
Drug Master Files Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Rick Ensor 240-402-2733, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

**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)**

**October 2019
Pharmaceutical Quality/CMC**

Revision 1

Drug Master Files Guidance for Industry

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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	TYPES OF DMFS.....	2
III.	DMF SUBMISSIONS	3
A.	Format and Delivery.....	3
B.	Original Submissions.....	4
1.	<i>Module 1</i>	<i>5</i>
2.	<i>Module 2</i>	<i>9</i>
3.	<i>Module 3</i>	<i>9</i>
4.	<i>Module 4</i>	<i>9</i>
5.	<i>Module 5</i>	<i>9</i>
C.	Subsequent Submissions.....	9
1.	<i>Cover Letter</i>	<i>10</i>
2.	<i>Administrative Amendments.....</i>	<i>10</i>
3.	<i>Quality Amendments</i>	<i>11</i>
4.	<i>Conversion of Existing DMFs To Comply With eCTD Format</i>	<i>11</i>
D.	Submission Recommendations, by DMF Type.....	12
1.	<i>Type II: Drug Substance, Drug Substance Intermediate, and Materials Used in Their Preparation, or Drug Product.....</i>	<i>12</i>
2.	<i>Type III: Packaging Material</i>	<i>13</i>
3.	<i>Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation.....</i>	<i>14</i>
4.	<i>Type V: FDA-Accepted Reference Information</i>	<i>16</i>
E.	Other Recommendations.....	16
1.	<i>English Translations</i>	<i>16</i>
2.	<i>Public Availability of Information in a DMF.....</i>	<i>16</i>
3.	<i>Holder Not the Manufacturer</i>	<i>16</i>
4.	<i>Primary and Secondary DMFs</i>	<i>17</i>
5.	<i>Referencing Own Application Material</i>	<i>17</i>
6.	<i>Retention of Reference Copy by the Holder.....</i>	<i>17</i>
IV.	ANNUAL REPORTS.....	17
V.	FDA PROCESSING AND REVIEWING POLICIES	18
A.	Administrative Review	18
B.	Technical Review	18
VI.	DMF CLOSURE	19
VII.	GLOSSARY.....	19
VIII.	REFERENCES.....	20

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**Drug Master Files
Guidance for Industry¹**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance provides FDA’s current thinking on drug master files (DMFs), which are submissions to FDA that may be used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products. DMFs can contain other types of information as well (e.g., toxicology information, shared system REMS (risk evaluation and mitigation strategy)).

DMF holders can authorize one or more applicants or sponsors to incorporate by reference information contained in the DMF without having to disclose that information to the applicants or sponsors. DMFs are submitted solely at the discretion of their holders and are not required by statute or regulation. They are not typically submitted for nonproprietary materials. Ordinarily, FDA neither independently reviews nor approves DMF submissions. Instead, FDA customarily reviews the technical contents of DMFs only in connection with the review of applications that reference them.²

DMFs can be used to support (but are not substitutes for) applications reviewed by FDA. This guidance focuses on the following submissions to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER):

- DMFs under 21 CFR 314.420 that are used to support new drug applications (NDAs), abbreviated new drug applications (ANDAs), and investigational new drug applications (INDs) under the Federal Food, Drug, and Cosmetic Act (FD&C Act).
- DMFs and other master files under 21 CFR 601.51(a) that are used to support biologics license applications (BLAs) under the Public Health Service Act (PHS Act).

¹ This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and in consultation with the Center for Veterinary Medicine at the Food and Drug Administration.

² In this guidance, the term *review* also means *assessment*. Both terms refer to the process of evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination.

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40
41 Additionally, information contained in DMFs can generally be referenced in premarket
42 submissions for devices (e.g., premarket approvals) and animal drugs (e.g., new animal drug
43 applications). Although the focus of this guidance is on the submissions to CDER and CBER
44 described above, in general, FDA believes the contents of this guidance will assist other master
45 file holders in providing complete and up-to-date master files to FDA.

46
47 This guidance provides information about preparing and submitting DMFs. It describes DMF
48 types, the information needed in DMF submissions, and FDA's DMF review processes. For
49 additional information, see FDA's DMF web pages.³

50
51 This guidance revises the guidance for industry *Drug Master Files: Guidelines* that published in
52 September 1989. Most of the information contained in the 1989 guidance has been retained here,
53 with significant reorganization.

54
55 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
56 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
57 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
58 the word *should* in Agency guidances means that something is suggested or recommended, but
59 not required.

60
61

62 II. TYPES OF DMFs

63
64

Four types of DMFs are covered by § 314.20, as illustrated in the table below.

65
66

Types of DMFs

DMF Type*	Subject of Information Provided in the DMF
Type II**	Drug substance, drug substance intermediate, and materials used in their preparation, or drug product
Type III	Packaging material
Type IV	Excipient, colorant, flavor, essence, or material used in their preparation
Type V	FDA-accepted reference information

67 * Type I DMFs were discontinued in 2000 but the numbering of the other DMF types has not changed. FDA's
68 approach to the terminology for types of master files used for products subject to approval under the PHS Act has
69 generally tracked its approach to the types of DMFs (e.g., Type II, Type III) used for products regulated under the
70 FD&C Act.

71 ** Although FDA's approach to the use of master files in BLAs under the PHS Act largely parallels its approach to
72 the use of DMFs in applications under the FD&C Act, there is a significant difference: a BLA holder is generally
73 expected to have knowledge of and control over the manufacturing process for the biological product for which it
74 has a license. For biological products in BLAs under the PHS Act, FDA has, as a scientific matter, generally not

³ For CDER, see <https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>; for CBER, see <https://www.fda.gov/vaccines-blood-biologics/new-drug-application-nda-process-cber/drug-master-files-cber-regulated-products>.

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75 permitted applicants to incorporate information about drug substance, drug substance intermediate, or drug product
76 by reference to a master file; rather, FDA generally expects such information to be submitted directly to the BLA.

79 III. DMF SUBMISSIONS

81 This section describes the format and delivery of DMF submissions, outlines the content of
82 original and subsequent DMF submissions, offers submission recommendations specific to the
83 four types of DMFs, and ends with some broader recommendations for DMF holders to consider
84 when submitting DMFs.

86 A. Format and Delivery

88 DMF submissions are subject to the electronic submission requirements as set forth in guidance
89 implementing section 745A of the FD&C Act, including the guidance for industry *Providing*
90 *Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product*
91 *Applications and Related Submissions Using the eCTD Specifications (Rev. 6) (Providing*
92 *Regulatory Submissions* guidance).⁴ The *Drug Master Files* guidance is not issued under section
93 745A of the FD&C Act and does not establish legally enforceable responsibilities. To the extent
94 it discusses binding requirements for DMFs, such requirements have been promulgated in
95 previously issued guidance under section 745A and FDA regulations.

97 Unless otherwise stipulated in the *Providing Regulatory Submissions* guidance or successor
98 guidance under section 745A, DMF submissions must have a DMF number, must be submitted
99 in the electronic format specified in such guidance, and, if 10 gigabytes or smaller, must be
100 submitted through the Electronic Submissions Gateway (ESG).⁵ Submissions over 10 gigabytes
101 can be submitted through ESG *or* they can be submitted on physical media (e.g., CD-ROM)
102 accompanied by a cover letter as described below and with prepaid delivery charges.⁶ The
103 standard electronic format for DMFs is electronic common technical document (eCTD) format.⁷

105 For proper routing of DMFs, it is important to choose the appropriate center—CDER or
106 CBER—from the menu of choices when submitting through ESG. DMF holders who wish to
107 submit information that may be reviewed in multiple centers should consult the respective
108 centers. See the CDER and CBER DMF web pages for contact information.⁸

⁴ Revision 7 of *Providing Regulatory Submissions* is available as a draft guidance. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁵ See the *Providing Regulatory Submissions* guidance.

⁶ *Ibid.*

⁷ For more information on electronic submissions, see FDA's Electronic Regulatory Submissions and Review web page at <https://www.fda.gov/drugs/forms-submission-requirements/electronic-regulatory-submission-and-review>, eCTD web page at <https://www.fda.gov/ectd>, ESG web page at <https://www.fda.gov/industry/electronic-submissions-gateway>, and *Transmitting Electronic Submissions Using eCTD Specifications* at <https://www.fda.gov/media/76812/download>.

⁸ See footnote 3.

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109
110 CDER’s DMF web page links to templates for certain submissions (e.g., cover letters, annual
111 reports) that recommend elements that DMF holders can include in these submissions.⁹ This
112 guidance refers to these templates where applicable rather than listing each element that FDA
113 recommends be included in a particular submission.

B. Original Submissions

114
115
116 Before submitting an original DMF in eCTD format, DMF holders must obtain a pre-assigned
117 number.¹⁰ For CDER submissions, see Requesting a Pre-Assigned Application Number at
118 [https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-](https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number)
119 [assigned-application-number](https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number). For CBER submissions, send requests for application numbers via
120 secure email to cberrims@fda.hhs.gov and include the sponsor/applicant name and address, point
121 of contact name and number, product name, and anticipated submission date.

122
123 Original submissions should contain a cover letter and complete administrative and technical
124 information in the appropriate eCTD modules. Although some eCTD module section headings
125 refer to *change* and *sponsor/applicant*, they are applicable to original and subsequent
126 submissions to DMFs.

127
128 This section reviews the eCTD modules and module sections that are relevant for original
129 submissions. For a complete list of eCTD section headings, see FDA’s *Comprehensive Table of*
130 *Contents Headings and Hierarchy*, which can be found in the eCTD Submission Standards on
131 FDA’s eCTD website (<https://www.fda.gov/ectd>). For additional formatting recommendations,
132 see the following:

- 133
134
- 135 • *Providing Regulatory Submissions* guidance.
 - 136
137 • International Council for Harmonisation (ICH) guidance for industry *M4 Organization*
138 *of the Common Technical Document for the Registration of Pharmaceuticals for Human*
139 *Use*.
 - 140
141 • ICH guidance for industry *M4Q: The CTD—Quality*.
 - 142
143 • Draft guidance for industry *Submitting Marketing Applications According to the ICH-*
144 *CTD Format—General Considerations*.¹¹
- 145
146

⁹ Holders submitting DMFs that contain information that is intended for use by applications for biological products may also use these templates.

¹⁰ See the *Providing Regulatory Submissions* guidance.

¹¹ When final, this guidance will represent FDA’s current thinking on this topic.

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147 1. *Module 1*

148

149 a. Cover letter (eCTD section 1.2)

150

151 FDA recommends using the cover letter template for original submissions on CDER's DMF web
152 page at <https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>.¹² As
153 laid out in this template, the cover letter should specify the submission type (e.g., original, agent
154 appointment). A table of submission types is available on CDER's DMF web page. The cover
155 letter should also include a statement of commitment signed by the DMF holder stating that the
156 DMF is current and that the holder will comply with the statements made in the DMF.

157 (Alternatively, the statement of commitment can be a separate document included in eCTD
158 section 1.2.) See the template for additional information to include.

159

160 b. Administrative information (eCTD section 1.3)

161

162 The administrative information section should include information about the DMF holder, the
163 agent (if applicable), the manufacturer, and debarment certification (for more information about
164 debarment certification, see section III.B.1.b.iv in this guidance).

165

166 i. DMF holder

167

168 DMF holders should provide their name and address. Only one company should be listed as the
169 DMF holder. Joint submissions are not accepted.

170

171 ii. Contact/Agent

172

173 DMF holders should provide the name, telephone and fax numbers, email address, and specific
174 responsibilities of the contact person and the responsible official (if different from the contact
175 person).

176

177 To facilitate communication, FDA strongly encourages foreign DMF holders to appoint an agent,
178 preferably in the United States, who is familiar with FDA regulations, guidances, and
179 procedures. However, DMF holders, not their agents, are responsible for the contents of their
180 DMFs (e.g., all aspects of the chemistry, manufacturing, and controls (CMC) information).

181 Agents can submit to the DMF on behalf of DMF holders. They can sign DMF submissions as
182 well, with the following exceptions:

183

- 184 • Agent appointment letters.
- 185 • Statements of commitment.
- 186 • Name changes.
- 187 • Holder transfers.
- 188 • New holder acceptance letters.
- 189 • DMF closure requests.

¹² FDA is developing a form to replace the cover letter used for original and subsequent submissions. The form should be available by the time this guidance is finalized.

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190
191 An agent for DMF purposes is not the same as an agent for the purposes of the Drug Listing and
192 Registration System (DRLS). DMF holders should not include the name of the agent for
193 registration purposes in the DMF unless the same person or company is the agent for both the
194 DMF and DRLS.

195
196 DMF holders can have different agents for different DMFs.

197
198 DMF holders should submit agent appointment letters in their original submissions or in
199 administrative amendments. The letter should be on the DMF holder's letterhead and should
200 contain the agent's name, address, contact person's name (if different from the agent's name),
201 telephone and fax numbers, and email address, among other information. FDA recommends
202 using the agent appointment letter template on CDER's DMF web page at
203 <https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>.

204
205 iii. Manufacturer

206
207 DMF holders should provide the manufacturer's name, site address, and contact person's name,
208 telephone and fax numbers, and email address.

209
210 iv. Debarment certification

211
212 DMF holders are included in the category of "Persons whose services were used in any capacity
213 in connection with the application" required under section 306(k)(1) of the FD&C Act. DMF
214 holders can submit their own debarment certifications in eCTD section 1.3.3.

215
216 For more information on debarment certifications, see draft guidance for industry *Submitting*
217 *Debarment Certification Statements*.¹³

218
219 c. References (eCTD section 1.4)

220
221 i. Letter of authorization

222
223 FDA will not review a DMF until the DMF holder submits a letter of authorization (LOA) to the
224 DMF regarding a specific application or other DMF (§ 314.420(d)). LOAs can be submitted as
225 part of the original submission or in a subsequent submission. The LOA permits FDA to review
226 the DMF and permits the authorized party (i.e., the company or individual who submits an
227 application or another DMF) to incorporate information into an application or another DMF by
228 reference (eCTD section 1.4.1). An LOA should still be submitted even if the authorized party
229 and the DMF holder are the same company.

230
231 The DMF holder should send a copy of the LOA to the authorized party. The authorized party
232 must include a copy of the LOA in its application (§ 314.50(a)(1)) or DMF (eCTD section 1.4.2).
233 An LOA does not give an authorized party permission to view or access a DMF.

¹³ When final, this guidance will represent FDA's current thinking on this topic.

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Note:

- An LOA should not be used to authorize an agent or representative to act on behalf of a company.
- An LOA should not be used to authorize DMF holder employees to submit information to the DMF.
- An LOA can be submitted by an agent but ultimately the DMF holder is responsible for the LOA.
- An LOA should not have multiple authorized parties; DMF holders should submit a separate LOA for each party.
- If the DMF holder changes its name, the DMF holder should submit a new LOA using the “Replace” function in the electronic submission.
- If an authorized party changes its name, the DMF holder should submit a new LOA using the “Replace” function in the electronic submission.
- An LOA does not need to include the name of the individual employed by the authorized party (i.e., a contact person). The name of the applicant is sufficient.
- An LOA should distinguish between those facilities that will be used for purposes of the authorization versus other facilities that are part of the DMF but are not applicable to the authorization. Unless this specification is present in the LOA, FDA will assume that all facilities listed in a DMF apply to the referencing application.

FDA recommends using the LOA template on CDER’s DMF web page at <https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>. As laid out in this template, the LOA should include, among other information, a statement of commitment signed by the DMF holder stating that the DMF is current and that the holder will comply with the statements made in the DMF. (Alternatively, the statement of commitment can be included in eCTD section 1.2 and referenced in the LOA.)

ii. List of authorized persons to incorporate by reference

In eCTD section 1.4.3, DMFs must list each party currently authorized to incorporate by reference any information in the DMF (§ 314.420(d)). The list should only contain authorized parties for which LOAs have been submitted and should be updated whenever a new LOA is submitted or an authorized party is withdrawn. The list should contain the following information for each authorized party:

- Name of the authorized party.

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- 280 • Date of the LOA.
281
282 • Specific products, items, or processes referenced by the LOA, including submission
283 dates, eCTD section numbers, and page numbers.
284
285 • Application number referencing the DMF (optional).
286

287 To withdraw authorization, DMF holders should submit a “Withdrawal of Authorization” letter
288 to the DMF and notify the authorized party. The withdrawal letter should replace the LOA in
289 eCTD section 1.4.1. FDA recommends using the withdrawal of authorization template on
290 CDER’s DMF web page at [https://www.fda.gov/drugs/forms-submission-requirements/drug-](https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs)
291 [master-files-dmfs](https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs).
292

293 d. Application status (eCTD section 1.5)
294

295 DMF holders can use eCTD section 1.5.5 to close a DMF. See section VI for information about
296 DMF closures.
297

298 e. Meetings (eCTD section 1.6)
299

300 Holders of Type II active pharmaceutical ingredient (API)¹⁴ DMFs referenced in ANDAs can
301 request teleconferences in response to first-cycle DMF deficiency letters.¹⁵
302

303 f. Information amendment: Information not covered under modules 2
304 through 5 (eCTD section 1.11)
305

306 In general, changes reported in eCTD section 1.11 should only include a summary of changes to
307 modules 2 through 5 or changes that do not fit in modules 2 through 5. Documents included in
308 eCTD section 1.11 should contain references and links to any sections in modules 2 through 5
309 that are changed. For example, a change in the drug substance specification should be mentioned
310 in eCTD section 1.11 but should also be changed in sections 2.3.S.4.1 and 3.2.S.4.1.
311

312 g. Other correspondence (eCTD section 1.12)
313

314 Because DMFs are neither approved nor disapproved, an environmental assessment should not
315 be submitted in a DMF (eCTD section 1.12.14).¹⁶ However, DMF holders should include in their
316 DMFs a commitment to operate their facilities in compliance with applicable environmental
317 laws.
318

¹⁴ This guidance uses the terms *API* and *drug substance* interchangeably.

¹⁵ See page 19 of “GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022” at <https://www.fda.gov/media/101052/download>.

¹⁶ See 21 CFR part 25 and the guidance for industry *Environmental Assessment of Human Drug and Biologics Applications (Rev. 1)*.

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319 h. Labeling (eCTD section 1.14)

320
321 For DMFs related to drug substances, drug substance intermediates, drug products covered by
322 Type II DMFs, and excipients covered by Type IV DMFs, DMF holders should provide a copy
323 of the shipping label in the Labeling section.

324
325 i. Risk evaluation and mitigation strategy (eCTD section 1.16)

326
327 In the REMS section, DMF holders should provide REMS-related documents, if applicable.¹⁷

328
329 2. *Module 2*

330
331 Module 2 summarizes the appropriate module 3 sections (and 4 and 5, if applicable).

332
333 3. *Module 3*

334
335 See section III.D in this guidance for information to include in this module, organized by DMF
336 type.

337
338 4. *Module 4*

339
340 This module is not necessary for DMFs unless nonclinical evaluations are included in the DMF.
341 The following information is appropriate to submit in module 4:

- 342
- 343 • Nonclinical evaluations to support the safety of:
 - 344 ○ An excipient whose CMC information is provided in module 3 in a Type IV
346 DMF; or
 - 347 ○ An impurity whose CMC information is provided in module 3 in a Type II DMF.
 - 348 ○ An impurity whose CMC information is provided in module 3 in a Type II DMF.
 - 349
 - 350 • Nonclinical evaluations in a Type V DMF.

351
352 5. *Module 5*

353
354 Module 5 should be submitted for clinical information only, such as in a Type V DMF.

355
356 **C. Subsequent Submissions**

357
358 Amendments and additions or deletions of information in the DMF, including LOAs, must be
359 submitted to the DMF (§ 314.420(c)). These subsequent submissions should contain a cover

¹⁷ For information on REMS submissions, see draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions* and the *Technical Conformance Guide for Shared System REMS Drug Master File Submissions*. When final, the guidance will represent FDA's current thinking on this topic.

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360 letter¹⁸ and updated administrative and technical information, as needed. DMF holder name
361 changes and acceptance notifications should also include the statement of commitment as
362 described in section III.B.1.a.

363
364 If information in a subsection (e.g., 3.2.S.2.3) of a DMF changes, DMF holders should replace
365 documents in that subsection. For more information, see the *eCTD Technical Conformance*
366 *Guide* at <https://www.fda.gov/media/93818/download>.

367
368 All amendments and LOAs should reference the updated DMF. A cumulative change history
369 should be submitted with each subsequent submission.

370
371 DMF holders must notify affected authorized parties of any DMF changes, additions, or
372 deletions (§ 314.420(c)) and should provide sufficient information to enable authorized parties to
373 determine the appropriate reporting procedure for their applications (see §§ 314.60, 314.70,
374 314.96, and 314.97). This notification should occur well before making any changes to permit
375 authorized parties to report application changes within an appropriate time frame.

376 377 1. *Cover Letter*

378
379 FDA recommends using the cover letter template for subsequent submissions on CDER's DMF
380 web page at <https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>.
381 Among other information as laid out in this template, the cover letter should specify the change
382 and reference the date and eCTD section or page number of any previous submission affected by
383 the change.

384
385 In addition, the cover letter should specify the submission type: for example, changes in
386 administrative information (e.g., change in agent) should be reported as an administrative
387 amendment, changes in technical information (e.g., change in a test procedure) should be
388 reported as a quality amendment (also referred to as a *technical amendment*), and changes in
389 REMS information (e.g., major REMS modification) should be reported as a REMS–Risk
390 Evaluation and Mitigation Strategy.

391
392 Multiple submission types (e.g., LOAs, administrative and quality amendments) can be
393 submitted together with a single cover letter and sequence number. In these cases, the DMF
394 holder should list each submission type in the cover letter. The DMF holder can also further
395 delineate the submission type by amendment type (e.g., change of holder). A table of submission
396 and amendment types is available on CDER's DMF web page at
397 <https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>.

398 399 2. *Administrative Amendments*

400
401 These types of amendments include, but are not limited to, the following changes.
402

¹⁸ See footnote 12.

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403 a. Name changes, acquisitions, or transfers of ownership

404

405 DMF holders must notify FDA of any name changes (§ 314.420(c)); such changes should be
406 submitted in an administrative amendment to each DMF they own. Name changes can occur
407 through a change in name only or because the DMF holder is acquired by or transfers ownership
408 to another company. If an agent had been appointed by the previous DMF holder and that agent
409 is being retained by the new DMF holder or if a new agent is being retained, the current DMF
410 holder should submit an agent appointment letter on the DMF holder's letterhead (eCTD section
411 1.3.1.2).

412

413 If transfer of ownership is involved, the original DMF holder should submit a transfer
414 notification to the DMF and the new DMF holder should submit an acceptance notification. A
415 statement of commitment signed by the new DMF holder should be included in name change and
416 acceptance notifications stating that the DMF is current and that the holder will comply with the
417 statements made in the DMF. (Alternatively, the statement of commitment can be included in
418 eCTD section 1.2 and referenced in these notifications.)

419

420 Templates for name changes, transfer notifications, and acceptance notifications are on CDER's
421 DMF web page at [https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-](https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs)
422 [dmfs](https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs).

423

424 b. Changes to the DMF subject

425

426 Changes to the DMF's subject (title) should be submitted in an administrative amendment. If a
427 title change is necessary because of a change in technical information (e.g., change in the grade
428 of a drug substance that is the subject of the DMF), a quality amendment should also be
429 submitted.

430

431 c. Changes to the DMF type

432

433 Changes to DMF type should be submitted in an administrative amendment. If the change in type
434 necessitates changes in the DMF's technical information, the DMF holder should submit those
435 changes in a quality amendment.

436

437 3. *Quality Amendments*

438

439 Any changes to technical information should be submitted in a quality amendment.

440

441 4. *Conversion of Existing DMFs To Comply With eCTD Format*

442

443 Although there is no requirement to resubmit existing DMF submissions in eCTD format, DMF
444 holders wishing to do so should include a list of content changes occurring as a result of the
445 conversion in an attachment to the cover letter.¹⁹ It is not necessary to request a new DMF

¹⁹ See the *eCTD Technical Conformance Guide* for more information on resubmission of non-eCTD documents.

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446 number. If the existing number is four digits (e.g., 1234), the DMF holder will need to add two
447 zeros to the front of the number to convert it to the eCTD six-digit format (e.g., 001234).

448

449 **D. Submission Recommendations, by DMF Type**

450

451 The information recommended below is not intended to be all-inclusive. Please refer to
452 supplemental guidances related to information to be included in DMFs as well as the DMF
453 website.²⁰

454

455 *1. Type II: Drug Substance, Drug Substance Intermediate, and Materials Used in* 456 *Their Preparation, or Drug Product*

457

458 Each Type II DMF should be limited to a single drug substance, drug substance intermediate,
459 type of material used in their preparation, or drug product.²¹ Drug product intermediates are also
460 included in the category of Type II DMF. Separate DMFs should be submitted for drug
461 substances manufactured using different processes.

462

463 DMFs for drug substances, drug substance intermediates, drug products, and drug product
464 intermediates should state that the material covered by the DMF is manufactured under current
465 good manufacturing practices (eCTD sections 3.2.S.2 or 3.2.P.3).

466

467 Type II DMFs for APIs submitted in support of ANDAs should follow the recommendations in
468 guidances for industry such as *Completeness Assessments for Type II API DMFs Under GDUFA*.
469 Such recommendations do not apply to Type II DMFs for APIs that are only used to support
470 INDs or NDAs.

471

472 *a. Drug substance or drug substance intermediate*

473

474 The definition and criteria for designating starting materials and intermediates are discussed in
475 ICH guidances for industry *Q7 Good Manufacturing Practice Guidance for Active*
476 *Pharmaceutical Ingredients (Rev. 1)* and *Q11 Development and Manufacture of Drug*
477 *Substances* and ICH Q7 and Q11's corresponding Questions and Answers guidances.

478

479 Drug substance manufacturers should collect stability data according to their stability protocol
480 and should continue to submit data from ongoing studies in a quality/stability amendment.²²

²⁰ See, e.g., guidances for industry *Completeness Assessments for Type II API DMFs Under GDUFA* and *Drug Master Files for Bulk Antibiotic Drug Substances*. See also draft guidance for industry *Postapproval Changes to Drug Substances*, which, when final, will represent FDA's current thinking on this topic.

²¹ Although FDA's approach to the use of master files in BLAs under the PHS Act largely parallels its approach to the use of DMFs in applications under the FD&C Act, there is a significant difference. A BLA holder is generally expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license. For biological products in BLAs under the PHS Act, FDA has, as a scientific matter, generally not permitted applicants to incorporate information about drug substance, drug substance intermediate, or drug product by reference to a master file; rather, FDA generally expects such information to be submitted directly to the BLA.

²² See ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*.

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481
482 For sterilization of drug substances to be used in sterile products, the same sterility assurance
483 information should be submitted as for sterile drug products, as outlined in the guidance for
484 industry *Submission Documentation for Sterilization Process Validation in Applications for*
485 *Human and Veterinary Drug Products (Submission Documentation guidance)* and other
486 supporting documents included on CDER’s DMF web page.²³ Building and facility information,
487 including floor plans, can be submitted in the Type II DMF if a Type V DMF is not cross-
488 referenced for this information.

- 489
490 b. Material used in the preparation of a drug substance or drug substance
491 intermediate

492
493 If material used in the preparation of a drug substance or drug substance intermediate requires
494 FDA review of CMC information (e.g., defined artificial cell growth media), this information
495 should be submitted in a Type II DMF.

- 496
497 c. Drug product or drug product intermediate

498
499 21 CFR 314.420 permits DMF submissions for drug products.

500 501 2. *Type III: Packaging Material*

502
503 Packaging materials should be identified by type (e.g., bottle) and material of construction
504 (MOC) (e.g., high-density polyethylene). Packaging materials can be combined to prepare a
505 container-closure system (e.g., a syringe barrel and a plunger).

506
507 Information, including safety information, about the components of an MOC can be provided
508 directly to the authorized party without filing a DMF.

509
510 For most MOCs (e.g., plastics and glass) and the packaging materials made from them, safety
511 and quality information can be provided by referring to appropriate sections of the Code of
512 Federal Regulations. Additional quality information can be provided by referring to appropriate
513 sections of the United States Pharmacopeia–National Formulary (USP–NF). MOCs should be
514 identified by their names as listed in the appropriate regulations, where applicable.

515
516 Data supporting the protection, compatibility, and performance of a packaging material or
517 container-closure system for its intended use should be submitted in the application for the drug
518 product that uses the packaging material.

519
520 Type III DMFs can include information about the packaging materials or container-closure
521 system’s components, MOCs, controls for release, and intended use. The names of the suppliers
522 or fabricators of the MOCs or components and the specifications for their acceptance can also be
523 provided.

²³ See footnote 3; see also FDA’s MAPP 5040.1 *Product Quality Microbiology Information in the Common Technical Document—Quality (CTD-Q)*.

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524
525 Information regarding mixtures of color additives and plastics (often called *masterbatches*) for
526 use in manufacturing plastic packaging components (e.g., to make a bottle blue) is appropriately
527 filed as a Type III DMF.

528
529 For sterilization and depyrogenation of packaging materials to be used in sterile products, the
530 same sterility assurance information should be submitted as for sterile drug products, as outlined
531 in the *Submission Documentation* guidance and other supporting documents included on
532 CDER's DMF web page.²⁴ Building and facility information, including floor plans, is
533 appropriately filed in the Type III DMF if a Type V DMF is not cross-referenced for this
534 information.

535
536 The different eCTD sections within 3.2.S or 3.2.P should be populated as appropriate. For multi-
537 item DMFs, each item (e.g., different MOCs) would have a different name (e.g., 3.2.S.[MOC 1],
538 3.2.S.[MOC 2]). It is appropriate for DMF holders to point to information that is common to
539 different products (e.g., analytical procedures) by reference (or via links in the case of an
540 electronic DMF) to the relevant section for that product (e.g., 3.2.P.4.2 [MOC 1]).

541
542 3. *Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their*
543 *Preparation*

544
545 Information for most excipients (e.g., lactose or microcrystalline cellulose) should be submitted
546 in eCTD section 3.2.S. Information for excipients that are mixtures of multiple compounds (e.g.,
547 flavor mixtures) should be submitted in eCTD section 3.2.P.

548
549 DMFs should be submitted only for excipients for which CMC and safety information is not
550 available through reference to appropriate regulations or quality information through the USP-
551 NF. These include new excipients and colorants, flavors, essences, and material used in their
552 preparation.

553
554 a. New excipients

555
556 As defined in guidance for industry *Nonclinical Studies for the Safety Evaluation of*
557 *Pharmaceutical Excipients*, new excipients are inactive ingredients that are not fully qualified by
558 existing safety data with respect to the currently proposed level of exposure, duration of
559 exposure, or route of administration.²⁵ Nonclinical evaluations to support the safety of an
560 excipient whose CMC information is provided in module 3 of a Type IV DMF can be provided
561 in module 4 of the same DMF. Alternatively, this information can be provided in module 4 of a
562 separate Type V DMF.

563
564 Excipients listed in the current USP–NF (i.e., compendial excipients) are usually considered to
565 be qualified when administered under conditions that would not be considered new, as defined

²⁴ See footnote 3.

²⁵ To search for inactive ingredients, consult FDA's web page Inactive Ingredient Search for Approved Drug Products at <https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>.

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566 above. However, use of such excipients in a drug product that leads to increased exposure may
567 require additional safety information, either in a DMF or in the drug product application.
568 Additionally, it is important to note that the inclusion of an excipient in a USP-NF monograph or
569 other non-FDA document is not an indication that FDA reviewed the substance or determined it
570 to be safe for use.

571
572 Manufacturers of excipients derived from animal sources (e.g., gelatin) should provide
573 information regarding safety of the material from contamination by infectious agents. This
574 information can be provided directly to the authorized party.

575
576 b. Colorant, flavor, essence, or material used in their preparation

577
578 Colorants are used to impart color to a drug product and are composed of one or more color
579 additives and other ingredients.

580
581 Flavor or essence is an excipient that is added to a drug product whose significant function is to
582 impart flavor and not to produce pharmacological activity.

583
584 DMFs for mixtures of materials used to prepare a flavor (e.g., artificial strawberry flavor) should
585 include information about the components and composition of mixtures. For example, for flavors
586 containing multiple components, a quantitative breakdown of the components in the mixture
587 should be provided.

588
589 Refer to USP-NF for quality information. Data to support the safety of colorant and flavor
590 mixtures can be provided by referring to FDA regulations, including:

- 591
- 592 • Color additives (21 CFR parts 70 through 82).
 - 593 • Direct food additives (21 CFR parts 170 through 173).
 - 594 • Indirect food additives (21 CFR parts 174 through 178).
 - 595 • Food substances (21 CFR parts 181 through 186).
- 596

597 Components should be identified by their names as cited in FDA regulations, where applicable.

598
599 Information about the components and compositions, as well as safety information, can be
600 provided directly to the authorized party without filing a DMF.

601
602 If provided in a DMF, information about excipients that are mixtures of multiple compounds
603 (e.g., flavor mixtures) should be submitted in eCTD section 3.2.P. The different sections within
604 3.2.S or 3.2.P should be populated as appropriate. For multi-item DMFs, each product (e.g.,
605 different flavors) would have a different name (e.g., 3.2.P.[Flavor 1], 3.2.P.[Flavor 2]). In this
606 case, the components and composition would be described in 3.2.P.1 [Flavor 1], 3.2.P.1 [Flavor
607 2]. DMF holders can access information that is common to different products (e.g., analytical
608 procedures) by reference (or via links in the case of an electronic DMF) to the relevant eCTD
609 section for that product (e.g., 3.2.P.5.2 [Flavor 1]).

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4. Type V: FDA-Accepted Reference Information

If a DMF holder wishes to submit information that is not covered by Types II through IV, the DMF holder can submit a Type V DMF (e.g., shared system REMS, sterile processing facility, toxicology studies for compound X) but must first email a letter of intent to the DMF staff at dmfquestion@fda.hhs.gov.²⁶ FDA will then contact the DMF holder to discuss the proposed submission.

The emailed letter of intent should include:

- The specific information to be included in the DMF.
- The proposed subject (title) of the DMF.
- A clear statement regarding why this information could not be submitted in an application (i.e., why the information is considered to be confidential).
- The clinical division(s) that should review the information, if applicable.

Information regarding the manufacturing site, facilities, operating procedures, and personnel for sterile manufacturing plants can be filed as a Type V DMF without first submitting a letter of intent. The subject field should specify what the DMF covers (e.g., sterile processing facility).

E. Other Recommendations

1. English Translations

Applicants must submit an accurate and complete English translation of each part of the NDA or ANDA that is not in English (§§ 314.50(g)(2), 314.94(a)(11)). The same is true for DMFs. A *certified* translation is not required.

2. Public Availability of Information in a DMF

Public availability of the information in a DMF is determined under 21 CFR part 20 and other applicable FDA disclosure regulations, including §§ 314.420(e), 314.430, and 601.51. DMF holders and authorized parties are free to share any information with each other.

3. Holder Not the Manufacturer

In general, FDA expects the DMF holder to be the manufacturer of the material covered by the DMF. If the DMF holder is not the manufacturer, the DMF should include a statement that the DMF holder assumes full responsibility for the manufacturing of the material covered by the DMF.

²⁶ See § 314.420(a)(5).

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655 4. *Primary and Secondary DMFs*

656
657 A primary DMF can incorporate information in a secondary DMF by reference. The secondary
658 DMF holder can submit an LOA authorizing either the primary DMF holder or the drug product
659 applicant to reference the secondary DMF. Where possible, consistent with confidentiality
660 agreements, secondary DMF holders are encouraged to submit LOAs authorizing drug product
661 applicants to reference the secondary DMF directly.

662 663 5. *Referencing Own Application Material*

664
665 An applicant need not create a new DMF when referencing its own material but can include the
666 information directly in its own application.

667 668 6. *Retention of Reference Copy by the Holder*

669
670 DMF holders and their agents should retain a complete reference copy that is identical to, and
671 maintained in the same chronological order as, their submissions to FDA.

672
673 When a DMF is transferred from one DMF holder to another, all documents associated with the
674 DMF should be transferred to the new DMF holder.

675 676 677 **IV. ANNUAL REPORTS**

678
679 Annual reports should not be used to report changes in the DMF. If it is necessary to submit an
680 amendment and an annual report, they must be submitted under separate eCTD sequence
681 numbers.²⁷

682
683 DMF holders should submit a cover letter²⁸ when submitting their annual report. The annual
684 report should include a statement of commitment signed by the DMF holder stating that the
685 DMF is current and that the holder will comply with the statements made in the DMF.
686 (Alternatively, the statement of commitment can be included in eCTD section 1.2 and referenced
687 in the annual report. However, agents submitting annual reports on behalf of DMF holders
688 should not refer to eCTD section 1.2 for the statement of commitment; rather they should include
689 a statement of commitment signed by the DMF holder with the annual report.) The annual report
690 should also include the appropriate administrative information, dates of any amendments
691 reporting changes since the last annual report (or original filing date), a list of authorized parties,
692 and a list of parties whose authorization has been withdrawn and the dates of withdrawal. See the
693 annual report template and subsequent submissions cover letter template on CDER's DMF web
694 page at <https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>.

695
696 Annual reports help assure FDA that the statement of commitment is current. Failure to submit
697 this report annually may result in the termination of a DMF (see section VI, DMF Closure).

²⁷ See the *Providing Regulatory Submissions* guidance.

²⁸ See footnote 12.

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V. FDA PROCESSING AND REVIEWING POLICIES

A. Administrative Review

If the administrative information in an original DMF is found acceptable, FDA sends an acknowledgment letter to the DMF holder (and agent, if applicable) listing the DMF number, subject (title), type, and holder's name as specified in the cover letter. For submissions with incomplete administrative information, FDA contacts the DMF holder (and the agent, if applicable) to request the missing information. The DMF will not be available for technical review until all administrative filing issues have been adequately addressed and the DMF is referenced in an application or another DMF (see section V.B).

FDA examines subsequent submissions (e.g., amendments, LOAs) to ensure that the subject, holder name, and type match the information for that DMF number on file at FDA. FDA also checks these submissions for other administrative information, such as the holder's address, agent's address (if applicable), and appropriate submission type and, if applicable, amendment type (e.g., change of holder, change of DMF subject). If administrative issues are noted, FDA contacts the DMF holder (and agent, if applicable) to request that the information be corrected or the discrepancies be resolved.

FDA does not send acknowledgment letters for subsequent submissions. If this practice changes, FDA intends to update the DMF web pages to describe which types of documents will be acknowledged.

B. Technical Review

FDA performs a complete review of the referenced technical information in a DMF when an authorized party submits a copy of the DMF holder's LOA in its application or in another DMF.²⁹ The review is performed to support a particular use (e.g., a drug substance used to manufacture a solid oral dosage form). Whether a DMF is acceptable depends on the specific use described in an application or in another DMF referencing the DMF.

Reviewers may find that additional information is needed to continue a review or that the DMF cannot be used to support approval of an ANDA, NDA, or BLA or, in the case of an IND, allow clinical trials to proceed. In these cases, FDA will contact the DMF holder and the agent, if applicable, regarding its concerns.

Certain Type II DMFs for APIs that require a user fee under the Generic Drug User Fee Amendments of 2017 (GDUFA II) will receive a completeness assessment.³⁰

²⁹ See the draft guidance for industry *Assessing User Fees Under the Generic Drug User Fee Amendments of 2017*. When final, this guidance will represent FDA's current thinking on this topic.

³⁰ See the guidance for industry *Completeness Assessments for Type II API DMFs Under GDUFA*.

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VI. DMF CLOSURE

DMFs may be closed either because the DMF holder requests closure or because FDA cannot be assured that the DMF is current. In the latter case, FDA will notify the holder or agent, as applicable, that the DMF needs to be updated. If the DMF holder or agent, as applicable, does not respond by submitting an annual report in a timely manner, FDA could close the DMF and would notify the holder or agent, as applicable, of this action.

To close a DMF, DMF holders should submit an administrative amendment requesting closure. The request should include a statement that all authorized parties have been notified of the closure (eCTD section 1.5.5). FDA recommends using the template for requesting closure on CDER's DMF web page at <https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs>.

A closed DMF cannot be reviewed in support of a new or amended application or another DMF, a new or amended supplement to an approved application, a new IND, or an amendment to an existing IND. Thus, an applicant can no longer incorporate the information from a closed DMF in support of its application and will need to submit an amendment or supplement to FDA to replace the information contained in the closed DMF.

If a DMF has been closed, the holder can submit a new DMF to FDA to replace the closed DMF. The new DMF should reference the closed DMF number.

VII. GLOSSARY

Active pharmaceutical ingredient (API): Any substance intended for incorporation into a finished drug product and intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body; does not include intermediates used in the synthesis of the substance (21 CFR 207.1).

Agent: A legal entity, whether a company or an individual, that is not employed but is appointed to act on behalf of a DMF holder.

Authorized party: Any person who is authorized to reference a DMF.

Contact person: An employee of the DMF holder or agent to whom communication from FDA should be sent. The contact person may or may not be the same individual as the responsible official.

DMF holder: A person who owns a DMF.

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784 **Drug product:** A finished dosage form (e.g., tablet, capsule, solution) that contains a drug
785 substance, generally, but not necessarily, in association with one or more other ingredients
786 (§ 314.3(b)).

787
788 **Drug product intermediate:** A defined mixture of one or more drug substances with one or
789 more inactive ingredients that is not a finished dosage form. This is to be distinguished from a
790 mixture when the drug substance is unstable or cannot be transported on its own.

791
792 **Drug substance:** An active ingredient that is intended to furnish pharmacological activity or
793 another direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to
794 affect the structure or any function of the human body but does not include intermediates used in
795 the synthesis of such an ingredient (§ 314.3(b)).

796
797 **Drug substance intermediate:** A material produced during steps of the processing of an API
798 that undergoes further molecular change or purification before it becomes an API. Drug
799 substance intermediates may or may not be isolated. See ICH Q7.

800
801 **Letter of authorization (LOA):** A letter from a DMF holder that authorizes an applicant or
802 another DMF holder to incorporate by reference all or part of the DMF's contents to support an
803 application, supplement, or another DMF or an amendment to any of these documents. The LOA
804 also authorizes FDA to review applicable portions of the DMF.

805
806 **Person:** An individual, partnership, corporation, or association (section 201(e) of the FD&C
807 Act).

808
809 **Primary DMF:** A DMF that references another DMF and itself may be referenced by an
810 application.

811
812 **Responsible official:** The employee of the DMF holder or agent who is responsible for
813 submitting information to the DMF.

814
815 **Risk evaluation and mitigation strategy (REMS):** A required risk management strategy that
816 employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its
817 risks. For more information, see section 505-1 of the FD&C Act.

818
819 **Secondary DMF:** A DMF that is incorporated by reference into a primary DMF.

820
821 **Subject:** Title of the DMF.

822 823 824 **VIII. REFERENCES**

825
826 FDA, 2018, Comprehensive Table of Contents Headings and Hierarchy.

827
828 FDA, 2018, eCTD Technical Conformance Guide.

829

Contains Nonbinding Recommendations

Draft — Not for Implementation

830 FDA, 2017, MAPP 5040.1 Product Quality Microbiology Information in the Common Technical
831 Document—Quality (CTD-Q).

832
833 FDA, 2017, Technical Conformance Guide for Shared System REMS Drug Master File
834 Submissions.

835
836 FDA, 2017, Transmitting Electronic Submissions Using eCTD Specifications.

837 838 *Guidances for Industry*

839
840 Guidance for industry *Completeness Assessments for Type II API DMFs Under GDUFA*,
841 October 2017

842
843 Guidance for industry *Drug Master Files for Bulk Antibiotic Drug Substances*, November 1999

844
845 Guidance for industry *Environmental Assessment of Human Drug and Biologics Applications*
846 *(Rev. 1)*, July 1998

847
848 Guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical*
849 *Excipients*, May 2005

850
851 Guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human*
852 *Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*
853 *(Rev. 6)*, January 2019 (see Rev. 7 in “Draft Guidances for Industry” below)

854
855 Guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic*
856 *Protein Product to a Reference Product*, April 2015

857
858 Guidance for industry *Submission Documentation for Sterilization Process Validation in*
859 *Applications for Human and Veterinary Drug Products*, November 1994

860
861 ICH guidance for industry *M4 Organization of the Common Technical Document for the*
862 *Registration of Pharmaceuticals for Human Use*, October 2017

863
864 ICH guidance for industry *M4Q: The CTD—Quality*, August 2001

865
866 ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*,
867 November 2003

868
869 ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active*
870 *Pharmaceutical Ingredients (Rev. 1)*, September 2016

871
872 ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active*
873 *Pharmaceutical Ingredients: Question and Answers*, April 2018

874

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 875 ICH guidance for industry *Q11 Development and Manufacture of Drug Substances*, November
876 2012
877
- 878 ICH guidance for industry *Q11 Development and Manufacture of Drug Substances: Questions*
879 *and Answers*, February 2018
880
- 881 **Draft Guidances for Industry**³¹
882
- 883 Draft guidance for industry *Assessing User Fees Under the Generic Drug User Fee Amendments*
884 *of 2017*, October 2017
885
- 886 Draft guidance for industry *Postapproval Changes to Drug Substances*, September 2018
887
- 888 Draft guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain*
889 *Human Pharmaceutical Product Applications and Related Submissions Using the eCTD*
890 *Specifications (Rev. 7)*, July 2019 (see Rev. 6 in “Guidances for Industry” above)
891
- 892 Draft guidance for industry *Submitting Debarment Certification Statements*, September 1998
893
- 894 Draft guidance for industry *Submitting Marketing Applications According to the ICH-CTD*
895 *Format—General Considerations*, August 2001
896
- 897 Draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions*,
898 November 2017

³¹ When final, these guidances will represent FDA’s current thinking on these topics.