. See below for  
814 additional information on process controls.

815

816 For NDAs, the description of the manufacturing process can be either a detailed narrative  
817 description or a proposed master production record (MPR).<sup>22</sup> However, CDER and  
818 CBER prefer that a detailed narrative be provided for an NDA. For ANDAs, the  
819 proposed MPR should be submitted. A narrative description should be submitted to  
820 supplement a MPR when appropriate, for example, when novel processes or technologies  
821 warrant description in greater level of detail. Executed Production Records should be  
822 provided in R.1.P

823

824 A statement should be provided that ruminant-derived materials from bovine spongiform  
825 encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9  
826 CFR 94.11) are not used or manipulated in the same facility. Submission of additional  
827 facility information could be warranted for multi-use facilities where there is a potential  
828 for cross-contamination with adventitious agents (see XI.A and XI.B). Additional  
829 facilities information for biotechnology-derived drug products should be included in A.1,  
830 when appropriate.

---

<sup>22</sup> A master production record is sometimes referred to as a master production and control record.

831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876

- **Process Controls**

Process controls is an all-inclusive term used to describe the controls used during production to monitor and, if appropriate, adjust the process and/or to ensure an in-process material with an established specification or the finished drug product will conform to its respective specification. The term includes:

- Operating parameters — conditions that can be adjusted to control the manufacturing process (e.g., temperature, pH, time, mixing speed)
- Environmental controls — conditions associated with the manufacturing facility (e.g., temperature, humidity, clean room classification)
- Process tests — measures used to monitor and assess the performance of the process
- In-process material tests — measures used to assess the quality attributes of an in-process material and ultimately lead to a decision to accept or reject the in-process material or drug product

Steps in the process should have the appropriate process controls identified. Associated numeric values can be presented as an expected range. All process controls, critical or otherwise, should be included in the description of the manufacturing process (MPR or narrative).

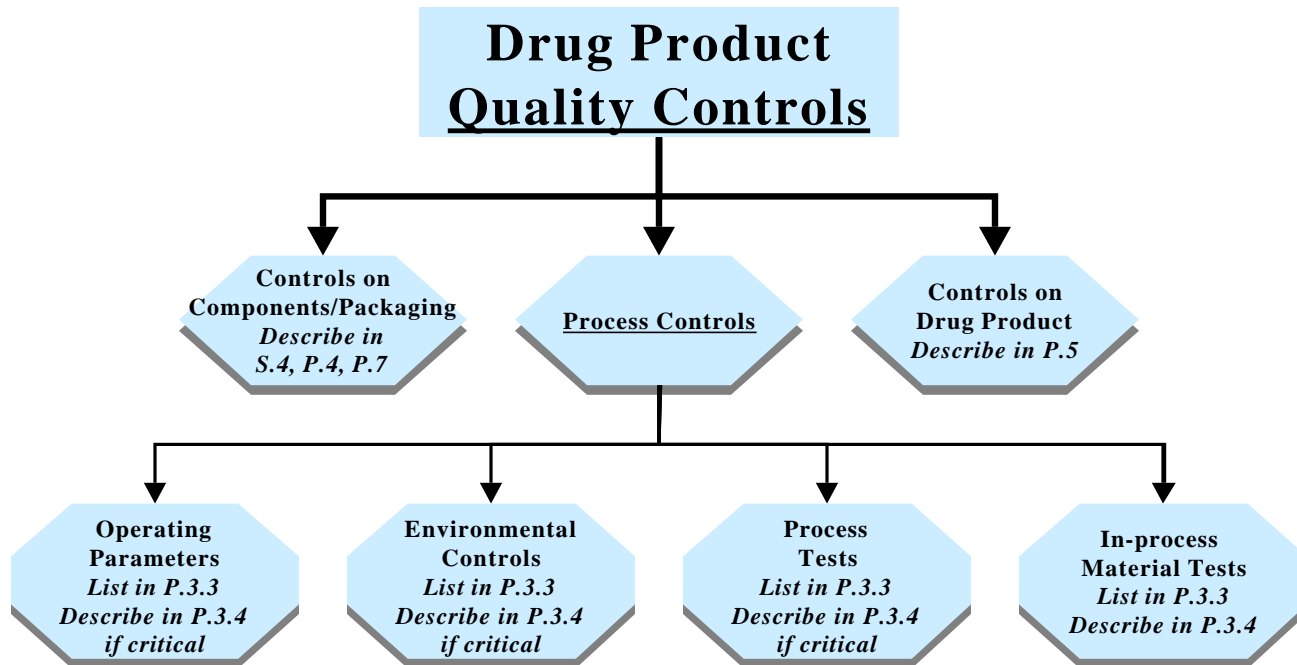
Depending on the drug product and the manufacturing process, a particular process control may or may not be critical as illustrated in the following examples:

- A mixing speed range can be critical for forming an emulsion, but may not be critical for mixing a chemical solution.
- The humidity in the manufacturing facility can be critical for an effervescent tablet but may not be critical for an ointment.
- The clean room classification, while critical for a sterile product, may not be critical for a nonsterile product.
- Time frames for certain unit operations or overall drug product production can be critical for some products (e.g., lagging time for metered dose inhalers, hold times during sterile processing).

All in-process material tests and any of the operating parameters, environmental conditions, and process tests that ensure each critical manufacturing step is properly controlled should be specifically identified as critical in the flow diagram and description of the manufacturing process in this section of the application (P.3.3) and in P.3.4. All in-process material tests are considered critical process controls by definition because they directly assess the quality attributes of an in-process material and ultimately lead to a decision to accept or reject the in-process material or drug product. A summary of where information on drug product quality controls should be located in applications submitted in CTD-Q format is provided in Figure 1.

877  
878  
879  
880  
881

Figure 1



882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904

### 3. *Reprocessing and Reworking*

Reprocessing is the introduction of an in-process material or drug product, including one that does not conform to a standard or specification, back into the process and repeating steps that are part of the approved manufacturing process. Continuation of a process step after a process test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing. For most drug products, reprocessing need not be described in the application. In general, the documentation of and data to support the reprocessing of a production batch should be retained by the manufacturer and be available for review by FDA upon request. However, if there is a significant potential for the reprocessing operation to adversely affect the identity, strength, quality, purity, or potency of the drug product, the reprocessing operations should be described and justified in this section (P.3.3) of the application. For example, reprocessing of proteins would be considered a reprocessing operation that should be described in the application. Any data to support a justification should be either referenced or submitted in P.3.3. However, validation data, when warranted to support the reprocessing operation, should be provided in P.3.5.

Reworking is subjecting an in-process material or drug product that does not conform to a standard or specification to one or more processing steps that are different from the

905 manufacturing process described in the application to obtain acceptable quality in-process  
906 material or drug product. In general, reworking operations are developed postapproval,  
907 and the application is updated through submission of a prior approval supplement.  
908 However, if reworking operations are anticipated at the time of the original submission,  
909 they should be described in this section of the application (P.3.3) with justification for the  
910 reworking operation and any data (or references to data) to support the justification.  
911 Validation data, when warranted to support the reworking operation, should be provided  
912 in P.3.5.

913  
914 Both reprocessing and reworking are considered nonroutine events. If reprocessing or  
915 reworking are expected to be used for the majority of batches, the procedures should be  
916 included as part of the manufacturing process described in the application.  
917

#### 918 **D. Controls of Critical Steps and Intermediates (P.3.4)**

919  
920 In this section of the application, all critical process controls (see section V.C.2) and their  
921 associated numeric ranges, limits, or acceptance criteria should be identified and justified  
922 and a brief description of the test provided. Any experimental data to support the  
923 justification should be included in this section (P.3.4) as well. For critical operating  
924 parameters and environmental controls, numeric ranges, limits, or acceptance criteria  
925 typically can be based on the experience gained during the development of the  
926 manufacturing process. (See section V.E for possible exceptions when process validation  
927 information is warranted.) Critical process control values from relevant batches (i.e.,  
928 those for which batch analyses have been provided in P.5.4) should be provided as part of  
929 the justification. Additional information should be provided in this section (P.3.4) under  
930 the following circumstances.

##### 931 932 • **Biological Tests**

933  
934 Analytical procedures and associated validation information should be provided for  
935 biological tests.<sup>23</sup>  
936

##### 937 • **In-Process Tests Used In Lieu of Finished Product Tests**

938  
939 In some cases, results from in-process tests (e.g., process tests, in-process material tests)  
940 during the manufacturing process can be used in lieu of testing the finished product to  
941 satisfy a test listed in the finished product specification. For example, testing the pH of a  
942 solution during the manufacturing process may be sufficient to satisfy a test listed in the  
943 finished product specification provided in P.5.1. This approach, however, should be  
944 supported with data that demonstrate test results or product performance characteristics  
945 do not change from the in-process stage to finished product. These data, along with the  
946 analytical procedure and associated validation information, should be provided in P.3.4.

---

<sup>23</sup> The term biological tests includes biological (i.e., using animal or cells), biochemical (e.g., enzyme reaction rates), and immunochemical procedures. Information on procedures from an official compendium to assess pyrogen, bacterial endotoxin, sterility, and microbial levels does not need to be provided, but the test procedure should be referenced.

947 Information should be included in the method validation package (R.3.P), as appropriate.  
948 When the same analytical procedure is used for both the in-process test and the finished  
949 product test, the acceptance criterion for the in-process test should be identical to or  
950 tighter than the acceptance criterion in the finished product specification.  
951

Additional guidance is available in:

- FDA: *Submitting Samples and Analytical Data for Methods Validation*<sup>24</sup>
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- 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*

952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970

#### **E. Process Validation and/or Evaluation (P.3.5)**

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical tests used in the manufacturing process, where appropriate. Validation information relating to the adequacy and efficacy of any sterilization process (e.g., drug product, packaging components) should be submitted in this section of the application. However, submission of other manufacturing process validation information in the application is not necessary for most drug products.<sup>25</sup> When applicable, validation information should be provided for processes used to control adventitious agents. This information should be included in A.2.

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., protein drug products).

---

<sup>24</sup> In August 2000 (65 FR 52776), the Agency made available a draft revision of this guidance entitled *Analytical Procedures and Methods Validation*. When finalized, this revision will be the primary reference source on this topic for NDA and ANDA applicants.

<sup>25</sup> All manufacturing processes should be validated. However, in most cases, the validation information is reviewed during facility audits under current good manufacturing practices (CGMP) regulations (21 CFR part 211).

971  
972

Additional guidance is available in:

- FDA: *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

973  
974  
975  
976

## VI. CONTROL OF EXCIPIENTS (P.4)

977 Information on the control of excipients is included in P.4 and, when warranted, A.3 of the  
978 application. The location of the excipient information in the application is described below.  
979 Additional information on excipients should be included in P.2.1.2, as appropriate.

- 980
- 981 • **Compendial- Non-novel Excipients:**<sup>26</sup> When a compendial excipient is tested according  
982 to the monograph standard with no additional testing and the applicant intends to  
983 perform full testing on each batch received, the excipient (e.g., Sodium Chloride, USP)  
984 can be listed under P.4 with no detailed information provided in P.4.1 through P.4.4. In  
985 any other circumstance, information should be included in P.4.1 through P.4.4 of the  
986 application. The P.4.1 to P.4.4 information for each individual excipient should be  
987 grouped together in the application.
- 988 • **Noncompendial- Non-novel Excipients:** Information should be included in P.4.1  
989 through P.4.4 of the application. The P.4.1 to P.4.4 information for each individual  
990 excipient should be grouped together in the application. Furthermore, depending on the  
991 circumstances, additional CMC information for the excipient can be warranted. When  
992 warranted, the additional CMC information or a cross-reference to a DMF that provides  
993 the additional CMC information should be included in A.3. See sections IV.B.2 and  
994 XI.C for additional guidance on the information that should be submitted to support the  
995 use of this type of excipient.
- 996 • **Novel Excipients:** Information on novel excipients should be included in P.4.6 and A.3.
- 997 • **Excipients of Human or Animal Origin:** Any excipient of human or animal origin  
998 should be identified in P.4.5.
- 999

1000 In general, the above information relates to excipients that are materials (i.e., chemicals)  
1001 combined with the drug substance. However, information on other components of the drug  
1002 product should also be included in section P.4, as appropriate. For example, information on the  
1003 components of a transdermal patch drug delivery system and the patch itself should be included  
1004 in P.4.1 through P.4.4. The development of the delivery system should be discussed in P.2.2.1.

<sup>26</sup> A compendial excipient is an excipient that has a monograph in an official compendium as defined in the Federal Food, Drug, and Cosmetic Act. Inclusion of an excipient in an official compendium does not ensure that the excipient has ever been used in an FDA-approved human drug product. Therefore, a compendial excipient can be a novel excipient.



1005  
1006  
1007  
1008  
1009  
1010  
1011  
1012  
1013  
1014  
1015  
1016  
1017  
1018  
1019  
1020  
1021  
1022  
1023  
1024  
1025  
1026  
1027  
1028  
1029  
1030  
1031  
1032  
1033  
1034  
1035  
1036  
1037  
1038  
1039  
1040  
1041  
1042

**A. Specifications (P.4.1)**

A specification for each excipient used in the manufacture of the drug product should be provided, regardless of whether or not the excipient appears in the finished drug product (e.g., processing agent). The specifications should be provided in this section of the application (P.4.1.), except specifications for novel excipients should be provided in P.4.6 and A.3.

The specification should confirm the quality of the excipient and should focus on those characteristics found to be useful in assessing its function, suitability, and safety. The specification sheet should list all tests to which the excipient 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. Presentation of information in a tabular format is recommended.

In addition to listing all the tests for an excipient, the specification should identify the tests that the drug product manufacturer will routinely perform and the test results that will be accepted from the excipient manufacturer's certificate of analysis (COA).<sup>27</sup> At a minimum, the drug product manufacturer must perform an appropriate identification test (21 CFR 211.84(d)(1)). However, when there are specific safety concerns relating to an excipient, testing in addition to an identity test would be warranted. For example, diethylene glycol contamination of polyols such as glycerin and propylene glycol has caused numerous fatalities, and the specification should include testing for potential impurities and contaminants for each batch received by the drug product manufacturer.

A compendial excipient should conform to the monograph standard. Only a citation to the appropriate official compendium need be provided when the excipient specification is identical to the compendial monograph and full monograph testing will be performed on each batch of excipient.<sup>28</sup> When the specification for a compendial excipient differs from the compendial monograph (e.g., additional tests, tighter acceptance criteria than in the monograph, different analytical procedures) or test results will be accepted from the excipient manufacturer's COA, the in-house specification should be provided. If the specification for an excipient is based on a compendium other than an official compendium, the excipient should still conform to the monograph in an official compendium if there is such a monograph.

---

<sup>27</sup> The 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.

<sup>28</sup> A compendial excipient is expected to comply with the monograph in the current revision of the official compendium cited. Therefore, when citing an official compendium, the version of the compendium should not be included in the citation. For example, the *National Formulary (NF)* should be cited rather than *NF 20*.

1043 Certain *General Chapters* in the USP contain a statement that the text of the USP is  
1044 harmonized with the corresponding texts of the *European Pharmacopoeia* (EP) and the  
1045 *Japanese Pharmacopoeia* (JP). However, where a difference appears, or in the event of  
1046 dispute, the result obtained from the USP procedure is conclusive.  
1047

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*

1048  
1049 **B. Analytical Procedures (P.4.2)**  
1050  
1051 The analytical procedures used by the applicant for testing the excipients, excluding those  
1052 for novel excipients, should be provided in P.4.2. The analytical procedures for novel  
1053 excipients should be included in A.3. When the analytical procedure used is in the  
1054 current revision of an official compendium or another FDA-recognized standard  
1055 reference (e.g., AOAC International Book of Methods) and the referenced analytical  
1056 procedure is not modified, a statement indicating the analytical procedure and reference  
1057 can be provided rather than the analytical procedure itself.  
1058

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*

1059  
1060 **C. Validation of Analytical Procedures (P.4.3)**  
1061  
1062 All analytical procedures for excipients should be validated. When analytical procedures  
1063 from the current revision of an official compendium or other FDA recognized standard  
1064 references (e.g., AOAC International Book of Methods, analytical procedures from EP or  
1065 JP that are interchangeable with a USP *General Chapter*) are used, they should be  
1066 verified to be suitable under actual conditions of use. Submission of validation  
1067 information in the application is normally not needed for excipients. Validation  
1068 information should be submitted if there are special circumstances. For example,  
1069 submission of validation information for an excipient can be appropriate if a  
1070 characteristic of the excipient or the excipient itself is critical to product quality (e.g.,  
1071 adjunct, carrier) but the critical nature of the excipient cannot be or is not assessed as part  
1072 of the drug product testing.  
1073

Additional guidance is available in:

- FDA: *Submitting Samples and Analytical Data for Methods Validation*<sup>29</sup>
- ICH: *Q2A Text on Validation of Analytical Procedures*
- ICH: *Q2B Validation of Analytical Procedures: Methodology*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

1074  
1075  
1076  
1077  
1078  
1079  
1080  
1081  
1082  
1083  
1084  
1085  
1086  
1087  
1088  
1089  
1090  
1091  
1092  
1093  
1094  
1095  
1096

#### **D. Justification of Specifications (P.4.4)**

Justifications for the proposed excipient specifications should be provided where appropriate. For compendial excipients, justification of the acceptance criteria for tests beyond those included in the monographs is recommended (e.g., particle size, flow properties, impurities). The specifications for noncompendial excipients should be justified as recommended for the drug substance (guidance will be provided in the discussion of section S.4.5 of the forthcoming drug substance guidance). The justification should be based on relevant development data (P.2.1.2), batch analyses (P.5.4, R.1.P), and any other relevant data, such as data from drug product stability studies (P.8). The discussion in this section should unify, either by reference or in summary, data and information that are located in other sections of the application.

A certificate of analysis (COA) from the manufacturer and the test results for the same batch from the drug product manufacturer should be provided for the components described in P.4. The information should be for the materials used to produce the batch described in the executed production record (R.1.P). Test results should be expressed numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of terms such as *conforms* or *meets specification* is discouraged.

Additional guidance is available in:

- ICH: *Q3C Impurities: Residual Solvents and Q3C Tables*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

<sup>29</sup> In August 2000 (65 FR 52776), the Agency made available a draft revision of this guidance entitled *Analytical Procedures and Methods Validation*. When finalized this revision will be the primary reference source on this topic for NDA and ANDA applicants. Although excipients are not included within the scope of the guidance, applicants can refer to this guidance for general principles on validation of analytical procedures.

1097  
1098  
1099  
1100  
1101  
1102  
1103  
1104  
1105  
1106  
1107  
1108  
1109  
1110  
1111  
1112

**E. Excipients of Human or Animal Origin (P.4.5)**

Excipients of human or animal origin should be identified. The genus, species, country of origin, source (e.g., pancreas), and manufacturer or supplier should be clearly indicated. Furthermore, for excipients derived from ruminant materials, the application should state whether the materials are from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11). Guidance is available from FDA on *The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use*.

The potential adventitious agents should be identified, and general information regarding control of these adventitious agents (e.g., specifications, description of the testing performed, and viral safety data) should be provided in this section. Details of the control strategy and the rationale for the controls should be provided in A.2.

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*

1113  
1114  
1115  
1116  
1117  
1118  
1119  
1120  
1121  
1122  
1123  
1124  
1125  
1126  
1127  
1128  
1129  
1130  
1131  
1132  
1133  
1134

**F. Novel Excipients (P.4.6)**

Novel excipients are excipients used for the first time in a human drug product in the United States or by a new route of administration. Any novel excipient should be identified and its specification included in this section of the application (P.4.6).

Additionally, full details of manufacture, characterization, and controls, with cross-references to supporting safety (nonclinical and/or clinical) data, should be provided. The information should provide the same level of detail as that provided for a drug substance, and according to the drug substance format (guidance will be provided in the forthcoming drug substance guidance). This detailed information should be provided in A.3 unless the information is provided in an appropriately referenced DMF.

**VII. CONTROL OF DRUG PRODUCT (P.5)**

**A. Specification(s) (P.5.1)**

The proposed specification for the drug product should be provided. The specification establishes criteria to which each batch of drug product should conform to be considered

1135 acceptable for its intended use. *Conformance to specification* means that the drug  
1136 product, when tested according to the listed analytical procedures, will meet the listed  
1137 acceptance criteria. A specification is one part of the strategy to control drug product  
1138 quality. They are proposed and justified by the manufacturer and approved by the  
1139 Agency. Specifications are established to confirm the quality of drug products rather  
1140 than to establish full characterization and should focus on those characteristics found to  
1141 be useful in ensuring product quality as it relates to safety and efficacy. Information on  
1142 periodic quality indicator tests is provided below.

1143  
1144 The specification sheet should list all tests to which each batch of a drug product will  
1145 conform and the associated acceptance criteria and should also include a reference to the  
1146 analytical procedures that will be used to perform each test. Acceptance criteria are  
1147 numerical limits, ranges, or other criteria for the tests described. If an analytical  
1148 procedure will be used only to generate stability data, the analytical procedure should be  
1149 described in P.8.3. Justified interim acceptance criteria and tests with sunset provisions  
1150 should be included in the specification (see section VII.F). Presentation of information in  
1151 a tabular format is suggested. The specification sheet should also identify:

- 1152
- 1153 • tests that can be performed in-process in lieu of testing the finished product (the  
1154 results of such tests performed in-process should be included in the batch analysis  
1155 report (e.g., certificate of analysis))
  - 1156 • all analytical procedures that will be used for a test; identifying which are regulatory  
1157 and which are alternative analytical procedures when multiple analytical procedures  
1158 can be used for a test<sup>30</sup>
  - 1159 • acceptance criteria for the test using the regulatory analytical procedure and  
1160 alternative analytical procedures when the criteria are different (e.g., conformance to  
1161 a spectrum for near infrared (NIR) or retention time for HPLC).
  - 1162 • release and shelf-life acceptance criteria when both are used
- 1163

1164 The ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for*  
1165 *New Drug Substances and New Drug Products: Chemical Substances* provides  
1166 recommendations on tests that should be included in the specification for solid oral drug  
1167 products, liquid oral drug products, and parenterals (small and large volume). Some tests  
1168 that are identified as appropriate for inclusion in the specification can be proposed as  
1169 periodic quality indicator tests when there are sufficient data and justification.  
1170 Recommendations on tests for other dosage forms are included in Attachment 1.

1171  
1172 An illustrative example of a specification sheet is provided in Table 3.

---

<sup>30</sup> See section VI.B for guidance on USP *General Chapters* that are interchangeable with EP or JP analytical procedures.

1173

1174

<b>Table 3: Specification for Trademark™ Tablets (100 mg)</b>			
Tests	Acceptance Criteria	Regulatory Analytical Procedure	Alternative Analytical Procedure
Description	White, biconvex, 11 mm diameter, 4 mm thick, film coated tablet, with “identifier code XYZ” on one side.	Visual	
Identification Test #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.	HPLC, AP <sup>1</sup> # EFG	
Identification Test #2	Responds to the tests for sulfate	USP <191>	
Core Weight <sup>2</sup>	440 mg ± 5%	AP # MOP	
Dissolution	NLT <sup>3</sup> 80% (Q) in 30 minutes	AP # BCD	
Uniformity of Dosage Units	As per USP	HPLC; AP # EFG	
Assay	95.0% to 105.0% LC <sup>4</sup> (release) 90.0% to 110.0% LC (shelf-life)	HPLC, AP # EFG	
Water Content	NMT <sup>5</sup> 1.0%	USP <921>; Method Ic	AP # PQR
Degradation Products		HPLC; AP # EFG	
Specified Degradation Products			
• Degradant A	NMT 0.5%		
• Degradant B	NMT 0.6%		
• Degradant at RRT <sup>6</sup> <u>XX</u>	NMT 0.3%		
Unspecified Degradation Product			
• Individual Unspecified	NMT 0.1%		
Total Degradation Products	NMT 1.2%		
Residual Solvent A	NMT 200 ppm	GC; AP # XYZ	
<sup>1</sup> AP = Analytical Procedure <sup>2</sup> Test will be performed on tablet cores in-process. <sup>3</sup> NLT = not less than <sup>4</sup> LC = label claim <sup>5</sup> NMT = not more than <sup>6</sup> RRT = relative retention time			

1175

1176

1177

1178

1179

1180

1181

1182

1183

1184

1185

1186

- **Periodic Quality Indicator Tests**

The CGMP regulations require that for each batch of drug product, there will be appropriate laboratory determination of satisfactory conformance to the drug product specification. Drug product failing to meet established standards or its specification and any other relevant quality control criteria must be rejected (21 CFR 211.165).

Occasionally and when justified, other tests and associated acceptance criteria and analytical procedures that assess product quality can be included in the application and not be listed in the drug product specification. These tests, referred to as periodic quality indicator tests (PQITs), augment the drug product specification. A PQIT is performed at release on preselected batches and/or at predetermined intervals, rather than on a batch-

1187 to-batch basis. A PQIT can be warranted when a test, performed and reported as part of  
1188 the batch analyses, has value as an indicator of product quality, but information indicates  
1189 that the test need not to be performed on each batch of drug product. PQITs can include,  
1190 for example, osmolality and microbiological testing for solid oral dosage forms.

1191 Designation of certain tests such as for description, identification, assay, impurities  
1192 (unless otherwise justified), dissolution or drug release, or content uniformity as PQITs  
1193 would not be considered appropriate. The appropriateness of a PQIT can depend on the  
1194 type of product. For example, justification for a PQIT would be likely for an oral dosage  
1195 form product than for a biological/biotechnology-derived parenteral drug product. Each  
1196 request will be considered on a case-by-case basis. PQITs, along with the drug product  
1197 specification, form a basis for approving the application (see, for example, section  
1198 505(b)(1)(D) and 505(d)(3) of the Federal Food, Drug, and Cosmetic Act).<sup>31</sup>  
1199

1200 Sufficient data should be available to support a proposal to designate a test as a PQIT. If  
1201 sufficient data (e.g., data from multiple batches, all proposed manufacturing sites and  
1202 processes) are available, a PQIT proposal can be included in the original application. A  
1203 proposal for a PQIT should include:

- 1204 • the reason the PQIT is being proposed
- 1205 • justification and data to support the periodic testing
- 1206 • the protocol (e.g., frequency) for performing the test, including when postapproval  
1207 changes are implemented
- 1208 • a commitment
- 1209

1210 The commitment should state that:

- 1211 • the PQIT will be performed according to the protocol approved in the application
- 1212 • failure to meet the acceptance criteria for the PQIT will be handled (e.g.,  
1213 investigation, batch rejection decision) in the same manner as a failure of a test  
1214 included in the drug product specification and the PQIT will be performed on each  
1215 subsequent batch until the failure is resolved
- 1216 • any investigation will assess the effect on all batches produced, in particular, the  
1217 batches between the last batch tested with a passing test result and the batch that  
1218 failed
- 1219 • if the result of the investigation confirms a batch failure or is inconclusive, a changes-  
1220 being-effected supplement will be submitted to include the test in the drug product  
1221 specification
- 1222

1223 A list of PQITs, with associated acceptance criteria and reference to analytical  
1224 procedures, should be included in P.5.1 of the application. The protocol and commitment  
1225 should also be included in P.5.1. Data and justification to support the designation of a  
1226 PQIT should be included in P.5.4 and P.5.6, as appropriate. The recommendations on  
1227 CMC information that should be provided in P.5.2, P.5.3, and P.5.5 also apply to PQITs.  
1228

---

<sup>31</sup> 21 U.S.C. 355 (b)(1) and 355 (d)(3).

1229 It is recognized that only limited data may be available at the time of submission of an  
1230 application. Therefore, this concept would generally be implemented postapproval once  
1231 sufficient data are available and after approval of a prior approval supplement.  
1232  
1233  
1234

Additional guidance is available in:

- ICH: *Q3B Impurities in New Drug 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*

1235  
1236  
1237

#### **B. Analytical Procedures (P.5.2)**

1238  
1239 The analytical procedures used for testing the drug product should be provided.  
1240 Recommendations on the content and format of analytical procedures will be provided in  
1241 a forthcoming FDA guidance on *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*. Information should be  
1242 provided for all analytical procedures listed in the specification (P.5.1). The following  
1243 additional guidance is provided on submitting analytical procedure information from  
1244 published sources.

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

1245  
1246  
1247  
1248  
1249  
1250 If the analytical procedure used is in the current revision of an official compendium or  
1251 another FDA-recognized standard reference (e.g., AOAC International Book of Methods)  
1252 and the referenced analytical procedure is not modified, the analytical procedure need not  
1253 be provided. A specific citation to the analytical procedure is sufficient.<sup>32</sup> When a  
1254 general chapter or monograph included in an official compendium or other FDA  
1255 recognized standard reference allows for the use of more than one analytical procedure  
1256 for a test, the specific analytical procedure that will be used should be cited here (P.5.2)  
1257 and in the specification (P.5.1). For example, when using USP <921> *Water*  
1258 *Determination*, the method should be specified (e.g., Method Ia). If an analytical  
1259 procedure is based on one of these sources but has been modified, the analytical  
1260 procedure should be provided.  
1261

---

<sup>32</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*.



1262  
1263  
1264  
1265  
1266  
1267  
1268

- **Analytical Procedures from Other Published Sources**

Analytical procedures from any other published source (e.g., another country's compendium, scientific journal) should be provided.

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*

1269  
1270  
1271  
1272  
1273  
1274  
1275  
1276  
1277  
1278  
1279  
1280  
1281  
1282  
1283

**C. Validation of Analytical Procedures (P.5.3)**

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product 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 (P.5.1). Stability data (S.7.3, P.8.3), 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 will be provided in a forthcoming FDA guidance on *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation*. The methods validation package should be provided in R.3.P.

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: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

1284  
1285  
1286  
1287  
1288  
1289  
1290  
1291

**D. Batch Analyses (P.5.4)**

Batch analysis data should be provided for all batches used for clinical efficacy and safety, bioavailability, bioequivalence, and 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

1292 (e.g., COAs) and collated batch analyses data should include a description of the batches.  
1293 This information can be presented (1) with the batch data as space permits or (2) in a  
1294 separate table with only the batch identity being included with the batch data. The  
1295 description should include:

- 1296
- 1297 • Batch identity (i.e., batch number), strength, and size
  - 1298 • Date of manufacture
  - 1299 • Site of manufacture
  - 1300 • Manufacturing process, where applicable
  - 1301 • Container closure system
  - 1302 • Use of batch (e.g., bioavailability, stability)
  - 1303 • Batch number of the drug substance used in the drug product
  - 1304 • Batch number of novel excipients or any excipients that are critical to product  
1305 performance (e.g., excipients used to form liposomes)
- 1306

1307 Test results should be expressed numerically or qualitatively (e.g., clear, colorless  
1308 solution), as appropriate. Use of terms such as *conforms* or *meets specification* is  
1309 discouraged.

1310

1311 *1. Batch Analysis Reports*

1312

1313 The batch analysis reports should include results from all tests performed on the batch,  
1314 including tests that are not part of the proposed specification. References to analytical  
1315 procedures should be provided.

1316

1317 A summary of any changes in the analytical procedures should be provided if the  
1318 analytical procedures (1) changed over the course of generating the batch analyses data  
1319 and/or (2) are different from the analytical procedure included in P.5.2. The summary  
1320 should identify when an analytical procedure changed, the differences between the  
1321 analytical procedures, and the impact of the differences with respect to the data being  
1322 reported. For example, a summary could state that the solvent system for the assay was  
1323 changed on December 15, 1999, from A to B so that impurities Y and Z that co-elute  
1324 using System A could be quantitated separately. If there are significant differences in the  
1325 analytical procedures (e.g., different fundamental principles such as titration and HPLC),  
1326 a more detailed summary describing the changes may be warranted

1327

1328 *2. Collated Batch Analyses Data*

1329

1330 Presentation of results from all batches for a particular test in tabular and/or graphical  
1331 format is often helpful in justifying the acceptance criteria. Collated batch analyses data  
1332 are not warranted for all tests. However, collated data should be provided for assay and  
1333 impurities (e.g., degradation products, residual solvents) and should be considered for  
1334 other tests such as water content.

1335

Additional guidance is available in:

- ICH: *Q3B Impurities in New Drug Products*
- 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*

1336

1337

## **E. Characterization of Impurities (P.5.5)**

1338

Information on the drug product impurities should be provided.

1339

1340

1341

### *1. List of Expected Impurities*

1342

1343

All expected drug product impurities (e.g., degradation products of the active ingredient, residual solvents, enantiomeric impurities, excipient degradants, leachables from the container closure system) should be listed in this section of the application whether or not the impurities are included in the drug product specification. For example, drug substance process impurities that could carry over to the drug product should be listed here even if they are normally controlled during drug substance testing and will not be included in the drug product specification. When qualified, the qualified level of an expected impurity with a cross reference to the appropriate studies (include study numbers) should be provided.

1344

1345

1346

1347

1348

1349

1350

1351

1352

The list of expected impurities should be based on information from batch release data (P.5.4), stability studies, including stress studies (S.7.3, P.8.3), development data (e.g., container closure system suitability studies (P.2.4)), knowledge of the manufacturing process (e.g., use of organic solvents), and published literature (e.g., known excipient degradants). The rationale for not including an expected impurity in the drug product specification should be provided in P.5.6.

1353

1354

1355

1356

1357

1358

1359

### *2. Identification of Impurities*

1360

1361

Information on the characterization (i.e., structural characterization) of impurities should be provided if not previously provided in S.3.2. An applicant is encouraged to discuss any questions about the identification of impurities with the appropriate review divisions.

1362

1363

1364

1365

#### **• Degradation Products**

1366

1367

Active ingredient related impurities not covered in S.3.2 can include, for example, degradation products of the active ingredient arising during drug product manufacture or reaction products of the active ingredient with an excipient and/or immediate container

1368

1369

1370

1371 closure system. Attempts should be made to identify all degradation products found at  
1372 significant levels in the drug product. CDER and CBER regulates a variety of drug  
1373 products; no single recommendation applies to all drug products for the level of a  
1374 degradation product that would warrant identification. Recommendations on  
1375 identification levels may be provided for specific situations. For example, the ICH  
1376 guidance *Q3B Impurities in New Drug Products* provides recommended identification  
1377 levels for certain types of impurities in various classes of drug products.  
1378

1379 When identification is warranted, the recommendations in S.3.2 of the forthcoming drug  
1380 substance guidance on approaches for identifying impurities are applicable. A summary  
1381 of attempts made to identify an impurity should be provided, if it has not been possible to  
1382 identify it.  
1383

1384 • **Residual Solvents**  
1385

1386 An applicant is aware of the solvents used in the manufacture of the drug product and, in  
1387 most cases, those being introduced from other sources (e.g., drug substance, excipients).  
1388 Because these are known, the identity and presence of residual solvents in the finished  
1389 drug product can usually be confirmed by using routine analytical techniques. In some  
1390 cases, structural characterization of an unknown impurity can determine that the impurity  
1391 is a residual solvent.  
1392

1393 • **Miscellaneous Drug Product Impurities**  
1394

1395 For purposes of this guidance, a miscellaneous drug product impurity is a drug product  
1396 impurity other than (1) a degradation product, (2) a residual solvent, or (3) an extraneous  
1397 contaminant that is more appropriately addressed as a good manufacturing practices issue  
1398 (e.g., metal shavings). Miscellaneous drug product impurities include, for example,  
1399 container closure system leachables, excipient degradants, heavy metals, aluminum, and  
1400 ethylene oxide residuals.  
1401

1402 Whether identification of a miscellaneous drug product impurity is warranted depends on  
1403 the circumstances associated with a specific drug product. In general, the factors that  
1404 contribute to the decision of whether structural characterization of such impurities is  
1405 warranted are the (1) observed levels, (2) potential for safety issues to arise from  
1406 exposure to the impurity (e.g., route of administration, patient population), (3) duration of  
1407 product use (acute or chronic), and (4) historical knowledge. For example, structure  
1408 characterization would more likely be requested for a container closure system leachable  
1409 found in a metered dose inhalation product than for a leachable found in an oral solution.

1410

Additional guidance is available in:

- ICH: *Q1B Photostability Testing of New Drug Substances and Products*
- ICH: *Q3B Impurities in New Drug Products*
- 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*

1411

1412

1413

1414

#### **F. Justification of Specification(s) (P.5.6)**

1415

1416

1417

1418

1419

1420

1421

1422

1423

1424

1425

1426

1427

1428

Justification for the proposed drug product specification should be provided. The justification should be based on relevant development data (P.2), standards in an official compendium, batch analyses (P.5.4), characterization of impurities (P.5.5), stability studies (P.8), 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. Data from the clinical efficacy and safety, bioavailability, bioequivalence, and primary stability batches and, when available and relevant, development and process validation batches should be considered in justifying the specification. If multiple manufacturing sites are planned, it can be valuable to consider data from these sites in establishing the tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug product at any particular site. Justification for an in-process test that is used in lieu of a finished product test should be included in P.3.4.

1429

- **Tests**

1430

1431

1432

1433

1434

1435

1436

1437

1438

1439

1440

1441

1442

Inclusion of a test in the drug product specification need not be justified. However, exclusion of a test that is normally performed on a type of drug product, one that is recommended in a relevant FDA guidance, or one that was reported in the batch analyses (P.5.4) should be justified. For example, the ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* recommends that a test for redispersibility be included in the specification for an injectable suspension. Data generated during product development can be sufficient to justify eliminating this attribute from the specification, and such justification should be included in this section of the application (P.5.6). Similarly, justification for excluding the expected impurities listed in P.5.5 from the drug product specification provided in P.5.1 should be provided in this section of the application (P.5.6).

1443  
1444 Justification for the designation of a test as a periodic quality indicator test should be  
1445 provided.

1446  
1447 Occasionally, it may appear that a test performed and reported as part of the batch  
1448 analyses may not be necessary. For example, the available test results for heavy metals  
1449 may be very low or below the limit of detection of the analytical procedure or osmolarity  
1450 results are very consistent for the batches produced in support of the application  
1451 indicating that there may be no need to perform the test. However, it is not certain if the  
1452 same type of results will continue to be observed for production batches because (1)  
1453 limited data are available at the time the application is submitted and/or (2) the  
1454 manufacturing process for production batches will be different (e.g., scale, equipment,  
1455 site) from that used to produce the batches used to support the application and the effect,  
1456 if any, of the differences has yet to be characterized. In these or similar circumstances,  
1457 an applicant could propose a *sunset test protocol* for a test, which would provide for the  
1458 test to be dropped from the specification after an agreed number of production batches  
1459 have met certain criteria.<sup>33</sup> The proposal should include the (1) reason why the sunset  
1460 provision is being proposed, (2) number of consecutive production batches that will be  
1461 produced and tested before inclusion of the test in the drug product specification is  
1462 reevaluated, (3) criteria that would be achieved, including data analysis plan, for the test  
1463 to be dropped, and (4) postapproval reporting mechanism for notifying CDER of the test  
1464 results when the criteria have been achieved. A *sunset test protocol* could also be  
1465 considered when FDA requests that a test be added to the specification.

1466  
1467 • **Acceptance Criteria**

1468  
1469 Justification should be provided for all proposed acceptance criteria included in the drug  
1470 product specification. Results from nonclinical, clinical, and stability studies and  
1471 manufacturing and analytical capability should be considered when proposing acceptance  
1472 criteria. Proposed acceptance criteria can include a reasonable allowance for analytical  
1473 and manufacturing variability. The justification should discuss the basis of the proposed  
1474 acceptance criteria from the perspectives of available data and analytical and  
1475 manufacturing capability and variability. Furthermore, any statistical approaches that are  
1476 used to establish the acceptance criteria should be described. In some cases, data  
1477 generated from testing samples of the reference listed drug can be used to support  
1478 acceptance criteria proposed in the application.

1479  
1480 Occasionally, an applicant may wish to propose *interim acceptance criteria* for a specific  
1481 test because there is some uncertainty whether the same type of results will continue to be  
1482 observed for production batches. This uncertainty often occurs when (1) there are limited  
1483 data available at the time the application is submitted and/or (2) the manufacturing  
1484 process for production batches will be different (e.g., scale, equipment, site) from that  
1485 used to produce the batches used to support the application and the effect, if any, of the  
1486 differences has yet to be characterized. The proposal should include the (1) reason why

---

<sup>33</sup> A proposal to drop a test, based on historical data, can also be submitted postapproval in a prior approval supplement.

1487 the interim acceptance criteria are being proposed, (2) number of consecutive production  
1488 batches that will be produced and tested and/or the time frame before the acceptance  
1489 criteria will be finalized, (3) data analysis plan, and (4) proposed reporting mechanisms  
1490 for finalizing the acceptance criteria when the proposed final acceptance criteria are  
1491 tighter, broader, or the same as the interim acceptance criteria. An applicant should not  
1492 propose using interim acceptance criteria as a substitute for providing recommended or  
1493 agreed upon (e.g., at pre-NDA meetings) information in an application. For example,  
1494 proposing interim acceptance criteria would not be appropriate when the stability data  
1495 package recommended in the ICH guidance *Q1A: Stability Testing of New Drug*  
1496 *Substances and Products* has not been provided.<sup>34</sup> For NDAs, finalization of interim  
1497 acceptance criteria will be a Phase 4 commitment.

1498  
1499 • **Analytical Procedures**

1500  
1501 The analytical procedures listed in the drug product specification normally need not be  
1502 justified because the appropriateness of the procedure is supported by information in  
1503 P.5.2, P.5.3, and R.3.P. In some instances, however, justification for the type of  
1504 analytical procedure used would be warranted. For example, justification should be  
1505 provided for the use of a non-stability-indicating assay procedure. The justification  
1506 should explain the scientific reasons why a stability indicating procedure is not viable and  
1507 which analytical procedures complement the assay procedure by qualitatively and/or  
1508 quantitatively monitoring impurities, including degradants.

1509  
Additional guidance is available in:

- ICH: *Q3B Impurities in New Drug 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*

1510  
1511  
1512 **VIII. REFERENCE STANDARDS OR MATERIALS (P.6)**

1513  
1514 Information on the reference standard or reference materials used in testing the drug product  
1515 should be provided if not previously provided in S.5. Information on the reference standards for  
1516 drug substance and drug substance impurities should be provided in S.5. A list of available  
1517 reference standards should be provided in this section (P.6) for any impurities that are unique to  
1518 the drug product.<sup>35</sup> The reference standards could be for impurities from drug substance and  
1519 excipient interactions, impurities formed during drug product manufacturing, or an excipient

<sup>34</sup> For those applications that fall within the scope of Q1A.

<sup>35</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)).

1520 impurity or leachable from the container closure system that is included in the drug product  
1521 specification.

1522  
1523 Information on other drug product related reference standards, such as those used in the testing  
1524 of excipients and packaging need not be included in the application.

1525  
1526

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*

1527  
1528  
1529

## **IX. CONTAINER CLOSURE SYSTEM (P.7)**

1530  
1531 A description of the container closure system for the drug product should be provided, including  
1532 the identity of materials of construction of each primary packaging component and its  
1533 specification. The same type of information should be provided for functional secondary  
1534 packaging components as is provided for primary packaging components. For nonfunctional  
1535 secondary packaging components (e.g., those that neither provide additional protection nor serve  
1536 to deliver the product), only a brief description should be provided. Information about the  
1537 suitability of a container closure system should be provided in P 2.4.

1538  
1539 If an NDA is submitted for a new plastic that will be used for blood component storage, adequate  
1540 information on the plastic should be submitted, including the composition of the plastic.  
1541

Additional guidance is available in:

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

1542



1543  
1544  
1545  
1546  
1547  
1548  
1549  
1550  
1551  
1552  
1553  
1554  
1555  
1556  
1557  
1558  
1559  
1560  
1561  
1562  
1563  
1564  
1565  
1566  
1567  
1568  
1569  
1570  
1571  
1572  
1573  
1574  
1575  
1576  
1577  
1578  
1579  
1580  
1581  
1582  
1583  
1584  
1585  
1586  
1587  
1588

**X. STABILITY (P.8)**

Information relating to the stability of the drug product should be provided in P.8.

**A. Stability Summary and Conclusion (P.8.1)**

The types of studies conducted, protocols used, and results of the studies should be summarized. The discussion should include, for example, (1) a summary of stability batches tested, storage conditions used, product attributes tested, shelf-life acceptance criteria, test schedule, amount of data available, and analysis of data (including a summary of the statistical analysis if performed), (2) conclusions regarding the labeled storage conditions and the proposed shelf life, and (3) conclusions regarding in-use storage conditions and shelf life, if applicable.

**B. Postapproval Stability Protocol and Stability Commitment (P.8.2)**

The postapproval stability protocol and stability commitment should be provided.

**C. Stability Data (P.8.3)**

Results of stability studies, including statistical analysis if performed, should be presented in an appropriate format (e.g. tabular, graphical, narrative).

*1. Formal Stability Studies*

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

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

- If the analytical procedure listed in the stability protocol is different from the analytical procedure described in P.5 for the corresponding test (i.e., batch release versus stability analytical procedure) or a test included in the stability protocol is not described in P.5 (e.g., weight loss), the analytical procedure, validation of analytical procedures, and justification of acceptance criteria, as appropriate, should be included.
- 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

1589 for the assay was changed on December 15, 1999, from A to B so that impurities Y  
1590 and Z that co-elute using System A could be quantitated separately. If there are  
1591 significant differences in the analytical procedures (e.g., different fundamental  
1592 principles such as titration and HPLC), a more detailed summary describing the  
1593 changes may be warranted  
1594

1595 Constitution or dilution studies performed as part of formal stability studies to confirm  
1596 product quality through shelf life should be reported in this section of the application.  
1597 Information regarding the compatibility of the drug product with any diluents (i.e.,  
1598 constitution, dilution of concentrates, admixing), dosage devices, or coadministered drug  
1599 products should be provided in P.2.6.  
1600

## 1601 2. *Supporting Stability Studies*

1602

1603 Data, other than those from formal stability studies, that support the analytical  
1604 procedures, the proposed shelf life, and label storage statements can be provided. Such  
1605 data can include, for example, stability data on small scale batches of drug product,  
1606 investigational formulations not proposed for marketing, related formulations, or product  
1607 presented in container closure systems other than those proposed for marketing. Stability  
1608 data to support holding in-process materials for longer than 30 days should also be  
1609 provided in this section. Information on the type of container closure system in which  
1610 the in-process material is held should be included with the stability data. The analytical  
1611 procedures should be identified, and when analytical procedures are different from those  
1612 described elsewhere in the application, information should be provided on the analytical  
1613 procedures to the extent warranted to support the use of the data.  
1614

## 1615 3. *Stress Studies*

1616

1617 Any results from drug product stress testing and thermal cycling studies should be  
1618 provided in this section of the application. The design of the stress studies should be  
1619 discussed briefly. The information should be used, as appropriate, to support the  
1620 validation of analytical procedures (P.5.3), the impurities acceptance criteria and/or  
1621 characterization of expected impurities (P.5.1, P.5.5), justification of the drug product  
1622 specification (P.5.6), and stability summary and conclusions (P.8.1).

1623

Additional guidance is available in:

- FDA: *Submitting Documentation for the Stability of Human Drugs and Biologics*<sup>36</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: *Q3B Impurities in New Drug Products*
- 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*

1624

1625

1626

## **XI. APPENDICES (A)**

1627

1628 Information relating to both drug substances and drug products should be included in the  
1629 Appendices (section A) of the application, when appropriate. If drug substance and drug product  
1630 information is provided in an appendix, the preferred presentation is drug substance information  
1631 followed by drug product information (e.g., A.1 drug substance then drug product, followed by  
1632 A.2). The recommendations provided below relate to drug products. Recommendations on the  
1633 information to include in the Appendices for drug substances will be provided in the forthcoming  
1634 drug substance guidance.

1635

### **A. Facilities and Equipment (A.1)**

1636

1637 Information on facilities and equipment, in addition to the information provided in other  
1638 sections of the application (e.g., P.3.1, P.3.3), is usually not needed. However, when  
1639 contamination with viral adventitious agents or transmissible spongiform encephalopathy  
1640 (TSE) agents is a concern or for protein products, additional information can be  
1641 warranted and should be included in this section of the application.  
1642

1643

#### **• Viral Adventitious Agents and TSE Agents**

1644

1645 All developmental or approved products manufactured or processed in the same areas as  
1646 the applicant's products should be identified when there is potential for cross-  
1647 contamination with TSE agents. For nonoral, nontopical products, this information  
1648 should also be provided when there is potential for cross-contamination with viral  
1649 adventitious agents. Information should be included on the design features of the facility  
1650 and procedures to prevent cross-contamination of areas and equipment.  
1651

---

<sup>36</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

1652  
1653 If ruminant-derived materials from BSE countries as defined by the U.S. Department of  
1654 Agriculture (9 CFR 94.11) are used or manipulated in the same facility, additional  
1655 information should be provided, such as whether dedicated equipment is used.  
1656

1657 • **For Protein Products**  
1658

1659 A diagram should be provided illustrating the manufacturing flow, including movement  
1660 of raw materials, personnel, waste, and intermediates in and out of the manufacturing  
1661 areas. Information should be presented with respect to adjacent areas or rooms that may  
1662 be of concern for maintaining integrity of the product.  
1663

1664 Information on all development or approved products manufactured or manipulated in the  
1665 same areas as the applicant's product should be included.  
1666

1667 A summary description of the product-contact equipment and its use (dedicated or multi-  
1668 use) should be provided. Information on preparation, cleaning, sterilization, and storage  
1669 of specified equipment and materials should be included, as appropriate.  
1670

1671 Information should be included on procedures (e.g., cleaning and production scheduling)  
1672 and design features of the facility (e.g., classifications) to prevent contamination or cross-  
1673 contamination of areas and equipment where operations for the preparation of cell banks  
1674 and product manufacturing are performed.  
1675

1676 For biotechnology derived protein products, additional recommendations will be  
1677 provided in the forthcoming guidance on the submission of CMC information for a  
1678 therapeutic recombinant DNA-derived product or a monoclonal antibody for in vivo use.  
1679

1680 **B. Adventitious Agents Safety Evaluation (A.2)**  
1681

1682 Information assessing the risk with respect to potential contamination with adventitious  
1683 agents should be provided. The recommendations provided below relate to the drug  
1684 product. Recommendations on the information to include in A.2 for drug substance will  
1685 be provided in the forthcoming drug substance guidance. For example, an applicant  
1686 should refer to the drug product guidance for recommendations on viral safety evaluation  
1687 studies when they are performed as part of the drug product manufacturing (e.g.,  
1688 assessment of a biotechnology-derived excipient). However, if studies are performed as  
1689 part of the drug substance manufacturing (e.g., evaluation of a cell line), the applicant  
1690 should refer to the forthcoming drug substance guidance. Furthermore, for  
1691 biotechnology derived products, additional recommendations will be provided in the  
1692 forthcoming guidance on the submission of CMC information for a therapeutic  
1693 recombinant DNA-derived product or a monoclonal antibody for in vivo use.  
1694

1695 In certain instances, reduced testing of excipients or drug product and/or validation of  
1696 removal and/or inactivation of adventitious agents can be appropriate, with justification.  
1697 Such instances can include drug products that are terminally sterilized when it has been

1698 demonstrated that terminal sterilization inactivates the adventitious agent. Early dialog  
1699 with FDA is encouraged in these circumstances.

1700

1701 *1. Nonviral Adventitious Agents*

1702

1703 Detailed information should be provided on the avoidance and control of nonviral  
1704 adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria,  
1705 mycoplasma, fungi). This information can include, for example, certification and/or  
1706 testing of raw materials and excipients, and control of the production process, as  
1707 appropriate for the material, process, and agent. In general, information provided  
1708 elsewhere in the application will address these issues (e.g., P.2.5, P.3.5). However, if  
1709 additional information is warranted to address the issue of nonviral adventitious agents,  
1710 the information should be included here. For example, information would be included  
1711 here on the capability of a production process to inactivate or remove TSE agents.

1712

1713 Certifications and/or certificates relating to use of ruminant-derived materials and  
1714 sourcing of materials from BSE countries as defined by the U.S. Department of  
1715 Agriculture (9 CFR 94.11) should be provided, as appropriate.

1716

1717 *2. Viral Adventitious Agents*

1718

1719 Detailed information from viral safety evaluation studies should be provided in this  
1720 section. Viral evaluation studies should demonstrate that the materials used in production  
1721 are considered safe and that the approaches used to test, evaluate, and eliminate the  
1722 potential risks during manufacturing are suitable.

1723

1724 Information essential to evaluate the virological safety of materials of animal or human  
1725 origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related  
1726 information in section VI.E).

1727

1728 The selection of virological tests that are conducted during manufacturing (e.g., post  
1729 viral clearance testing) should be justified. The type of test, sensitivity and specificity of  
1730 the test, if applicable, and frequency of testing should be included. Test results to  
1731 confirm, at an appropriate stage of manufacture, that the product is free from viral  
1732 contamination should be provided. (See related information in section V.D).

1733

1734 The rationale and action plan for assessing viral clearance and the results and evaluation  
1735 of the viral clearance studies should be provided. Data can include those that  
1736 demonstrate the validity of the scaled-down model compared to the commercial scale  
1737 process; the adequacy of viral inactivation or removal procedures for manufacturing  
1738 equipment and materials; and manufacturing steps that are capable of removing or  
1739 inactivating viruses. (See related information in section V.E).

1740

Additional guidance is available in:

- ICH: *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*
- ICH: *Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products*
- ICH: *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

1741

1742

1743

### C. Excipients (A.3)

1744

1745

- **Novel Excipients**

1746

1747

Novel excipients are excipients used in the United States for the first time in a human drug product or by a new route of administration. The chemistry, manufacturing, and controls information for a novel excipient should be provided in the same level of detail and in the same format as the information provided for a drug substance (see the forthcoming drug substance guidance).

1748

1749

1750

1751

1752

1753

The suitability of the novel excipient for the intended route of administration should be discussed. Cross-references to supporting safety (nonclinical and/or clinical) data should be provided. Information to support safety can include, for example, references to FDA's regulations, Food Chemical Codex, citations or supporting toxicology data provided in the application (include study numbers).

1754

1755

1756

1757

1758

1759

- **Other Excipients**

1760

1761

Information in addition to that provided in P.4.1 through P.4.4 can be warranted for certain excipients. See sections IV.B.2 and VI for additional guidance on the information that should be submitted to support the use of excipients.

1762

1763

1764

1765

Depending on the functionality (e.g., complexing agent) and the route of administration of the drug product, additional information, up to and including the level of information recommended for novel excipients, can be warranted for noncompendial–non-novel excipients. The additional CMC information or a cross-reference to a DMF that provides the additional CMC information should be included in A.3. An applicant is encouraged to discuss the use of noncompendial–non-novel excipients with the appropriate review division prior to submitting its application to ascertain the level of information that would be warranted to support the use of the excipient.

1766

1767

1768

1769

1770

1771

1772

1773

1774 When a component that is usually identified as an excipient contributes to the intrinsic  
1775 pharmacological activity of the drug substance (e.g., levonordefrin or epinephrine for  
1776 local anesthesia), CMC information for the component should be provided in the  
1777 application or incorporated by reference from a DMF. The information should be  
1778 provided in the same level of detail as that for a drug substance. The CMC information or  
1779 a cross-reference to a DMF that provides the CMC information should be included in  
1780 A.3.

1781  
1782

## 1783 **XII. REGIONAL INFORMATION (R)**

1784

1785 Information relating to both drug substances and drug products should be included in the  
1786 Regional Information section (section R) of the application, when appropriate. The  
1787 recommendations provided below relate to drug products. Recommendations on the information  
1788 to include in the Regional Information section for drug substances will be provided in the  
1789 forthcoming drug substance guidance.

1790

### 1791 **A. Executed Production Records (R.1.P)**

1792

1793 Executed Production Records (EPRs) for representative batches used in Phase III clinical,  
1794 bioavailability, bioequivalence, or primary stability studies and supporting production  
1795 information must be provided (21 CFR 314.50(d)(1)(ii)(b)).

1796

#### 1797 *1. Executed Production Records*

1798

1799 For NDA submissions, an EPR for a batch manufactured on at least a pilot scale should  
1800 be submitted. In cases where clinical batches used in Phase III trials were less than pilot  
1801 scale, submission of the EPR for the largest scale clinical batch is also recommended.  
1802 Discussion of which EPRs should be included in the NDA can be a topic at pre-NDA  
1803 meetings. For ANDA submissions, EPRs should be submitted for the batches produced  
1804 in support of the application.

1805

#### 1806 *2. Information on Components*

1807

1808 The following information must be provided for the components used to produce the drug  
1809 product batches for which the EPRs are provided (21 CFR 314.50(d)(1)(ii)(b)):

1810

- 1811 • The name and address of the drug substance manufacturer
- 1812 • The names and addresses of sources of noncompensial excipients
- 1813 • Names and addresses of sources of the container closure system for the drug product
- 1814 • The name and address of each contract facility involved in the manufacture,  
1815 processing, packaging, or testing of the drug product and identification of the  
1816 operation performed by each contract facility
- 1817 • Results of any test performed on the components. This should include a certificate of  
1818 analysis (COA) from the component manufacturer and the test results for the same  
1819 batch from the drug product manufacturer. Test results should be expressed

1820 numerically or qualitatively (e.g., clear, colorless solution), as appropriate. Use of  
1821 terms such as *conforms* or *meets specification* is discouraged. For excipients, cross-  
1822 reference to section P.4.4 can be provided if the information has been included there.

1823

1824 **B. Comparability Protocols (R.2.P)**

1825

1826 A comparability protocol is a protocol describing the specific tests and studies and  
1827 acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified  
1828 types of postapproval manufacturing changes on the identity, strength, quality, purity,  
1829 and potency of the drug product as these factors may relate to the safety and effectiveness  
1830 of the drug product. Comparability protocols are optional. If a comparability protocol is  
1831 proposed, it should be included in this section (R.2.P). Approval of a comparability  
1832 protocol can justify a reduced reporting category for the particular postapproval change  
1833 described in the protocol.

1834

1835 **C. Methods Validation Package (R.3.P)**

1836

1837 Methods validation is the process of demonstrating that analytical procedures are suitable  
1838 for their intended use. Part of the methods validation process can include FDA  
1839 laboratory analysis to demonstrate that an analytical procedure is reproducible by  
1840 laboratory testing. A methods validation package (multiple copies for paper applications)  
1841 must be submitted in the application (21 CFR 314.50(e)(2)(i) and 314.94(a)(10)) and  
1842 should be included in R.3.P.

1843

Additional guidance is available in:

- FDA: *Submitting Samples and Analytical Data for Methods Validation*

1844

1845

1846 **XIII. LITERATURE REFERENCES (3.3)**

1847

1848 References to the scientific literature relating to both drug substances and drug products should  
1849 be included in the Literature References (3.3) section of the application, when appropriate.

1850

1851 The full bibliographic reference should be cited close to where the reference appears in the text  
1852 of the application (e.g. in a footnote or section endnote). The full text of the literature cited (e.g.,  
1853 journal article) should be included in the Literature References section, except when otherwise  
1854 indicated. For example, as previously stated in this guidance, monographs from an official  
1855 compendium need not be included in the application.



ATTACHMENT 1

Drug Product Specification<sup>37</sup>

Test Recommendations for Specific Dosage Forms

1856  
1857  
1858  
1859  
1860  
1861  
1862  
1863  
1864  
1865  
1866  
1867  
1868  
1869  
1870  
1871  
1872  
1873  
1874  
1875  
1876  
1877  
1878  
1879  
1880  
1881  
1882  
1883  
1884  
1885  
1886  
1887  
1888  
1889  
1890  
1891  
1892  
1893  
1894  
1895  
1896  
1897  
1898

The ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* provides recommendations on tests that should be included in the specification for solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Recommendations on tests for some other dosage forms are provided below. Tests other than those listed below can be warranted in particular situations or as new information becomes available. Moreover, test recommendations may be available in dosage form specific guidances such as the FDA's guidance on *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products* or guidances for a type of product such as ICH guidance *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*.

The tests recommended below are in addition to the universal tests recommended in Q6A. The universal tests are (1) description, (2) identification, (3) assay, and (4) impurities.

**Semisolids (e.g., Creams, Ointments, and Gels)**

Semisolids include a variety of dosage forms with different routes of administration (e.g., topical, ophthalmic). The drug products, depending on their use, can be sterile or nonsterile. In general, the following tests are applicable to semisolid drug products. However, depending on the specific dosage form and route of administration, some of the tests listed below may not be applicable or additional tests could be warranted in the specification. For example, although not listed in the tests below, the specification for an ophthalmic ointment should include a test for metal particles (e.g., USP <751> *Metal Particles in Ophthalmic Ointments*).

- Homogeneity

Assay of the product at the top, middle, and bottom of the container should be performed to ensure that the product is homogeneous. If the size of the container is too small to allow sampling of all of these locations, sampling at top and bottom can be performed.

- Uniformity of Dosage Units

A test for the uniformity of dosage units should be included.

- Rheology

Testing of rheological characteristics should be included in the specification. In many cases, a viscosity procedure described in USP <911> *Viscosity* can be used. However, the

---

<sup>37</sup> Some tests that are identified as appropriate for inclusion in the specification can be proposed as periodic quality indicator tests when there is sufficient data and justification (see section VII.A).

1899 suitability of the specified viscosity procedure should be evaluated based on the specific drug  
1900 product (e.g., non-Newtonian fluids) being tested.

1901

- Minimum Fill

1903

1904 A test for minimum fill should be specified, such as USP <755> *Minimum Fill*.

1905

- pH

1907

1908 Acceptance criteria for pH should be provided where applicable and the proposed range  
1909 justified.

1910

- Sterility and Microbial Limits

1912

1913 If the product is sterile (e.g., ophthalmics, drug products for open wounds), sterility should be  
1914 part of the product specification.

1915

1916 In general, it is advisable to perform microbial limit testing of a nonsterile drug product  
1917 unless its components are tested before manufacture and the manufacturing process is  
1918 known, through validation studies, not to carry a significant risk of microbial contamination  
1919 or proliferation. A proposal to exclude microbial limit testing from the specification should  
1920 be scientifically justified (rationale provided in P.2.5 and justification, as appropriate, in  
1921 P.5.6). Acceptance criteria should be provided for total aerobic microbial count, for total  
1922 combined molds and yeasts count, and for absence of designated microbial species (e.g.,  
1923 *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* species, *Pseudomonas aeruginosa*).  
1924 These criteria should be determined by suitable procedures such as those specified in USP  
1925 <61> *Microbial Limit Tests*.

1926

- Antimicrobial Preservative and Antioxidant Content

1928

1929 If antimicrobial preservatives or antioxidants are used in the product, tests for their content  
1930 should be included in the specification. Acceptance criteria for the content should be based  
1931 upon the level that will maintain product quality throughout shelf life.

1932

- Particle Size Distribution (for dispersions)

1934

1935 Particle size, if known to influence bioavailability or bioequivalence, is normally controlled  
1936 as part of the drug substance specification. However, if formulation and process  
1937 development studies indicate the possibility for changes in particle size or aggregation of  
1938 particles during manufacture or storage of the drug product, appropriate controls should be  
1939 included in the specification.

1940

- Performance Testing

1942

1943 Characterization of product performance can be appropriate depending on the drug product  
1944 and/or container closure system.

1945  
1946  
1947  
1948  
1949  
1950  
1951  
1952  
1953  
1954  
1955  
1956  
1957  
1958  
1959  
1960  
1961  
1962  
1963  
1964  
1965  
1966  
1967  
1968  
1969  
1970  
1971  
1972  
1973  
1974  
1975  
1976  
1977  
1978  
1979  
1980  
1981  
1982  
1983  
1984  
1985  
1986  
1987

## **Solutions and Suspensions**

Solutions and suspensions include a wide variety of drug products with different routes of administration (e.g., topical, ophthalmic, inhalation). The drug products, depending on their use, can be sterile or nonsterile. ICH *Q6A* provides recommendations on tests for solutions and suspensions as part of its discussion of oral liquids and parenteral drug products. In general, the recommendations in ICH *Q6A* are applicable to any solution or suspension. The applicant should consider the relevance of any individual test recommended in ICH *Q6A* and whether additional tests are warranted based on the specific drug product and its use. Moreover, FDA may provide recommendations on tests for a specific type of solution or suspension in a separate guidance such as *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products*.

## **Transdermal Drug Delivery Systems**

Transdermal drug delivery systems are self-contained, discrete dosage forms that, when applied to intact skin, are designed to deliver drug through the skin to the systemic circulation. The following tests can be applicable to transdermal systems.

- Uniformity of Dosage Units

A test for the uniformity of dosage units should be included, such as USP <905> *Uniformity of Dosage Units*. Content uniformity should be determined for the active ingredient and penetration enhancers, when used.

- Drug Release

A drug release test should be included that assesses the release of the drug substance at a number of time points spanning the total dosing time. General drug release standards for transdermal delivery systems are included in USP <724> *Drug Release*. The test procedure and test time points used should be demonstrated as suitable for the specific drug product. Drug release should be assessed at a minimum of three time points, including an early time point to demonstrate the absence of dose dumping, one or more intermediate time points to define the release rate profile, and a final time point to show the total delivered dose. More time points can be appropriate depending on the length of time the system will be used or if the delivery rate is not constant. The results should be reported as percent of label claim dissolved per unit of time.

- Residual Monomers

Residual monomers are generally from the pressure sensitive adhesive component of the drug product. A test for residual monomers should be included in the specification unless the omission of the test has been justified in P.5.6.

1988  
1989  
1990  
1991  
1992  
1993  
1994  
1995  
1996  
1997  
1998  
1999  
2000  
2001  
2002  
2003  
2004  
2005  
2006  
2007  
2008  
2009  
2010  
2011  
2012  
2013  
2014  
2015  
2016  
2017  
2018  
2019  
2020  
2021  
2022  
2023  
2024  
2025  
2026  
2027  
2028  
2029  
2030  
2031  
2032  
2033

- Enhancer

Any component used to increase the partitioning of drug substance to the skin and to enhance percutaneous absorption should be defined as an enhancer and identified as such in P.1 and P.2.1.2 of the application. An assay for the enhancer should be included in the specification. Furthermore, inclusion of a release rate test for the enhancer should be considered.

- Functionality Tests (Peel Force and Adhesion Strength)

Tests should be proposed to assess the peel force necessary to remove the protective liner and the adhesion shear strength of the transdermal system (force necessary to remove the transdermal system from a substrate).

- Pouch Integrity Test

A test to assess the seal integrity of the pouch used for packaging the transdermal drug delivery system should be included in the specification.

- Microbial Limits

See information provided under semisolids.

## Suppositories

Suppositories are solid bodies of various weights and shapes for introduction into the rectal, vaginal, or urethral orifice.

- Homogeneity

For suppositories in which the drug substance is suspended in a suppository base, homogeneous distribution should be demonstrated.

- Uniformity of Dosage Units

A test for the uniformity of dosage units should be included, such as USP <905> *Uniformity of Dosage Units*.

- Particle Size Distribution

Particle size, if known to influence bioavailability or bioequivalence, is normally controlled as part of the drug substance specification. If formulation and process development studies indicate the possibility for changes in particle size or aggregation of particles during manufacture or storage of the drug product, appropriate controls should be included in the specification.

2034  
2035  
2036  
2037  
2038  
2039  
2040  
2041  
2042  
2043  
2044  
2045  
2046  
2047  
2048  
2049  
2050  
2051  
2052  
2053  
2054  
2055  
2056  
2057  
2058  
2059  
2060  
2061  
2062  
2063  
2064  
2065  
2066  
2067  
2068  
2069  
2070  
2071  
2072  
2073  
2074  
2075  
2076  
2077  
2078  
2079

- Morphology

For suppositories in which the drug substance is suspended in the suppository base and there is evidence the morphic form can change during drug product manufacture or storage, appropriate controls of the drug product should be established to assess the morphic form.

- Softening Point or Melting Range

The softening or dropping point of the suppository, its melting range, or the time required for complete melting should be included in the specification. The studies are usually performed at 37°C.

- Dissolution or Drug Release

The specification for suppositories should include an appropriate test to measure dissolution or drug release. The test design should be appropriate for the specific product and conditions of use.

- Sterility and Microbial Limits

For vaginal and rectal suppositories, see information provided under semisolids for microbial limits. Urethral suppositories should be sterile, and sterility should be part of the product specification.

- Antimicrobial Preservative and Antioxidant Effectiveness Testing

If antimicrobial preservatives or antioxidants are used in the product, tests for their content should be included in the specification. Acceptance criteria for the content should be based upon the level that will maintain product quality throughout shelf life.

## **Implantable Drug Delivery Systems**

Implantable drug delivery systems are reservoirs or matrices containing drug substance, with or without excipients. Implants are inserted into the body (e.g., subdermal, vaginal, intrauterine), where the drug substance is very slowly absorbed over a specified period of time. The drug delivery system can be either biodegraded and subsequently absorbed or removed after the specified period of time

- Particle Size Distribution

The particle size of the drug substance in implants can affect the rate of absorption. The particle size is normally controlled as part of the drug substance specification. However, if formulation and process development studies indicate the possibility for changes in particle size or aggregation of particles during manufacture or storage of the implant, appropriate controls should be included in the specification. If the implant is in the form of

2080 biodegradable microspheres, there should be a test procedure and acceptance criteria for  
2081 particle size of the microspheres.

2082

- Morphology

2084

2085 If there is evidence the morphic form of the drug substance can change during drug product  
2086 manufacture or storage, appropriate controls of the drug product should be established to  
2087 assess the morphic form.

2088

- Physical Characteristics of Delivery System

2090

2091 If polymers are used as a drug delivery system, appropriate controls for their physical  
2092 properties (such as tensile strength, elongation, thickness, diameter) should be established.

2093

- Uniformity of Dosage Units

2095

2096 A test for uniformity of dosage units should be included.

2097

- Drug Release

2099

2100 The specification should include a test for in vitro drug release. The test should be  
2101 performed over a sufficient period of time and include a number of time points sufficient to  
2102 simulate the in vivo use of the drug delivery system. The test design should be appropriate  
2103 for the specific product and conditions of use and should be designed to assess the variability  
2104 of the release rate of individual implants. The results should be reported as percent of label  
2105 claim dissolved per unit of time.

2106

- Sterility

2108

2109 Implants, except vaginal implants, should be sterile, and sterility should be part of the  
2110 product specification.

2111

- Antimicrobial Preservative and Antioxidant Content

2113

2114 If antimicrobial preservatives or antioxidants are used in the product, tests for their content  
2115 should be included in the specification. Acceptance criteria for the content should be based  
2116 upon the level that will maintain product quality throughout shelf life.

## GLOSSARY

- 2117  
2118  
2119  
2120 **Acceptance Criteria:** Numerical limits, ranges, or other suitable measures for acceptance of  
2121 results of analytical procedures (ICH Q6A)  
2122  
2123 **Batch:** A specific quantity of a drug or other material that is intended to have uniform character  
2124 and quality, within specified acceptance criteria, and is produced according to a single  
2125 manufacturing order during the same cycle of manufacture (21 CFR 210.3(b)(2))  
2126  
2127 **Bioavailability Batch:** Batch used in determining the rate and extent to which the active  
2128 ingredient or active moiety is absorbed from a drug product and becomes available at the site of  
2129 action  
2130  
2131 **Bioequivalence Batch:** Batch used to determine the absence of a significant difference in the  
2132 rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or  
2133 pharmaceutical alternatives becomes available at the site of drug action when administered at the  
2134 same molar dose under similar conditions in an appropriately designed study  
2135  
2136 **Clinical Batch:** Batch used to support the efficacy, safety, bioavailability, or bioequivalence of  
2137 the drug product  
2138  
2139 **Combination Product:** A drug product that contains more than one drug substance (ICH Q6A)  
2140  
2141 **Component:** Any ingredient intended for use in the manufacture of a drug product, including  
2142 those that may not appear in such drug product (21 CFR 210.3(b)(3))  
2143  
2144 **Container Closure System:** The sum of packaging components that together contain and protect  
2145 the dosage form. This includes primary packaging components and secondary packaging  
2146 components, if the latter are intended to provide additional protection to the drug product. A  
2147 packaging system is equivalent to a container closure system.  
2148  
2149 **Degradation Product:** A molecule resulting from a chemical change in the drug molecule  
2150 brought about over time and/or by the action of light, temperature, pH, water, or by reaction with  
2151 an excipient and/or the immediate container/closure system. Also called decomposition product  
2152 (ICH Q6A).  
2153  
2154 **Dosage Form:** The physical form (e.g., tablet, capsule, solution) of the drug product. Standard  
2155 dosage form terminology can be found in the CDER Data Standards Manual  
2156 (<http://www.fda.gov/cder/dsm>).  
2157  
2158 **Drug Substance:** An active ingredient that is intended to furnish pharmacological activity or  
2159 other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to  
2160 affect the structure or any function of the human body, but does not include intermediates used in  
2161 the synthesis of such ingredient (21 CFR 314.3(b))  
2162

2163 **Drug Product:** A finished dosage form (e.g., tablet, capsule, solution) that contains a drug  
2164 substance, generally, but not necessarily, in association with one or more other ingredients (21  
2165 CFR 314.3(b))

2166  
2167 **Enantiomeric Impurity:** A compound with the same molecular formula as the drug substance  
2168 that differs in the spatial arrangement of atoms within the molecule and is a non-superimposable  
2169 mirror image (ICH Q3A)

2170  
2171 **Established Name:** The designated FDA official name, the compendial name, the USAN  
2172 Council name, or the common or usual name (section 502(e)(3) of the Act and 21 CFR 299.4).  
2173 Ordinarily, the established name of a drug will be the compendial name. However, FDA may  
2174 designate an established name in cases where a monograph does not exist (CDER Data Standards  
2175 Manual).

2176  
2177 **Executed Production Records:** The manufacturing record prepared from the master production  
2178 record for each batch of drug product produced. This is sometimes called the batch production  
2179 and control record.

2180  
2181 **Extended Release:** Products that are formulated to make the drug available over an extended  
2182 period after ingestion (ICH Q6A)

2183  
2184 **Excipient:** Any intended component other than the drug substances in the dosage form. This is  
2185 sometimes called an inactive ingredient.

2186  
2187 **Formulation:** The qualitative and quantitative composition of the drug product. This is often  
2188 called the composition statement.

2189  
2190 **Immediate Release:** For oral products, a drug product that allows the drug to dissolve in the  
2191 gastrointestinal contents, with no intention of delaying or prolonging the dissolution or  
2192 absorption of the drug (ICH Q6A)

2193 .  
2194 **Impurity:** Any component of the drug product that is not the chemical entity defined as the drug  
2195 substance or an excipient in the drug product (ICH Q6A)

2196  
2197 **In-process Material:** Any material fabricated, compounded, blended, or derived by chemical  
2198 reaction that is produced for, and used in, the preparation of the drug product (21 CFR  
2199 210.3(b)(9))

2200  
2201 **Lot:** A batch, or a specific identified portion of a batch, having uniform character and quality  
2202 within specified acceptance criteria. In the case of a drug product produced by continuous  
2203 process, it is a specific identified amount produced in a unit of time or quantity in a manner that  
2204 ensures its having uniform character and quality within specified acceptance criteria (21 CFR  
2205 210.3(b)(10)).

2206



2207 **Master Production Record:** A record containing the method of manufacture of the drug  
2208 product, including, in part, the master formula of defined size, complete manufacturing and  
2209 control instructions, in-process tests and acceptance criteria, equipment and operating  
2210 parameters, yield and yield reconciliation calculations, and provisions for packaging and labeling  
2211 (see 21 CFR 211.186(b))  
2212

2213 **Miscellaneous Drug Product Impurity:** For purposes of this guidance, a drug product impurity  
2214 other than a (1) degradation product, (2) residual solvent, or (3) extraneous contaminant that is  
2215 more appropriately addressed as good manufacturing practices issues  
2216

2217 **Modified Release:** Dosage forms whose drug-release characteristics of time course and/or  
2218 location are chosen to accomplish therapeutic or convenience objectives not offered by  
2219 conventional dosage forms such as a solution or an immediate release dosage form. Modified  
2220 release solid oral dosage forms include both delayed and extended release drug products (ICH  
2221 Q6A).  
2222

2223 **Pilot Scale:** The manufacture of a drug product by a procedure fully representative of and  
2224 simulating that to be applied to a production scale batch. For solid oral dosage forms, a pilot  
2225 scale is generally a minimum one-tenth of full production scale or 100,000 tablets or capsules,  
2226 whichever is the larger.  
2227

2228 **Primary Stability Batch:** Batch used to generate primary stability data  
2229

2230 **Primary Stability Data:** Data on the drug product stored in the proposed container/closure for  
2231 marketing under storage conditions that support the proposed shelf life  
2232

2233 **Production Batch:** A batch of drug product manufactured at production scale by using  
2234 production equipment in a production facility as specified in the application (ICH Q1A)  
2235

2236 **Quality:** The suitability of either a drug substance or drug product for its intended use. This  
2237 term includes such attributes as the identity, strength, purity, and potency (ICH Q6A)  
2238

2239 **Specific Test:** A test that is considered to be applicable to particular drug substances or  
2240 particular drug products depending on their specific properties and/or intended use (ICH Q6A)  
2241

2242 **Specification:** The quality standard (i.e., tests, analytical procedures, and acceptance criteria)  
2243 provided in an application to confirm the quality of drug substances, drug products,  
2244 intermediates, raw materials, reagents and other components including container closure system,  
2245 and in-process materials. A specification sheet includes the list of tests, references to analytical  
2246 procedures, and acceptance criteria.  
2247

2248 **Specified Degradation Product:** An identified or unidentified degradation product that is  
2249 selected for inclusion in the drug product specification and is individually listed and limited in  
2250 order to ensure the safety and quality of the drug product (Q3B)  
2251

2252 **Universal Test:** A test that is considered to be potentially applicable to all drug substances, or  
2253 all drug products (e.g., appearance, identification, assay, impurity tests) (ICH Q6A)

2254  
2255 **Unspecified Degradation Product:** A degradation product that is not included in the list of  
2256 specified degradation products (ICH Q3B)