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# Guidance for Industry

## Changes to an Approved NDA or ANDA

### *DRAFT GUIDANCE*

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For questions on the content of the draft document contact Nancy Sager, 301-594-5633 (CDER).

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

**June 1999  
CMC #**

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**U.S. Department of Health and Human Services  
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## TABLE OF CONTENTS

<b>I.</b>	<b>INTRODUCTION</b> .....	<b>1</b>
<b>II.</b>	<b>REPORTING CATEGORIES</b> .....	<b>2</b>
<b>III.</b>	<b>GENERAL REQUIREMENTS</b> .....	<b>3</b>
<b>IV.</b>	<b>ASSESSING THE EFFECT OF MANUFACTURING CHANGES</b> .....	<b>4</b>
<b>V.</b>	<b>COMPONENTS AND COMPOSITION</b> .....	<b>7</b>
<b>VI.</b>	<b>SITES</b> .....	<b>7</b>
<b>VII.</b>	<b>MANUFACTURING PROCESS</b> .....	<b>12</b>
<b>VIII.</b>	<b>SPECIFICATIONS</b> .....	<b>16</b>
<b>IX.</b>	<b>PACKAGE</b> .....	<b>19</b>
<b>X.</b>	<b>LABELING</b> .....	<b>23</b>
<b>XI.</b>	<b>MISCELLANEOUS CHANGES</b> .....	<b>25</b>
<b>XII.</b>	<b>MULTIPLE CHANGES</b> .....	<b>26</b>
	<b>GLOSSARY OF TERMS</b> .....	<b>27</b>

## **GUIDANCE FOR INDUSTRY<sup>1</sup>**

### **Changes to an Approved NDA or ANDA**

*(Due to the complexity of this draft document, please identify specific comments by line number.  
Use the pdf version of the document whenever possible)*

#### **1 I. INTRODUCTION**

2 On November 21, 1997, the President signed the Food and Drug Administration Modernization  
3 Act (the Modernization Act).<sup>2</sup> Section 116 of the Modernization Act amended the Food, Drug,  
4 and Cosmetic Act (the Act) by adding section 506A (21 U.S.C. 356a), which provides  
5 requirements for making and reporting manufacturing changes to an approved application and for  
6 distributing a drug product made with such change. The Food and Drug Administration (FDA) is  
7 proposing to amend its regulations on supplements and other changes to an approved application  
8 (21 CFR 314.70) to conform to section 506A of the Act.

9 The purpose of this draft guidance is to provide recommendations to holders of new drug  
10 applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make  
11 postapproval changes in accordance with Section 506A and the proposed amended regulations at  
12 21 CFR 314.70. The guidance covers recommended reporting categories for postapproval  
13 changes for drugs, other than specified biotechnology and specified synthetic biological products.  
14 Recommendations are provided for postapproval changes in: (1) components and composition,  
15 (2) sites, (3) manufacturing process, (4) specification(s), (5) package, (6) labeling, and (7)  
16 miscellaneous changes. This draft guidance document, which cites proposed 21 CFR 314.70, will  
17 be revised based on public comments and implemented for use as a companion document when 21  
18 CFR 314.70 is finalized.

19 Recommendations on reporting categories for changes relating to specified biotechnology and

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<sup>1</sup> This guidance has been prepared under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the reporting categories for manufacturing changes to approved NDAs and ANDAs. 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 statute, regulations, or both.

<sup>2</sup> Pub. L. 105-115.

20 specified synthetic biological products regulated by CDER are found in the guidance for industry  
21 entitled *Changes to an Approved Application for Specified Biotechnology and Specified*  
22 *Synthetic Biological Products* (July 1997).<sup>3</sup>

23 This guidance does not provide recommendations on the specific information that should be  
24 developed by an applicant to validate the effect of the change on the identity, strength (e.g., assay,  
25 content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g.,  
26 impurities and degradation products), or potency (e.g., biological activity, bioavailability,  
27 bioequivalence) of a product as they may relate to the safety or effectiveness of the product.  
28 CDER has published guidances, including the SUPAC (Scale-up and Postapproval Changes)  
29 guidances, that provide recommendations on reporting categories and/or the type of information  
30 that should be developed by the applicant to validate the effect of the change on the identity,  
31 strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness  
32 of the product. To the extent that the recommendations on reporting categories in this guidance,  
33 when finalized, are found to be inconsistent with prior published guidance, such as the SUPACs,  
34 the recommended reporting categories in such prior guidance will be superseded by this guidance.  
35 CDER intends to update the prior published guidances to make them consistent with this  
36 guidance. An applicant should consider all relevant CDER guidance documents for  
37 recommendations on the information that should be submitted to support a given change. If  
38 guidance for either recommended filing categories and/or information that should be submitted to  
39 support a particular change is not available, the appropriate CDER chemistry or microbiology  
40 review staff should be consulted.

## 41 II. REPORTING CATEGORIES

42 FDA's proposed amended regulations at 21 CFR 314.70 provide for three categories of change:  
43 major, moderate, and minor. These types of changes are distinguished in the following  
44 paragraphs. Citations are to the proposed rule.

45 A **major change** is a change that has a substantial potential to have an adverse effect on the  
46 identity, strength, quality, purity, or potency of a product as they may relate to the safety or  
47 effectiveness of the product. A major change requires the submission of a supplement and  
48 approval by FDA prior to distribution of the product made using the change. This type of  
49 supplement is called and should be clearly labeled a **Prior Approval Supplement** (21 CFR  
50 314.70(b)). An applicant may ask FDA to expedite its review of a prior approval supplement for  
51 public health reasons (e.g., drug shortage) or if a delay in making the change described in it would  
52 impose an extraordinary hardship on the applicant. This type of supplement is called and should  
53 be clearly labeled a **Prior Approval Supplement-Expedited Review Requested** (21 CFR

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<sup>3</sup> FDA is currently revising the 1997 guidance and intends to issue it in draft for public comment.

54 314.70(b)(4).<sup>4</sup> Requests for expedited review based on extraordinary hardship should be  
55 reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events  
56 that could not be reasonably foreseen and for which the applicant could not plan.

57 A *moderate change* is a change that has a moderate potential to have an adverse effect on the  
58 identity, strength, quality, purity, or potency of the product as they may relate to the safety or  
59 effectiveness of the product. A moderate change requires the submission of a supplement to FDA  
60 at least 30 days before the distribution of the product made using the change. This type of  
61 supplement is called and should be clearly labeled a ***Supplement--Changes Being Effectuated in 30***  
62 ***Days*** (21 CFR 314.70(c)(3)). The product made using a moderate change can not be distributed  
63 if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval  
64 supplement is required (21 CFR 314.70(c)(5)(i)). Also, if FDA informs the applicant within 30  
65 days of receipt of the supplement that information required under 21 CFR 314.70(c)(4) is missing,  
66 distribution must be delayed until the missing information is provided and FDA determines that  
67 the additional information is in compliance with this section of the regulations (21 CFR  
68 314.70(c)(5)(ii)). FDA may identify certain moderate changes for which distribution can occur  
69 when FDA receives the supplement (21 CFR 314.70(c)(6)). This type of supplement is called and  
70 should be clearly labeled a ***Supplement--Changes Being Effectuated***. If after review FDA  
71 disapproves a changes being effectuated in 30 days supplement or changes being effectuated  
72 supplement, FDA may order the manufacturer to cease distribution of the drugs that have been  
73 made using the disapproved change (21 CFR 314.70(c)(7)).  
74

75 A *minor change* is a change that has minimal potential to have an adverse effect on the identity,  
76 strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness  
77 of the product. The applicant must describe minor changes in its next ***Annual Report*** (21 CFR  
78 314.70(d)).

79 Under 21 CFR 314.70(e), an applicant may submit one or more protocols (i.e., comparability  
80 protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate  
81 the absence of an adverse effect from specified types of changes. A comparability protocol can be  
82 used to reduce the reporting category for specified changes. A proposed comparability protocol  
83 must be submitted as a prior approval supplement (21 CFR 314.70(e)). FDA intends to issue  
84 separate guidance(s) on comparability protocols.

### 85 III. GENERAL REQUIREMENTS

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<sup>4</sup>Policies and procedures relating to requests for expedited review of supplements to approved ANDAs are documented in MAPP 5240.1 which can be located on the Internet at <http://www.fda.gov/cder/mapp.htm>.

86 An applicant must notify FDA about each change in each condition established in an approved  
87 application beyond the variations already provided for in the application. The notice is required to  
88 describe the change fully (21 CFR 314.70(a)(1)). **The applicant must list all changes included**  
89 **in the supplement or annual report in the cover letter (21 CFR 314.70(a)(6)).**

90 An applicant making a change to an approved application pursuant to 21 CFR 314.70 must also  
91 conform to other applicable laws and regulations, including current good manufacturing practice  
92 (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21  
93 of the *Code of Federal Regulations* (e.g., 210, 211, 314). For example, manufacturers must  
94 comply with the record-keeping requirements and ensure that relevant records are readily  
95 available for examination by authorized FDA personnel during an inspection and comply with  
96 relevant CGMP validation requirements.

97 A changes being effected supplement for labeling changes must include 12 copies of final printed  
98 labeling (21 CFR 314.70(c)(1)). Also, an applicant must promptly revise all promotional labeling  
99 and drug advertising to make it consistent with any labeling change implemented in accordance  
100 with the regulations (21 CFR 314.70(a)(4)).

101 Except for a supplemental application providing for a change in labeling, an applicant must  
102 include a statement in a supplemental application certifying that a field copy of the supplement has  
103 been provided to the applicant's FDA district home office (21 CFR 314.70(a)(5)).

#### 104 **IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES**

##### 105 **A. Validate the Effects of the Change<sup>5</sup>**

106 A drug made with a manufacturing change, whether a major manufacturing change or  
107 otherwise, may be distributed only after the holder validates the effects of the change on  
108 the identity, strength, quality, purity, and potency of the product as these factors may  
109 relate to the safety or effectiveness of the product (21 CFR 314.70(a)(2)). For each  
110 change, the supplement or annual report must contain information determined to be  
111 appropriate by FDA and include the information developed by the applicant in validating  
112 (assessing) the effects of the change (section 506A of the Act). The type of information

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<sup>5</sup> *Validate the effects of the change* means to assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug (21 CFR 314.3). The term validate or validation, as used in this guidance, is not the same as CGMP validation. Unless otherwise specified by FDA, CGMP validation (e.g., process, equipment) data need not be filed in the application but should be retained at the facility and be available for review by FDA at its discretion. Some CGMP validation information, in addition to the information validating the effects of the change specified in 506A(b) of the Act, should be submitted in an NDA or ANDA (e.g., sterilization process validation).

113 that should be included in a supplemental application or annual report is specified in 21  
114 CFR 314.70(b)(3), (c)(4), and (d)(3).

115 **1. Conformance to Specifications**

116 An assessment of the effect of a change on the identity, strength, quality, purity, or  
117 potency of the drug product should include a determination that the drug  
118 substance intermediates, drug substance, in-process materials and/or drug product  
119 affected by the change conform to the approved specifications<sup>6</sup>. A *specification* is  
120 a quality standard (i.e., tests, analytical procedures, and acceptance criteria)  
121 provided in an approved application to confirm the quality of drug substances,  
122 drug products, intermediates, raw materials, reagents, and other components,  
123 including container closure systems, and in-process materials (21 CFR 314.3). For  
124 the purpose of defining specification in 21 CFR 314.3, *acceptance criteria* are  
125 numerical limits, ranges, or other criteria for the tests described (21 CFR 314.3).  
126 Conformance to a specification means that the material, when tested according to  
127 the analytical procedures listed in the specification, will meet the listed acceptance  
128 criteria.

129 **2. Additional Testing**

130 In addition to confirmation that the material affected by the manufacturing  
131 change(s) continues to meet its specification, the applicant should perform  
132 additional testing, when appropriate, to assess whether the identity, strength,  
133 quality, purity, or potency of the product as they may relate to the safety or  
134 effectiveness of the product have been affected. The assessment should include, as  
135 appropriate, evaluation of any changes in the chemical, physical, microbiological,  
136 biological, bioavailability and/or stability profiles. This additional assessment could  
137 involve testing of the postchange drug product itself or, if appropriate, the  
138 component directly affected by the change. The type of additional testing that an  
139 applicant should perform would depend on the type of manufacturing change, the  
140 type of drug substance and/or drug product, and the effect of the change on the  
141 quality of the product. For example, evaluation of changes in the impurity or  
142 degradant profile could first involve profiling by high pressure liquid  
143 chromatography (HPLC) and then, depending on the observed changes in the  
144 impurity profile, toxicology tests to qualify a new impurity or degradant or to  
145 qualify an impurity that is above a previously qualified level. Assessment of the  
146 effect of a change on bioequivalence when required under 21 CFR part 320 could

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<sup>6</sup> If a specification needs to be revised as a result of the change, this would be considered a multiple change (See Sections VIII and XII).

147 include for example, multipoint and/or multimedia dissolution profiling and/or an in  
148 vivo bioequivalence study.

149 An applicant should consider all relevant FDA guidance documents for  
150 recommendations on the information that should be submitted to support a given  
151 change. If guidance for information that should be submitted to support a  
152 particular change is not available, the appropriate CDER chemistry or  
153 microbiology review staff should be consulted.

#### 154 B. Equivalence

155 When testing is performed, the applicant should usually assess the extent to which the  
156 manufacturing change has affected the identity, strength, quality, purity, or potency of the  
157 drug product. Typically this is accomplished by comparing test results from pre- and  
158 postchange material and determining if the test results are equivalent. Simply stated -- is  
159 the product made after the change equivalent to the product made before the change? An  
160 exception to this general approach is when redocumentation of bioequivalence should  
161 occur for certain ANDA postapproval changes, the prechange material selected for  
162 comparison should be the reference listed drug. Equivalence comparisons frequently  
163 require a criterion for comparison with calculation of confidence intervals relative to a  
164 predetermined equivalence interval. For this, as well as for other reasons, *equivalence*  
165 does not necessarily mean identical. Equivalence may also relate to maintenance of a  
166 quality characteristic (e.g., stability) rather than a single test of an attribute.

#### 167 C. Adverse Effect

168 Sometimes manufacturing changes have an adverse effect on the identity, strength, quality,  
169 purity, or potency of the drug product. In many cases the applicant chooses not to  
170 implement these manufacturing changes, but sometimes the applicant wishes to do so. If  
171 an assessment concludes that a change has adversely affected the identity, strength,  
172 quality, purity, or potency of the drug product, **the change should be filed in a prior**  
173 **approval supplement, regardless of the recommended reporting category for the**  
174 **change.** For example, a type of process change, with a recommended filing category of a  
175 supplement--changes being effected in 30 days, could cause a new degradant to be formed  
176 that requires qualification and/or identification. However, the applicant's degradation  
177 qualification procedures may indicate that there are no safety concerns relating to the new  
178 degradant. The applicant should submit this change in a prior approval supplement with  
179 appropriate information to support the continued safety and effectiveness of the product.  
180 The FDA will assess the impact of any adverse effect on a product as it may relate to the  
181 safety or effectiveness of the product during the review of the prior approval supplement.

182 An applicant is encouraged to consult with the appropriate CDER chemistry or  
183 microbiology review staff if it has any questions on whether a change in a characteristic  
184 would be viewed by CDER as adversely affecting the identity, strength, quality, purity, or  
185 potency of the product.

## 186 V. COMPONENTS AND COMPOSITION

187 Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided  
188 in the approved application are considered major changes and should be filed in a prior approval  
189 supplement, unless exempted by regulation or guidance (21 CFR 314.70(b)(2)(i)). The deletion  
190 or reduction of an ingredient intended to affect only the color of a product may be reported in an  
191 annual report (21 CFR 314.70(d)(2)(ii)). Guidance on changes in components and composition  
192 that may be filed in a changes being effected supplement or annual report is not included in this  
193 document because of the complexity of these recommendations, but may be covered in one or  
194 more guidance documents describing postapproval changes (e.g., SUPAC documents).

## 195 VI. SITES

### 196 A. General Considerations

197 Changes in sites for which FDA should be notified include those facilities or  
198 establishments used to (1) manufacture or process drug products,<sup>7</sup> in-process materials,  
199 drug substances or drug substance intermediates, (2) package drug products, (3) label  
200 drug products, and (4) test components, drug product containers, closures, packaging  
201 materials, in-process materials, or drug products. Testing facilities include those  
202 performing physical, chemical, biological, and microbiological testing to monitor, accept,  
203 or reject materials as well as those performing stability testing. Facilities used to label  
204 drug products are considered those that perform labeling of the drug product's primary or  
205 secondary packaging components. Facilities performing operations that place identifying  
206 information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered  
207 to be facilities that manufacture or process the drug product. Sites include those owned  
208 by the applicant or contract facilities. The supplement or annual report should identify  
209 whether the proposed site is an alternative or replacement to those provided for in the  
210 approved application.

211 A move to a site that is routinely subject to FDA inspection, should be filed as a prior

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<sup>7</sup> Manufacturing or processing drug product would also include the preparation (e.g., sterilization) of container closure systems.

212 approval supplement if (1) the facility has never been inspected by FDA for the type of  
213 operation that is being moved to that facility, (2) the type of operation used to be  
214 performed at the facility but at some time it had been discontinued and is now being  
215 restarted, or (3) the facility does not have a satisfactory CGMP inspection<sup>8</sup> for the type of  
216 operation being moved. A prior approval supplement also should be submitted if the  
217 manufacturing process at the new or refurbished facility will differ materially from that  
218 described in the approved application. Under these circumstances, a change involving a  
219 move to a new site or a refurbished site is considered to have a substantial potential to  
220 have an adverse effect on the identity, strength, quality, purity, or potency of a product as  
221 they may relate to the safety or effectiveness of the product.

222 For labeling, secondary packaging and testing site changes, the potential for adverse effect  
223 on the identity, strength, quality, purity, or potency of a product as they may relate to the  
224 safety or effectiveness of the product is considered to be independent of the type of drug  
225 product dosage form or specific type of operation being performed. Therefore, the  
226 recommended reporting category for any one of these site changes will be the same for all  
227 types of drug products and operations. For sites used to (1) manufacture or process drug  
228 products, in-process materials, drug substances, or drug substance intermediates or (2)  
229 perform primary packaging operations, the potential for adverse impact and, consequently,  
230 the recommended reporting category depends on various factors such as the type of  
231 product and operation being performed. For this reason, recommended reporting  
232 categories may differ depending on the type of drug product and operations.

233 Factors used to assess whether a change in a site that manufactures or processes drug  
234 products, in-process materials, drug substances or drug substance intermediates or  
235 performs primary packaging operations is considered major include whether (1) the  
236 formulation and/or primary packaging components of the drug product control (or  
237 modify) the dose delivered to the patient and as a result the bioavailability of the product  
238 or (2) the production process involves certain technology (e.g., aseptic processing).

239 In general, the recommended reporting category for the primary packaging site of the drug  
240 product is the same as that for the manufacturing or processing site of the drug product.  
241 However, for certain products where a prior approval supplement is recommended for the  
242 drug product manufacturing or processing site, a supplement -- changes being effected in  
243 30 days may be recommended for the primary packaging facility.

#### 244 **B. Major Changes (Prior Approval Supplement)**

245 The following are examples of changes that are considered to have a substantial potential  
246 to have an adverse effect on the identity, strength, quality, purity, or potency of a product

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<sup>8</sup> Information on what constitutes a satisfactory CGMP inspection is provided in the glossary.

- 247 as they may relate to the safety or effectiveness of the product.
- 248 1. A move to any site, except one used to manufacture or process a drug  
249 substance intermediate, when the new facility has never been inspected by  
250 FDA for the type of operation that is being moved or the type of operation  
251 being moved used to be performed at the new facility, but at some time it  
252 had been discontinued and is now being restarted.
- 253 2. A move to a site, except those used to manufacture or process a drug  
254 substance intermediate, when the new facility does not have a satisfactory  
255 CGMP inspection for the type of operation being moved.
- 256 3. A move to a new site or refurbishing of an existing site where the operation  
257 being performed will differ materially from that described in the approved  
258 application. For example: (1) changes in the synthesis of a drug substance,  
259 (2) changes that could affect contamination or cross contamination  
260 precautions, (3) changing methods of sterilization or microbiological  
261 controls.
- 262 4. A move to a site on a different campus for the manufacture or processing  
263 of (1) drug products when the formulation and/or primary packaging  
264 components of the drug product control (or modify) the dose delivered to  
265 the patient or (2) in-process materials with modified release characteristics.  
266 Examples of these types of drug products include modified release solid  
267 oral dosage forms, transdermal systems, liposomal products, oral and nasal  
268 metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray  
269 pumps.
- 270 5. Transfer of manufacturing of an aseptically processed sterile drug  
271 substance or sterile drug product to a newly constructed, refurbished, or  
272 different aseptic processing facility. Once this change has been approved,  
273 subsequent site changes to the facility for similar product types and  
274 processes may be filed as a supplement -- changes being effected in 30  
275 days.
- 276 6. Except for modified release solid oral dosage form products, a move to a  
277 site on a different campus for the primary packaging of a drug product that  
278 falls within the scope of examples 4 or 5 (above).  
279

280 **C. Moderate Changes (Supplement--Changes Being Effected)**

*Draft — Not for Implementation*

281 The following are examples of changes that are considered to have a moderate potential to  
282 have an adverse effect on the identity, strength, quality, purity, or potency of a product as  
283 they may relate to the safety or effectiveness of the product.

284 1. Supplement--Changes Being Effected in 30 Days

285 a. A move to a site on a different campus for the manufacture or  
286 processing of any drug product, in-process material or drug  
287 substance that is not otherwise listed as a major change.

288 b. A move to a site on the same campus (e.g., building changes) or  
289 within a single facility (e.g., room changes) for the manufacture or  
290 processing of sterile drug substance or drug product that is not  
291 otherwise listed as a major change.

292 c. A move to a site on a different campus for the primary packaging of  
293 any drug product that is not otherwise listed as a major change.

294 d. A move to a testing facility on a different campus if (1) the test  
295 procedure(s) approved in the application or procedures that have  
296 been implemented under 21 CFR 314.70(d) are used, (2) all  
297 postapproval commitments made by the applicant relating to the  
298 test procedure(s) have been fulfilled (e.g., providing methods  
299 validation samples), and (3) the new testing facility has the  
300 capability to perform the intended testing.

301  
302 2. Supplement--Changes Being Effected

303 a. A move to a new site on the same or different campus for the  
304 manufacturing or processing of the final intermediate.

305 b. A move to a new site on the same or different campus for the  
306 manufacturing or processing of drug substance intermediates when  
307 the new site is owned by a contract manufacturer not previously  
308 approved for the application, or approved in the application but not  
309 approved for the manufacturing step(s) being transferred.

310 **D. Minor Changes (Annual Report)**

311 The following are examples of changes that are considered to have a minimal potential to  
312 have an adverse effect on the identity, strength, quality, purity, or potency of a product as

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- 313 they may relate to the safety or effectiveness of the product.
- 314 1. A move to a new secondary packaging site on the same (i.e., contiguous)  
315 or different campus.
- 316 2. A move to a new labeling site on the same or different campus.
- 317 3. A move to a new testing site on the same campus.
- 318
- 319 4. A move to a site on the same campus (i.e., building changes) for the  
320 manufacture or processing (including primary packaging) of nonsterile  
321 drug substance, in-process material, or drug product, except as otherwise  
322 listed.
- 323
- 324 5. Site changes within a single facility (e.g., room changes) for the  
325 manufacture or processing of drug product or in-process material, or  
326 primary packaging, except as otherwise listed for sterile drug products.<sup>9</sup>  
327
- 328 6. A move to a new site on the same or different campus to manufacture or  
329 process drug substance intermediates, other than the final intermediate,  
330 when the new site is owned either by the applicant or by a contract  
331 manufacturer previously approved in the application for the manufacturing  
332 step(s) being transferred.
- 333 7. A change in the simple floor plan that does not affect the production  
334 process or contamination precautions. This includes a facility "build-out."
- 335 8. Improvements to manufacturing areas that provide greater assurance of  
336 quality.
- 337 9. Change in the contract sterilization site for packaging components when  
338 the process is not materially different from that provided for in the  
339 approved application and the facility has a satisfactory CGMP inspection  
340 for the type of operation being performed.

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<sup>9</sup> Site changes within a single facility for the manufacture or processing of drug substance or drug substance intermediates need not be filed with the Agency, except as otherwise noted for sterile drug substances. However, installation qualification (IQ) and operation qualification (OQ) information should be retained in-house and is subject to FDA's review at its discretion.

341 VII. MANUFACTURING PROCESS

342 A. General Considerations

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The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as they may relate to the safety or effectiveness of the product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product. In some cases, there is a substantial potential for adverse effects, regardless of whether the applicant has determined that there has been no effect on the quality of the drug substance or drug product. This potential exists because the testing performed by the applicant to demonstrate the quality of the product may not be adequate or an important test may not have been performed to rule out such adverse effects. When there is a substantial potential for adverse effects, a change should be filed in a prior approval supplement. CDER considers that there is a substantial potential for adverse effects relating to a manufacturing process change when (1) changes may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient and as a result the bioavailability of the product, (2) changes may affect product sterility assurance, (3) the production process involves certain technologies (e.g., certain production aspects for natural products),<sup>10</sup> (4) fundamental changes are made in the process or technology from that currently used, and (5) certain changes in drug substance manufacture.

361 B. Major Changes (Prior Approval Supplement)

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The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

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1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient including the addition of a code imprint by embossing, debossing, or engraving on a modified release solid oral dosage form.

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2. Changes that may affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:

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<sup>10</sup> For the purposes of this guidance, *natural product* refers to products such as those derived from plants, animals, or microorganisms. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals).

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- 373 ● Changes in the sterilization method(s).
  - 374 ● Addition, deletion, or substitution of steps in an aseptic processing
  - 375 operation.
  - 376 ● Replacing sterilizers which operate by one set of principles with
  - 377 sterilizers that operate by another principle (e.g., substituting
  - 378 gravity displacement steam autoclaves with autoclaves using
  - 379 superheated water spray).
  - 380 ● New equipment added to an aseptic processing line and made of
  - 381 different materials that come in contact with sterilized bulk solution
  - 382 or sterile drug components, or deletion of equipment from an
  - 383 aseptic processing line.
  - 384 ● Replacing a Class 100 aseptic fill area with a barrier system for
  - 385 aseptic filling.
  - 386 ● Replacement or addition of lyophilization equipment of a different
  - 387 size, that uses different operating parameters or lengthens the
  - 388 overall process time.
  - 389 ● Changes from bioburden based terminal sterilization to the use of
  - 390 an overkill process, and vice versa.
  - 391 ● Changes to aseptic processing methods, including scale, that extend
  - 392 the filling time into additional aseptic filling shifts or increases bulk
  - 393 solution storage time by more than 50 percent beyond the validated
  - 394 limits in the approved application.
  - 395 ● Changes in scale of manufacturing for terminally sterilized products
  - 396 that increase the bulk solution storage time by more than 50 percent
  - 397 beyond the validated limits in the approved application.
  - 398 ● Changes in sterilizer load configurations that are outside the range
  - 399 of previously validated loads.
  - 400 ● Changes to filtration parameters (including filter materials or filter
  - 401 size) requiring new validation studies for the new parameters.
- 402 3. The following changes for a natural product:
- 403 ● Changes in the virus or adventitious agent removal or inactivation
  - 404 method(s).
  - 405 ● Changes in the source material (e.g., microorganism, plant) or cell
  - 406 line.
  - 407 ● Establishment of a new master cell bank or seed.
- 408 4. Any fundamental change in the manufacturing process or technology from
- 409 that which is currently used by the applicant. For example:

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- 410 ● Dry to wet granulation or vice versa.
  - 411 ● Change from one type of drying process to another (e.g., oven tray,
  - 412 fluid bed, microwave).
  - 413 ● Filtration to centrifugation or vice versa.
  - 414 ● Change in the route of synthesis of a drug substance.
- 415 5. The following changes for drug substance:
- 416 ● Any process change made after the final intermediate processing
  - 417 step in drug substance manufacture.
  - 418 ● Changes in the synthesis or manufacture of the drug substance that
  - 419 may affect its impurity profile and/or the physical, chemical, or
  - 420 biological properties.
- 421 6. Addition of an ink code imprint or change in the ink used for an existing
- 422 imprint code for a solid oral dosage form drug product when the ink is not
- 423 currently used on CDER-approved products.
- 424 7. Establishing a new procedure for reprocessing a batch of drug product that
- 425 fails to meet the approved specification.

426 **C. Moderate Changes (Supplement--Changes Being Effected)**

427 The following are examples of changes that are considered to have a moderate potential to

428 have an adverse effect on the identity, strength, quality, purity, or potency of a product as

429 they may relate to the safety or effectiveness of the product.

- 430 1. Supplement--Changes Being Effected in 30 Days
- 431 a. Any change in the process, process parameters and/or equipment,
  - 432 except as otherwise noted.
  - 433 b. For sterile products, drug substances and components, as
  - 434 appropriate:
    - 435 ● Changes in dry heat depyrogenation processes for glass
    - 436 container systems for products that are produced by
    - 437 terminal sterilization processes or aseptic processing.
    - 438 ● Changes to filtration parameters (such as flow rate,
    - 439 pressure, time, or volume, but not filter materials or size)
    - 440 that require additional validation studies for the new

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- 441 parameters.
- 442 ● Filtration process changes that provide for a change from
- 443 single to dual product sterilizing filters, or for repeated
- 444 filtration of a bulk.
- 445 ● Elimination of in-process filtration performed as part of the
- 446 manufacture of a terminally sterilized product.
- 447 ● Changes from one qualified sterilization chamber to another
- 448 for in-process or terminal sterilization that results in changes
- 449 to validated operating parameters (time, temperature,  $F_0$ ,
- 450 and others). When terminal sterilization autoclaves are
- 451 replaced, the range of thermal input (F-value) for the load
- 452 should be demonstrated to fall within the range previously
- 453 validated, such that the minimum thermal input does not
- 454 reduce sterility assurance and the maximum thermal input
- 455 does not reduce product stability or adversely affect
- 456 container and closure integrity.
- 457 ● Changes in scale of manufacturing for aseptically processed
- 458 products that do not require additional aseptic filling shifts
- 459 or do not increase bulk solution storage time by more than
- 460 50 percent beyond the validated limits in the approved
- 461 application.
- 462 ● Changes in scale of manufacturing for terminally sterilized
- 463 products that increase the bulk solution storage time by no
- 464 more than 50 percent beyond the validated limits in the
- 465 approved application.
- 466 c. For drug substances, redefinition of an intermediate, excluding the
- 467 final intermediate, as a starting material.
- 468 d. For natural protein products:
- 469 ● An increase or decrease in production scale during finishing
- 470 steps that involves new or different equipment.
- 471 ● Replacement of equipment with that of similar, but not
- 472 identical, design and operating principle that does not affect
- 473 the process methodology or process operating parameters.
- 474 2. Supplement--Changes Being Effected
- 475 No changes have been identified.

476 **D. Minor Changes (Annual Report)**

477 The following are examples of changes that are considered to have a minimal potential to  
478 have an adverse effect on the identity, strength, quality, purity, or potency of a product as  
479 they may relate to the safety or effectiveness of the product.

- 480
- 481 1. Changes to equipment of the same design and operating principle and/or  
482 changes in scale, except as otherwise noted.
  
  - 483 2. A minor change in an existing code imprint for a dosage form. For  
484 example, changing from a numeric to alphanumeric code.
  
  - 485 3. To add an ink code imprint or to change the ink used in an existing code  
486 imprint for a solid oral dosage form drug product when the ink is currently  
487 used on CDER-approved products.
  
  - 488 4. To add a code imprint by embossing, debossing, or engraving on a solid  
489 dosage form drug product other than a modified release dosage form.
  
  - 490 5. A change in the order of addition of ingredients for solution dosage forms.  
491

492 **VIII. SPECIFICATIONS**

493 **A. General Considerations**

494 All changes in specifications from those in the approved application must be submitted in a  
495 prior approval supplement unless otherwise exempted by regulation or guidance (21 CFR  
496 314.70(b)(2)(i)). A *specification* is the quality standard (i.e., tests, analytical procedures,  
497 and acceptance criteria) provided in an approved application to confirm the quality of drug  
498 substances, drug products, intermediates, raw materials, reagents, and other components  
499 including container and closure systems, and in-process materials. For the purpose of  
500 defining specification in 21 CFR 314.70, *acceptance criteria* are numerical limits, ranges,  
501 or other criteria for the tests described. The recommendations in this section also apply to  
502 specifications associated with monitoring of the production environment (e.g.,  
503 environmental monitoring for particulates and/or microorganisms) that are included in  
504 NDA and ANDA submissions.

505 A regulatory analytical procedure is the analytical procedure proposed by the applicant  
506 and approved by FDA for evaluation of a defined characteristic of the drug substance or  
507 drug product. The analytical procedures in the *U.S. Pharmacopeia/National Formulary*

508 (USP/NF) are those legally recognized under section 501(b) of the Act as the regulatory  
509 analytical procedures for compendial items. The applicant may include in its application  
510 alternative procedures to the approved regulatory procedure for testing the drug substance  
511 and drug product. However, for purposes of determining compliance with the Act, the  
512 regulatory analytical procedure is used.

513 **B. Major Changes (Prior Approval Supplement)**

514 The following are examples of changes that are considered to have a substantial potential  
515 to have an adverse effect on the identity, strength, quality, purity, or potency of a product  
516 as they may relate to the safety or effectiveness of the product.

- 517 1. Relaxing an acceptance criterion, except as otherwise listed.
- 518 2. Deleting a test, except as otherwise listed.
- 519 3. Establishing a new regulatory analytical procedure.
- 520 4. Deleting a regulatory analytical procedure.
- 521 5. A change in a regulatory analytical procedure for drug substance or drug  
522 product or an analytical procedure used for testing components, packaging  
523 components, the final intermediate, or starting material(s) introduced after  
524 the final intermediate that does not provide the same or increased assurance  
525 of the identity, strength, quality, purity, or potency of the material being  
526 tested as the analytical procedure described in the approved application,  
527 except as otherwise noted. For example, a change from an HPLC  
528 procedure that distinguishes impurities to (1) one that does not, (2)  
529 another type of analytical procedure (e.g., titrimetric) that does not, or (3)  
530 one that distinguishes impurities but the limit of detection and/or limit of  
531 quantitation is higher.

532 **C. Moderate Changes (Supplement--Changes Being Effected)**

534 The following are examples of changes that are considered to have a moderate potential to  
535 have an adverse effect on the identity, strength, quality, purity, or potency of a product as  
536 they may relate to the safety or effectiveness of the product.

- 537 1. Supplement--Changes Being Effected in 30 Days
- 538 a. Any changes in a regulatory analytical procedure other than those

- 539 identified as major changes.
- 540 b. Relaxing an acceptance criterion or deleting a test for raw materials  
541 used in drug substance manufacturing, starting materials introduced  
542 prior to the final drug substance intermediate, or drug substance  
543 intermediates (excluding final intermediate).<sup>11</sup>
- 544 c. A change in an analytical procedure used for testing raw materials  
545 used in drug substance manufacturing, starting materials introduced  
546 prior to the final drug substance intermediate, or drug substance  
547 intermediates (excluding final intermediate) that does not provide  
548 the same or increased assurance of the identity, strength, quality,  
549 purity, or potency of the material being tested as the analytical  
550 procedure described in the approved application.
- 551 d. A change in an analytical procedure used for testing components,  
552 packaging components, the final intermediate, or starting materials  
553 introduced after the final intermediate that provides the same or  
554 increased assurance of the identity, strength, quality, purity, or  
555 potency of the material being tested as the analytical procedure  
556 described in the approved application.
- 557 2. Supplement--Changes Being Effected
- 558 a. An addition to a specification or changes in methods or controls to  
559 provide increased assurance that the drug will have the  
560 characteristics of identity, strength, purity, or potency which it  
561 purports or is represented to possess. For example, adding a new  
562 test and associated analytical procedure and acceptance criterion.

563 **D. Minor Changes (Annual Report)**

564 The following are examples of changes that are considered to have a minimal potential to  
565 have an adverse effect on the identity, strength, quality, purity, or potency of a product as  
566 they may relate to the safety or effectiveness of the product.

- 567 1. Any change made to comply with an official compendium that is consistent

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<sup>11</sup> For raw material changes discussed in VIII.C.1.b and c, if changes can be justified without the need to generate test data, then filing in an annual report may be appropriate. In those situations, the appropriate chemistry review staff should be contacted for concurrence.

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568 with FDA requirements and that provides the same or greater level of  
569 assurance of the identity, strength, quality, purity, or potency of the  
570 material being tested as the analytical procedure described in the approved  
571 application.

572 2. For drug product and drug substance, the addition, deletion or revision of  
573 an alternative analytical procedure that provides the same or greater level  
574 of assurance of the identity, strength, quality, purity, or potency of the  
575 material being tested as the analytical procedure described in the approved  
576 application.

577 3. Tightening of acceptance criteria.

578 4. A change in an analytical procedure used for testing raw materials used in  
579 drug substance synthesis, starting materials introduced prior to the final  
580 drug substance intermediate, or drug substance intermediates (excluding  
581 final intermediate) that provides the same or increased assurance of the  
582 identity, strength, quality, purity, or potency of the material being tested as  
583 the analytical procedure described in the approved application.

584 5. Tightening of specifications for existing reference standards to provide  
585 increased assurance of product purity and potency.

586 **IX. PACKAGE**

587 **A. General Considerations**

588 The potential for adverse effect on the identity, strength, quality, purity, or potency of a  
589 product as they may relate to the safety or effectiveness of the product for a change in a  
590 package depends on the type of product and the functionality of the packaging. In some  
591 cases there is a substantial potential for adverse effect regardless of whether the applicant  
592 has determined that there has been no effect on the quality of the final product. This  
593 potential exists because the testing performed by the applicant to demonstrate the quality  
594 of the product may not be adequate or an important test may not have been performed to  
595 rule out such adverse effects. When there is a substantial potential for adverse effects, a  
596 change should be filed in a prior approval supplement. CDER considers the following  
597 package changes to have a substantial potential for adverse effects: (1) new plastics or  
598 rubbers are used in the primary packaging components of liquid dosage form products and  
599 the material has never been approved by CDER for use with that particular liquid dosage  
600 form; (2) new inks and/or adhesives are used on permeable or semipermeable container

601 closure systems and the ink and/or adhesive has never been approved by CDER for use  
602 with that particular liquid dosage form and type of container closure system; (3) the  
603 primary packaging components of the drug product control (or modify) the dose delivered  
604 to the patient and hence the bioavailability of the product; (4) changes may affect product  
605 sterility assurance; and (5) deletion of a secondary packaging component that is intended  
606 to provide additional protection to the drug product.

607 **B. Major Changes (Prior Approval Supplement)**

608 The following are examples of changes that are considered to have a substantial potential  
609 to have an adverse effect on the identity, strength, quality, purity, or potency of a product  
610 as they may relate to the safety or effectiveness of the product.

- 611
- 612 1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams,  
613 ointments) dosage forms, a change to or in polymeric materials (e.g.,  
614 plastic, rubber) of primary packaging components, when the composition  
615 of the component as changed has never been approved by CDER for use  
616 with that particular liquid dosage form or semisolid dosage form.
  
  - 617 2. Where ink and/or adhesive is used on a semipermeable or permeable  
618 container closure system a change to an ink and/or adhesive that has never  
619 been approved by CDER for use with that particular liquid or semisolid  
620 dosage form and type of permeable or semipermeable packaging  
621 component (e.g., low density polyethylene, polyvinyl chloride).
  
  - 622 3. A change in the primary packaging components for any product where the  
623 primary packaging components control (or modify) the dose delivered to  
624 the patient.
  
  - 625 4. For sterile products, any other change that may affect product sterility  
626 assurance such as:<sup>12</sup>  
627
    - 628 ● A change from a glass ampule to a glass vial with an elastomeric  
629 closure.
    - 630 ● A change to a flexible container system (bag) from another  
631 container system.
    - 632 ● A change to a prefilled syringe dosage form from another container  
633 system.

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<sup>12</sup> Some of these identified changes, depending on the circumstances, may have to be filed as a new NDA or ANDA. An applicant should consult the appropriate CDER chemistry division/office if it has any questions.

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- 634 ● A change from a single unit dose container to a multiple dose  
635 container system.  
636 ● Changes that add or delete silicone treatments to container closure  
637 systems (such as elastomeric closures or syringe barrels).  
638 ● Changes in the size and/or shape of a container for a sterile drug  
639 substance or sterile drug product.

- 640 5. Deletion of a secondary packaging component that is intended to provide  
641 additional protection to the drug product.

642 **C. Moderate Changes (Supplement--Changes Being Effected)**

643 The following are examples of changes that are considered to have a moderate potential to  
644 have an adverse effect on the identity, strength, quality, purity, or potency of a product as  
645 they may relate to the safety or effectiveness of the product.

- 646 1. Supplement--Changes Being Effected in 30 Days

- 647 a. A change in primary or secondary packaging components, except as  
648 otherwise listed.

- 649 2. Supplement--Changes Being Effected

- 651 a. A change in the size and/or shape of a container for a nonsterile  
652 drug product, except for solid dosage forms.

653 **D. Minor Changes (Annual Report)**

654 The following are examples of changes that are considered to have a minimal potential to  
655 have an adverse effect on the identity, strength, quality, purity, or potency of a product as  
656 they may relate to the safety or effectiveness of the product.

- 657 1. A change in the container closure system for a nonsterile drug product,  
658 based upon a showing of equivalency to the approved system under a  
659 protocol approved in the application or published in an official  
660 compendium.

- 661 2. A change in the size and/or shape of a container containing the same  
662 number of dose units, for a nonsterile solid dosage form.

- 663 3. The following changes in the container closure system of solid oral dosage

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664 form products as long as the new package provides the same or better  
665 protective properties (e.g., light, moisture) and any new primary packaging  
666 component materials have been used in and been in contact with CDER-  
667 approved solid oral dosage form products:<sup>13</sup>

- 668 ● Adding or changing a child-resistant closure, changing from a metal
- 669 to plastic screw cap, or changing from a plastic to metal screw cap.
- 670 ● Changing from one plastic container to another of the same type of
- 671 plastic (e.g., high density polyethylene (HDPE) to HDPE).
- 672 ● Changes in packaging materials used to control odor (e.g., charcoal
- 673 packets).
- 674 ● Changes in bottle filler (e.g., change in weight of cotton or amount
- 675 used) without changes in the type of filler (e.g., cotton to rayon).
- 676 ● Increasing the wall thickness of the container.
- 677 ● A change in or addition of a cap liner.
- 678 ● A change in or addition of a seal (e.g., heat induction seal).
- 679 ● A change in an antioxidant, stabilizer or mold releasing agent for
- 680 production of the container and/or closure to one that is used at
- 681 similar levels in the packaging of CDER-approved solid oral dosage
- 682 form products.

683 4. The following changes in the container closure system of nonsterile liquid  
684 oral and topical dosage form products as long as the new package provides  
685 the same or better protective properties and any new primary packaging  
686 component materials have been used in and been in contact with CDER-  
687 approved liquid oral or topical dosage form products, as appropriate (i.e.,  
688 the material in contact with a liquid topical should already be used in  
689 CDER-approved liquid topical products):

- 690 ● Adding or changing a child-resistant closure, changing from a metal
- 691 to plastic screw cap, or changing from a plastic to metal screw cap.
- 692 ● Increasing the wall thickness of the container.
- 693 ● A change in or addition of a cap liner.
- 694 ● A change in or addition of a seal (e.g., heat induction seal).

695 5. A change in the container closure system of unit dose packaging (e.g.,  
696 blister packs) for nonsterile solid dosage form products as long as the new

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<sup>13</sup> For sections IX.D.3 to 6, changes in the container closure system that result in product contact with a component material that has never been used in any CDER-approved product of the same type should be filed as supplement — changes being effected in 30 days (IX.C.1) or prior approval supplement (IX.B.1).

697 package provides the same or better protective properties and any new  
698 primary packaging component materials have been used in and been in  
699 contact with CDER-approved products of the same type (e.g., solid oral  
700 dosage form, rectal suppository).

701  
702 6. The following changes in the container closure system of nonsterile  
703 semisolid products as long as the new package provides the same or better  
704 protective properties and any new primary packaging component materials  
705 have been used in and been in contact with CDER-approved semisolid  
706 products:

- 707 ● Changes in the closure or cap.
- 708 ● Increasing the wall thickness of the container.
- 709 ● A change in or addition of a cap liner.

710  
711 7. Changes in secondary packaging components when the secondary  
712 packaging components are not intended to provide additional protection to  
713 the drug product.

## 714 X. LABELING

### 715 A. General Considerations

716 A labeling change includes changes in the package insert, package labeling, or container  
717 label. An applicant must promptly revise all promotional labeling and drug advertising to  
718 make it consistent with any labeling change implemented in accordance with the  
719 regulations (21 CFR 314.70(a)(4)). All labeling changes for ANDA products must be  
720 consistent with section 505(j) of the Act.

### 721 B. Major Changes (Prior Approval Supplement)

722 Under 21 CFR 314.70(b)(2)(v), any proposed change in the labeling, except those that are  
723 designated as moderate or minor changes by regulation (21 CFR 314.70(c) or (d)) or  
724 guidance, is required to be submitted as a prior approval supplement. The following list  
725 contains some examples of changes that are currently considered by CDER to fall into this  
726 reporting category.

- 727 1. Changes based on postmarketing study results, including, but not limited  
728 to, labeling changes associated with new indications and usage.

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- 729  
730
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.
- 731  
732
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.
- 733
4. Changes based on data from preclinical studies.
- 734
5. Revision (expansion or contraction) of population based on data.
- 735
6. Claims of superiority to another product.
- 736  
737
7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

738 **C. Moderate Changes (Supplement--Changes Being Effected)**

739 Under 21 CFR 314.70(c)(6)(iii), a changes being effected supplement must be submitted  
740 for any labeling change that (1) adds or strengthens a contraindication, warning,  
741 precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse,  
742 dependence, psychological effect, or overdose, (3) adds or strengthens an instruction  
743 about dosage and administration that is intended to increase the safe use of the product,  
744 (4) deletes false, misleading, or unsupported indications for use or claims for effectiveness,  
745 or (5) is specifically requested by FDA. The submission should include 12 copies of final  
746 printed labeling. The following list includes some examples of changes that are currently  
747 considered by CDER to fall into this reporting category.

- 748  
749
1. Addition of an adverse event due to information reported to the applicant or Agency.
- 750
2. Addition of a precaution arising out of a post-marketing study.
- 751  
752
3. Clarification of the administration statement to ensure proper administration of the product.
- 753  
754  
755
4. Labeling changes, normally classified as major changes, that FDA specifically requests be implemented using a changes being effected supplement.

756 **D. Minor Changes (Annual Report)**

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757 Under 21 CFR 314.70(d)(2)(ix) and (x), labeling with editorial or similar minor changes or  
758 with a change in the information concerning the description of the drug product or  
759 information about how the drug is supplied that does not involve a change in the dosage  
760 strength or dosage form must be described in an annual report. The following list includes  
761 some examples that are currently considered by CDER to fall into this reporting category.

- 762 1. Changes in the layout of the package or container label that are consistent  
763 with FDA regulations (e.g., 21 CFR part 201), without a change in content  
764 of the labeling.
- 765 2. Editorial changes such as adding a distributor's name.
- 766 3. Foreign language versions of the labeling, if no change is made to the  
767 content of the approved labeling and a certified translation is included.

768 **XI. MISCELLANEOUS CHANGES**

769 **A. Major Changes (Prior Approval Supplement)**

770 The following are examples of changes that are considered to have a substantial potential  
771 to have an adverse effect on the identity, strength, quality, purity, or potency of a product  
772 as they may relate to the safety or effectiveness of the product.

- 773 1. Changes requiring completion of studies in accordance with 21 CFR part  
774 320 to demonstrate equivalence of the drug to the drug as manufactured  
775 without the change or reference listed drug (21 CFR 314.70(b)(2)(ii)).
- 776 2. Changes that may affect product sterility assurance (21 CFR  
777 314.70(b)(2)(iii)).
- 778 3. Approval of a comparability protocol (21 CFR 314.70(e)).
- 779 4. Extension of the expiration dating period of the drug product based on data  
780 obtained under a new or revised stability testing protocol that has not been  
781 approved in the application or based on pilot scale batch data.
- 782 5. Changes to an approved stability protocol or comparability protocol (21  
783 CFR 314.70(e)) unless otherwise listed.

784 **B. Moderate Changes (Supplement--Changes Being Effected)**

785 No changes have been identified.

786 **C. Minor Changes (Annual Report)**

787 The following are examples of changes that are considered to have a minimal potential to  
788 have an adverse effect on the identity, strength, quality, purity, or potency of a product as  
789 they may relate to the safety or effectiveness of the product.

790 1. An extension of an expiration dating period based upon full shelf-life data  
791 on full production batches obtained from a protocol approved in the  
792 application (21 CFR 314.70(d)(2)(vi)).

793 2. Addition of time points to the stability protocol.

794 3. Reference standards:

- 795 ● Replacement of an in-house reference standard or reference panel  
796 (or panel member) according to procedures in an approved  
797 application.
- 798 ● Tightening of specifications for existing reference standards to  
799 provide greater assurance of product purity and potency.

800 **XII. MULTIPLE CHANGES**

801 Multiple changes involve various combinations of related changes. For example a site change  
802 may also involve equipment and manufacturing process changes or a components and  
803 composition change may necessitate a change in a specification. For multiple related changes,  
804 FDA recommends that the filing be in accordance with the most restrictive of those recommended  
805 for the individual changes.

806

## GLOSSARY OF TERMS

807 **Acceptance Criteria:** Numerical limits, ranges, or other criteria for the tests described (21 CFR  
808 314.3).

809 **Active Ingredient/Drug Substance:** Any component that is intended to furnish pharmacological  
810 activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a  
811 disease, or to affect the structure or any function of the human body, but does not include  
812 intermediates used in the synthesis of such ingredient. The term includes those components that  
813 may undergo chemical change in the manufacture of the drug product and are present in the drug  
814 product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7)  
815 and 314.3).

816 **Container Closure System:** The sum of packaging components that together contain and protect  
817 the dosage form. This includes primary packaging components and secondary packaging  
818 components, if the latter are intended to provide additional protection to the drug product.

819 **Contiguous Campus:** Continuous or unbroken site or a set of buildings in adjacent city blocks.

820 **Component:** Any ingredient intended for use in the manufacture of a drug product, including  
821 those that may not appear in such drug product (21 CFR 210.3(b)(3)).

822 **Drug Product:** A finished dosage form, for example, tablet, capsule or solution, that contains an  
823 active ingredient, generally, but not necessarily, in association with inactive ingredients (21 CFR  
824 210.3(b)(4)).

825 **Final Intermediate:** The last compound synthesized before the reaction that produces the drug  
826 substance. The final step forming the drug substance must involve covalent bond formation; ionic  
827 bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the  
828 drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base  
829 itself, should be considered the final intermediate.

830 **Inactive Ingredients:** Any intended component of the drug product other than an active  
831 ingredient.

832 **In-process Material:** Any material fabricated, compounded, blended, or derived by chemical  
833 reaction that is produced for, and used in, the preparation of the drug product (21 CFR  
834 210.3(b)(9)).

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- 835 **Intermediate:** A material produced during steps of the synthesis of a drug substance that must  
836 undergo further molecular change before it becomes a drug substance.
- 837 **Installation Qualification (IQ):** The documented verification that all key aspects of the  
838 equipment and ancillary systems installations adhere to the approved design intentions (plans) and  
839 that the recommendations of the manufacturer are suitably considered.
- 840 **Operational Qualification (OQ):** The documented verification that the equipment and ancillary  
841 systems perform as intended throughout anticipated operating ranges (i.e., pressures,  
842 temperatures, times).
- 843 **Package:** Refers to the container closure system and labeling, associated components (e.g.,  
844 dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap).
- 845 **Packaging Component:** Any single part of a container closure system.
- 846 **Primary Packaging Component:** A packaging component that is or may be in direct contact  
847 with the dosage form.
- 848 **Reference Listed Drug:** The listed drug identified by FDA as the drug product upon which an  
849 applicant relies in seeking approval of its abbreviated application (21 CFR 314.3).
- 850 **Satisfactory Current Good Manufacturing Practice (CGMP) Inspection:** A satisfactory  
851 CGMP inspection is one during which (1) no objectionable conditions or practices were found  
852 during an FDA inspection (No Action Indicated (NAI)) or (2) objectionable conditions were  
853 found, but, corrective action is left to the firm to take voluntarily and the objectionable conditions  
854 will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated  
855 (VAI)).
- 856 Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality  
857 Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP  
858 reports information on the CGMP compliance status of firms which manufacture, package,  
859 assemble, repack, relabel or test human drugs, devices, biologics and veterinary drugs. All FOI  
860 requests must be in writing and should follow the instructions found in the reference entitled *A*  
861 *Handbook for Requesting Information and Records from FDA*. An electronic version of this  
862 reference is available on the Internet at <http://www.fda.gov/opacom/backgrounders/foiahand.html>.
- 863 **Secondary Packaging Component:** A packaging component that is not and will not be in direct  
864 contact with the dosage form.
- 865 **Specification:** The quality standard (i.e., tests, analytical procedures, and acceptance criteria)

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866 provided in an approved application to confirm the quality of drug substances, drug products,  
867 intermediates, raw materials, reagents, and other components including container closure systems,  
868 and in-process materials (21 CFR 314.3).

869 **Validate the Effects of the Change:** To assess the effect of a manufacturing change on the  
870 identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or  
871 effectiveness of the drug (21 CFR 314.3).