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# Guidance for Industry

## Providing Regulatory Submissions in Electronic Format — Standardized Study Data

### *DRAFT GUIDANCE*

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For questions regarding this draft document contact (CDER) Ron Fitzmartin at 301-796-5333, (CBER) Office of Communication, Outreach and Development (OCOD) at 301-827-1800 or 1-800-835-4709.

**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)**

**February 2014  
Electronic Submissions  
Revision 1**

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## Providing Regulatory Submissions in Electronic Format — Standardized Study Data

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40 this guidance because it is not an accurate description of the effects of this guidance. Insofar as  
41 this guidance specifies the format for electronic submissions, or provides “criteria for . . .  
42 exemptions” pursuant to section 745A(a) of the FD&C Act, it will have binding effect.  
43

44 This guidance supersedes the draft guidance for industry *Providing Regulatory Submissions in*  
45 *Electronic Format – Standardized Study Data* that was issued in February 2012.  
46

## 47 **II. REQUIREMENT TO SUBMIT ELECTRONIC STANDARDIZED STUDY DATA**

### 48 **A. For what submission types is an electronic submission of standardized study** 49 **data required?**

50  
51  
52 Electronic submissions of standardized study data will be required for the following submission  
53 types:

- 54 • Certain investigational new drug applications (INDs)
- 55 • New drug applications (NDAs)
- 56 • Abbreviated new drug applications (ANDAs)
- 57 • Certain biologics license applications (BLAs)

58  
59 This also includes all subsequent submissions, including amendments, supplements, and reports  
60 to one of the submission types identified above. Study data contained in amendments,  
61 supplements, and reports must be submitted electronically in the specified format, even if the  
62 original application was submitted to FDA prior to implementation of the electronic submission  
63 requirements. Study data in submissions that are not submitted electronically will not be filed,  
64 unless exempt from the electronic submission requirements or unless FDA has granted a waiver.  
65 See section II.D below for information on waivers of the requirement to use the specified  
66 standards, formats, or terminologies.  
67

### 68 **B. What types of submissions are exempted from the electronic submission** 69 **requirements for standardized study data?**

70  
71 The statute allows FDA to set forth criteria for exemptions from the electronic submission  
72 requirements. Accordingly, FDA will exempt all submissions regarding devices that are  
73 regulated by CBER as biological products under Section 351 of the PHS Act,<sup>3</sup> and study data  
74 contained in noncommercial INDs from the electronic submission requirement under section  
75 745A(a). For purposes of this guidance, the term “noncommercial products” refers products that  
76 are not intended to be distributed commercially and includes investigator-sponsored INDs,  
77 emergency use INDs, and treatment INDs. Although these submissions of study data will be  
78 exempt, FDA also accepts their submission in a standardized electronic format as described in  
79 this guidance document.  
80

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<sup>3</sup> Devices regulated by CBER as biological products under Section 351 of the PHS Act are generally those intended for use in screening donated blood for transfusion-transmissible diseases.

81 **C. What are the requirements that must be followed for electronic submission**  
82 **of standardized study data?**  
83

84 Under section 745A(a) of the FD&C Act, electronic submissions “shall be in such electronic  
85 format as specified by [FDA].” FDA has determined that study data contained in the electronic  
86 submissions described in section II.A must be in a format that the Agency can process, review,  
87 and archive. Currently, the Agency can process, review, and archive electronic submissions of  
88 study data that use the standards, formats, and terminologies specified in the Data Standards  
89 Catalog<sup>4</sup> posted to the FDA’s Study Data Standards Resources Web page and incorporated by  
90 reference into this document.

91  
92 The Data Standards Catalog provides a listing of supported<sup>5</sup> and/or required standards, their uses,  
93 the date FDA will begin (or has begun) to support a particular standard, and the date support  
94 ends (or will end), the date the requirement to use a particular standard will begin (or has begun)  
95 and the date such requirement ends (or will end), as well as other pertinent information. The  
96 Agency may refuse to file an electronic submission unless its study data conforms to the required  
97 standards, formats, and terminologies specified in the Data Standards Catalog.

98  
99 When planning a study (including the design of case report forms, data management systems,  
100 and statistical analysis plans), the sponsor or applicant must determine which FDA-supported  
101 standards, formats and terminologies to use or request a waiver as described in section II.D.  
102 FDA-supported standards include the following:

103  
104 *1. File Format Standard*  
105

106 A file format standard specifies a particular way that information is encoded in a computer file.  
107 Specifications for a format permit the file to be written according to a standard, opened for use or  
108 alteration, and written back to a storage medium for later access. Some file formats in  
109 widespread use are proprietary; others are open source. Examples of file format standards  
110 currently supported by FDA include: Adobe Acrobat Portable Document (.pdf), SAS Institute  
111 Transport File format (.xpt), text files (.txt), and Extensible Markup Language (.xml).

112  
113 *2. Study Data Exchange Standard*  
114

115 Study data exchange standards describe a standard way of exchanging data between computer  
116 systems. Exchange standards may describe the data elements and relationships necessary to  
117 achieve the unambiguous exchange of information between disparate information systems. The  
118 Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model  
119 (SDTM) is an example of an exchange standard for study data that is currently supported.

120  
121 *3. Analysis Standard*

---

<sup>4</sup> Available at <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>.

<sup>5</sup> For the purposes of this document, “supported” means the receiving Center has established processes and technology to support receiving, processing, reviewing, and archiving files in the specified file format.

122  
123 Analysis standards describe a standard presentation of the data intended to support analysis.  
124 Analysis standards include extraction, transformation, and derivations of the original data. An  
125 example is the CDISC Analysis Data Model (ADaM) which specifies standards for analysis  
126 datasets currently supported by FDA. As a practical matter, most of the existing data standards  
127 are not in one-to-one correspondence with the various types of data standards. For example, the  
128 CDISC SDTM may be used as an exchange standard (when combined with the SAS transport  
129 file format standard) and as an analysis standard to support simple analyses (e.g., simple analyses  
130 of demographics or adverse events).

#### 131 132 *4. Terminology Standard*

133  
134 The use of terminology standards, also known as controlled terminologies or vocabularies, is an  
135 important component of study data standardization and is a critical component of achieving  
136 semantically interoperable data exchange.<sup>6</sup> Terminology standards specify the key concepts that  
137 are represented as preferred terms, definitions, synonyms, codes, and code system. Terminology  
138 standards are maintained by external organizations (i.e., external to the sponsor or applicant).  
139 Sponsor- or applicant-defined custom terms are not considered controlled terminologies.  
140 Examples of controlled terminologies include:

- 141
- 142 • The National Drug File (NDF)— Reference Terminology for drug classifications<sup>7</sup>
- 143 • CDISC Controlled Terminology<sup>8</sup>
- 144 • Medical Dictionary for Regulatory Activities (MedDRA)<sup>9</sup>
- 145

#### 146 **D. Will FDA issue waivers of the electronic submission requirements for** 147 **standardized study data?**

148  
149 Electronic submissions of study data must be in a format that FDA can review, process, and  
150 archive. Currently, the Agency can process, review, and archive electronic submissions of study  
151 data that use the standards, formats, and terminologies specified in the Data Standards Catalog<sup>10</sup>  
152 posted to the FDA’s Study Data Standards Resources Web page.

153  
154 FDA will not provide waivers to submit data that do not conform to any FDA-supported study  
155 data standard. However, sponsors or applicants may apply for a waiver from the requirement to  
156 use specific versions of standards, formats, or terminologies. If granted, the waiver enables a

---

<sup>6</sup> See the Study Data Technical Conformance Guide for a detailed discussion of semantic interoperability. The Study Data Technical Conformance Guide is available at <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>.

<sup>7</sup> NDF is available at <http://ncit.nci.nih.gov/ncitbrowser/pages/vocabulary.jsf?dictionary=National%20Drug%20File%20-%20Reference%20Terminology>.

<sup>8</sup> CDISC Controlled Terminology is available at <http://www.cancer.gov/cancertopics/cancerlibrary/terminologyresources/cdisc>.

<sup>9</sup> MedDRA is available at <http://www.meddra.org/>.

<sup>10</sup> Available at <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>.

157 sponsor or applicant to submit study data electronically using a non-current version of a standard  
158 that was previously supported by FDA.

159  
160 To apply for a study-specific waiver from the requirement to submit study data in a non-current  
161 version of the standards set forth in the Data Standards Catalog, a written request should contain  
162 the following:

- 163
- 164 1. The specific requirement or requirements from which the sponsor or applicant is  
165 requesting a waiver
  - 166 2. The reason the sponsor believes that the waiver is necessary
  - 167 3. A description of the alternative or alternatives that the sponsor intends to use
- 168

169 FDA encourages the sponsor or applicant to discuss the waiver request prior to or at the pre-IND  
170 meeting with the appropriate review division in CDER or CBER and submit the request in  
171 writing prior to submitting the IND.<sup>11</sup> FDA will notify the sponsor or applicant in writing as to  
172 whether the waiver request is denied or granted.

173  
174 **E. When will electronic submission of standardized study data be required?**

175  
176 For additional information on how FDA intends to implement the electronic submission  
177 requirements of section 745A(a) of the FD&C Act, including timetable for implementation,  
178 please see the 745A Implementation Guidance.

179  
180 *1. Initial Timetable for the Implementation of Electronic Submission Requirements*

181  
182 After we publish a notice of availability of the final guidance in the *Federal Register*, all studies  
183 with a start date<sup>12</sup> twenty-four months after the *Federal Register* notice must use the appropriate  
184 FDA-supported standards, formats, and terminologies specified in the Data Standards Catalog  
185 (see section II.C) for NDA, ANDA, and certain BLA submissions. Study data contained in  
186 certain IND submissions must use the specified formats for electronic submission in studies with  
187 a start date thirty-six months after the *Federal Register* notice of availability.

188  
189 The following is an example of how a new electronic submission requirement would be  
190 implemented:

191  
192 *On November 15, 2016, FDA publishes a Federal Register notice announcing the*  
193 *availability of the final eStudy Data Guidance. For studies with a start date after*  
194 *November 15, 2018, sponsors or applicants must use the appropriate FDA-supported*  
195 *standards, formats and terminologies specified in the Data Standards Catalog for NDA,*

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<sup>11</sup> If no pre-IND meeting is held, sponsors or applicants are encouraged to contact the review division prior to the pre-BLA meeting to discuss a waiver request.

<sup>12</sup> For purposes of this guidance, the study start date is the earliest date of informed consent among any subject that enrolled in the study. For example, see Study Start Date in the SDTM Trial Summary Domain (TSPARMCD = SSTDTC), <http://www.cdisc.org>.

196 *ANDA, and certain BLA submissions. The Data Standards Catalog will list November*  
197 *15, 2018 as the “date requirement begins.”*

198  
199 *2. Version Updates to FDA-Supported Standards, Formats and Terminologies*  
200

201 Periodically, version updates to FDA-supported study data standards, formats, and terminologies  
202 are released by Standards Development Organizations (SDOs). Version updates may include:  
203 (1) Content or structural changes (e.g., new SDTM domains or variables) and (2) Typographical  
204 errors, corrections, or clarifications that do not result in content or structural changes. Generally,  
205 version updates that include content or structural changes would require FDA to execute a testing  
206 and acceptance process, while errata, corrections or clarifications would not.

207  
208 After this guidance is finalized (and the 24- and 36-month timeframes described in section II.E.1  
209 have passed), content or structural version updates will be required in submissions for studies  
210 with a start date<sup>13</sup> that is no earlier than 12 months after the *Federal Register* notice of  
211 availability. The *Federal Register* notice of availability will specify the effective date for all  
212 version updates that will correspond to a specific calendar month (e.g., in the examples below,  
213 March).

214  
215 The following are examples of these types of updates and how they would be implemented:  
216

217 *Example 1: CDISC releases a data exchange standard SDTM 4.1 as a version update to*  
218 *SDTM 4.0 on February 15, 2016. The version update includes domain and variable*  
219 *changes to the standard. Following the release by CDISC, FDA will execute an*  
220 *acceptance testing process to determine whether it is able to support the updated version,*  
221 *SDTM 4.1. The acceptance testing process confirms that FDA is able to support the*  
222 *updated version. On May 6, 2016, FDA publishes a Federal Register notice announcing*  
223 *support for the new version, SDTM 4.1, and updates the Data Standards Catalog. The*  
224 *effective date posted in the Federal Register notice is March 15, 2017. Although the new*  
225 *SDTM version 4.1 is supported by FDA as of May 6, 2016 and sponsors or applicants are*  
226 *encouraged to begin using it, the new version will only be required in submissions for*  
227 *studies that start after March 15, 2018. The Data Standards Catalog will list March 15,*  
228 *2018 as the “date requirement begins.”*

229  
230 *Example 2: CDISC releases a data exchange standard SDTM 4.1.1 as a version update*  
231 *to SDTM 4.1 on September 18, 2016. The version update SDTM 4.1.1 includes*  
232 *clarifications and corrections to typographical errors in SDTM version 4.1, but no new*  
233 *content or structural changes. FDA will determine when it is able to support the updated*  
234 *version, SDTM 4.1.1, but generally FDA testing will not be required for version updates*  
235 *for errata. On October 3, 2016, FDA updates the Data Standards Catalog indicating*

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<sup>13</sup> For purposes of this guidance, the study start date is the earliest date of informed consent among any subject that enrolled in the study. For example, see Study Start Date in the SDTM Trial Summary Domain (TSPARMCD = SSTDTC), <http://www.cdisc.org>.

236 support for the new version, SDTM 4.1.1. The effective date posted in the Federal  
237 Register notice is March 15, 2017. Although the new SDTM version 4.1.1 is supported  
238 by FDA as of October 3, 2016 and sponsors or applicants are encouraged to begin using  
239 it, the new version will only be required in submissions for studies that start after March  
240 15, 2018, according to the date when SDTM 4.1 was supported by FDA (see example 1  
241 above). The Data Standards Catalog will list March 15, 2018 as the “date requirement  
242 begins.”

243  
244 *Example 3: On January 15, 2018, the SDO releases the PDF version 2.X file format as*  
245 *an update to PDF version 1.7. Following the release by the SDO, FDA will execute an*  
246 *acceptance testing process to determine whether it is able to support PDF version 2.X for*  
247 *study data submissions. The acceptance testing process confirms that FDA is able to*  
248 *support the updated version. On June 28, 2018, FDA publishes a Federal Register notice*  
249 *of availability announcing support for the new version, PDF 2.X, and updates the Data*  
250 *Standards Catalog. The effective date posted in the Federal Register notice is March 15,*  
251 *2019. Although the new PDF version is supported by FDA and sponsors or applicants*  
252 *are encouraged to begin using it, PDF 2.X will only be required in submissions for*  
253 *studies that start after March 15, 2020. The Data Standards Catalog will list March 15,*  
254 *2020 as the “date requirement begins.”*

### 255 256 3. New Standards, Formats and Terminologies

257  
258 After this guidance is finalized (and the 24- and 36 month milestones discussed above have been  
259 reached), FDA may announce in a *Federal Register* notice of availability (and guidance, if  
260 necessary) its support for new standards, formats and terminologies. New standards, formats and  
261 terminologies are those that have not been supported by FDA and are not listed in the Data  
262 Standards Catalog at the time this draft guidance is finalized. The *Federal Register* notice of  
263 availability will specify the effective date for new standards, formats and terminologies that will  
264 correspond to a specific calendar month (e.g., in the examples below, March). New standards,  
265 formats or terminologies will be required in submissions for studies that start 24 months (for  
266 NDAs, ANDAs, and certain BLAs) and 36 months (for certain INDs) after the publication of a  
267 notice of availability in the *Federal Register*.

268  
269 The following is an example of a new standard and how it would be implemented:

270  
271 *Following an evaluation, pilot testing, and public input, FDA publishes a Federal*  
272 *Register notice on March 15, 2016 announcing the retirement of the SAS Transport File*  
273 *Format version 5 standard, FDA’s support of a new open study data transport standard,*  
274 *and FDA’s update to the Data Standards Catalog. The effective date posted in the*  
275 *Federal Register notice is March 15, 2017. Although the new study data transport*  
276 *standard will be supported by FDA as of March 15, 2016 and sponsors or applicants will*  
277 *be encouraged to use it, the new standard for study data transport will only be required*  
278 *in submissions for studies that start after March 15, 2019. The Data Standards Catalog*  
279 *will list March 15, 2019 as the “date requirement begins.”*

281 **III. ADDITIONAL SUPPORT**

282

283 **A. Meetings with FDA**

284

285 Sponsors and applicants may use established FDA-sponsor meetings (e.g., pre-IND, and end-of-  
286 phase 2) to discuss the study data standardization plan and quality parameters, and raise data  
287 standardization issues (if any). Discussions about nonclinical study data standardization plans  
288 may be initiated at the pre-IND stage and should continue throughout development. Initial  
289 discussions about which data standards to use for clinical study data should take place as early as  
290 possible during drug development, especially for safety data, but should occur no later than the  
291 end of phase 2. In general, the premarketing application meeting is considered too late to initiate  
292 data standardization discussions.

293

294 Sponsors and applicants may submit technical questions related to data standards at any time to  
295 the technical support team identified by each Center (see the Study Data Standards Resources  
296 Web page for specific contact information<sup>14</sup>). Sponsors and applicants may also request a  
297 separate Type C meeting to discuss substantive data standardization issues. An example of such  
298 an issue might be a sponsor's desire to use a non-supported standard. The request should include  
299 adequate information to identify the appropriate FDA staff necessary to discuss the proposed  
300 agenda items.

301

302 **B. Implementation Support**

303

304 The Draft Study Data Technical Conformance Guide (Conformance Guide) provides nonbinding  
305 specifications, recommendations, and general considerations on how to submit standardized  
306 study data. The Conformance Guide supplements the requirements described in this guidance  
307 and is intended to assist sponsors and applicants in the electronic submission of standardized  
308 study data. Once FDA completes its review of the draft Conformance Guide, including  
309 comments submitted (if any), the Agency will publish a notice in the *Federal Register*  
310 announcing the availability on the FDA Web site of the final Conformance Guide. After the  
311 Conformance Guide is finalized, FDA will update the Conformance Guide on a regular basis and  
312 announce the availability of any updates in a *Federal Register* notice.

313

314 Sponsors and applicants with questions on how to implement the FDA-supported study data  
315 standards should contact and work with FDA technical staff. Contact information is provided on  
316 the Study Data Standards Resources Web page. Sponsors and applicants may also arrange to  
317 submit sample data for a pre-submission technical review. The technical staff also welcomes  
318 any additional feedback or comments regarding the information posted on the Web page.

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<sup>14</sup> <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>.