
Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications Guidance for Industry and FDA Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Quynh Nhu Nguyen, 301-796- 6273, 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)**

**September 2018
Procedural**

Contains Nonbinding Recommendations

Draft — Not for Implementation

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications Guidance for Industry and FDA Staff

Additional copies are available from:

Office of Communications, Division of Drug Information

Center for Drug Evaluation and Research

Food and Drug Administration

10001 New Hampshire Ave., Hillandale Bldg., 4th Floor

Silver Spring, MD 20993-0002

Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

Email: druginfo@fda.hhs.gov

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

and/or

Office of Communication, Outreach and Development

Center for Biologics Evaluation and Research

Food and Drug Administration

10903 New Hampshire Ave., Bldg. 71, Room 3128

Silver Spring, MD 20993-0002

Phone: 800-835-4709 or 240-402-8010

Email: ocod@fda.hhs.gov

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

**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)**

**September 2018
Procedural**

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	SUBMISSION TYPES, COVER LETTER, AND FDA FORMS.....	3
	A. Types of Submissions.....	3
	B. Cover Letter	3
	C. Form FDA 1571 or Form FDA 356h.....	3
IV.	CONTENTS OF THRESHOLD ANALYSES AND HUMAN FACTORS SUBMISSIONS	4
	A. Use-Related Risk Analysis.....	4
	B. Human Factors Validation Study Protocol	5
	C. Human Factors Validation Study Report.....	7
	D. Threshold Analyses.....	9
	E. Comparative Use Human Factors Study Protocol.....	10
	F. Comparative Use Human Factors Study Results Report.....	11
V.	WHERE TO SEND A THRESHOLD ANALYSIS OR HUMAN FACTORS SUBMISSION	12
	A. Drug Products, Including Biologics, and Combination Products, That Are the Subject of an IND Paper Submission	13
	B. Drug-Device Combination Products Under Development for Submission Under ANDA	13
	C. Electronic Submissions	14
VI.	REVIEW TIMELINE	14
VII.	HOW TO OBTAIN ADDITIONAL INFORMATION.....	15
VIII.	REFERENCES.....	16
	GLOSSARY.....	18
	APPENDIX A	21
	APPENDIX B	22
	APPENDIX C	22
	APPENDIX D	23

Contains Nonbinding Recommendations

Draft — Not for Implementation

1 **Contents of a Complete Submission for Threshold Analyses and**
2 **Human Factors Submissions to Drug and Biologic Applications**
3 **Draft Guidance for Industry and FDA Staff¹**
4

5
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
10 for this guidance as listed on the title page.
11

12
13
14
15 **I. INTRODUCTION**
16

17 This document provides guidance to industry and FDA staff on the contents of and submission
18 procedures for *threshold analyses*² and human factors (HF) submissions³ that will support
19 efficient Agency review, and presents timelines for FDA’s review of such submissions.⁴
20

21 This guidance applies to the following types of products⁵:

- 22
- 23 • Human prescription drug products, including biologics, that are the subject of an
24 investigational new drug application (IND)⁶, a new drug application (NDA), a
25 biologics license application (BLA), or an abbreviated new drug application
26 (ANDA),⁷ and supplements to these applications
27
 - 28 • Human nonprescription drug products that are the subject of an IND, NDA, or ANDA
29

¹ This guidance has been prepared by the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health, and the Office of Combination Products (OCP) at the Food and Drug Administration.

² All terms presented in *bold italic* at first use in this guidance are defined in the Glossary.

³ See section III of this guidance for the types of submissions.

⁴ This document is one of several documents FDA is issuing to fulfill the performance goals under the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI). This document also provides information on what to include in submissions for products under other user fee programs.

⁵ This includes combination products. See definition of combination product in 21 CFR 3.2. For the purposes of this guidance, we are referring to combination products assigned to CDER or CBER as the lead center.

⁶ Sponsors can engage FDA on human factors issues as early as the pre-IND phase.

⁷ The recommendations in this guidance apply to ANDA submissions covering drug-device combination products.

Contains Nonbinding Recommendations

Draft — Not for Implementation

30 All such products in this guidance are jointly referred to as *products*,⁸ and persons responsible
31 for making submissions are referred to as *sponsors*.

32
33 This guidance does not describe when threshold analyses or HF submissions are warranted for
34 any particular application pathway, the processes or procedures associated with their review, or
35 the methods used by the Agency for evaluation. Furthermore, this guidance does not describe the
36 methods used to design, conduct, or analyze HF studies. In addition to the information described
37 in this guidance, FDA recommends that sponsors refer to other relevant guidance documents
38 related to product design and human factors (see section VIII).

39
40 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
41 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
42 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
43 the word *should* in Agency guidances means that something is suggested or recommended, but
44 not required.

45

46

47 **II. BACKGROUND**

48

49 The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that drug products submitted
50 for approval under section 505(b) be proven safe and demonstrate substantial evidence of
51 effectiveness for the product’s intended use (21 U.S.C. 355(b)). Under section 351 of the Public
52 Health Service Act, FDA licenses a biological product based on a demonstration that it is safe,
53 pure, potent, and it is manufactured in a facility designed to ensure that the product continues to
54 be safe, pure, and potent.

55

56 As part of evaluating drug and biologic products for safety and effectiveness, FDA will evaluate
57 HF data submitted by sponsors in support of the product *user interface* when submission of such
58 data is warranted. For products that sponsors intend to submit as an ANDA, the sponsor can rely
59 on the Agency’s previous finding that its listed drug is safe and effective so long as the sponsor
60 can demonstrate certain findings.⁹ Certain products, including drug-device combination products,
61 may warrant threshold analyses and additional data, such as data from comparative HF studies.¹⁰

62

⁸ For purposes of this guidance, unless otherwise specified, references to “products” include drugs submitted for approval or approved under sections 505(b) or 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b) or 355(j)) and biological products licensed under section 351 of the PHS Act.

⁹ See Section 505(j)(2)(A), 505(j)(4) of the FD&C Act (21 U.S.C. 355(j)(2)(a), 355(j)(4)); 21 CFR 314.127.

¹⁰ See draft guidance for industry and FDA staff *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Comparative Analyses Draft Guidance), available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf>. 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 Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

63 **III. SUBMISSION TYPES, COVER LETTER, AND FDA FORMS**

64

65 **A. Types of Submissions**

66

67 Listed below are the different threshold analysis and human factors submission types:

68

69 1) *Use-Related Risk Analysis*

70

71 2) *HF Validation Study Protocol*

72

73 3) *HF Validation Study Results Report*

74

75 4) *Threshold Analyses*

76

77 5) *Comparative Use HF Study Protocol*

78

79 6) *Comparative Use HF Study Results Report*

80

81 See section IV for information regarding the content of each submission type listed in this
82 section:

83

84 **B. Cover Letter**

85

86 Each submission should include a cover letter that includes the statement “**REQUEST FOR**
87 **[*Type of Submission*] REVIEW**” in bolded capital letters.

88

89 For submission amendments, the cover letter should include the statement “**AMENDMENT TO**
90 **REQUEST FOR [*Type of Submission*] REVIEW**” in bolded capital letters.¹¹

91

92 See Appendix A for examples.

93

94 **C. Form FDA 1571 or Form FDA 356h**

95

96 All electronic submissions should include only fillable forms and electronic signatures to enable
97 automated processing. A submission that is the subject of an active IND should include Form
98 FDA 1571, “Investigational New Drug Application (IND).” A submission that is the subject of a
99 marketing application should include Form FDA 356h, “Application to Market a New or
100 Abbreviated New Drug or Biologic for Human Use.” Refer to the FDA Forms website for the
101 latest versions of these forms and their corresponding instruction files.¹²

102

103

¹¹ See section VI for additional considerations for amendments.

¹² See the FDA Forms website for latest versions of forms and instruction files at:
<http://www.fda.gov/aboutfda/reportsmanualsforms/forms/default.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

104 IV. CONTENTS OF THRESHOLD ANALYSES AND HUMAN FACTORS 105 SUBMISSIONS 106

107 This section describes the information that a sponsor should include for each respective
108 submission type.
109

110 A. Use-Related Risk Analysis¹³ 111

112 A comprehensive use-related risk analysis may be a separate submission or may be included as
113 part of another submission (e.g. with the HF validation study protocol (see section IV.B) or
114 Human Factors Engineering (HFE) Report (see section IV.C)).¹⁴ The risk analysis submission
115 should include:
116

- 117 • A comprehensive and systematic evaluation of all the steps involved in using the
118 proposed product (e.g., based on a *task analysis*)
119
- 120 • The errors that intended product *users* might commit or the tasks they might fail
121 to perform, taking into consideration known problems with similar products
122
- 123 • The potential negative clinical consequences of *use errors* and task failures
124 including the severity of the resulting harm
125
- 126 • User task description and categorization (e.g., critical)
127
- 128 • The mitigation strategies employed to reduce identified risks or eliminate hazards
129
- 130 • The proposed methods used to validate these mitigation strategies
131
- 132 • Description of intended product users, uses, *use environments*, and training (if
133 applicable)
134
- 135 • Graphical depiction and written description of product user interface (see
136 Appendix C for example)
137
- 138 • Summary of known use problems with previous or similar products¹⁵

¹³ ANSI/AAMI/ISO 14971, *Medical Devices – Application of risk management to medical devices*, defines risk as the combination of the probability of occurrence of harm and the severity of the potential harm. However, because probability is very difficult to determine for use errors, and in fact many use errors cannot be anticipated until product use is simulated and observed, the severity of the potential harm may be more meaningful for determining the need to eliminate (design out) or reduce resulting harm. Therefore, it may be appropriate when conducting the use-related risk analysis to focus on the resulting harm, and including estimated occurrence rates may not be needed.

¹⁴ See guidance *Applying Human Factors and Usability Engineering to Medical Devices* available at <https://www.fda.gov/downloads/medicaldevices/.../ucm259760.pdf>

¹⁵ In certain circumstances, there may be post-marketing experience that is relevant to the product under consideration. Such information might include known use problems with previous models of the subject product or known use problems with similar products.

Contains Nonbinding Recommendations

Draft — Not for Implementation

139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177

- Summary of preliminary analyses and evaluations, including ***formative evaluation***

See Appendix B for an example of how to present some of the key information for a use-related risk analysis.

A sponsor can employ the use-related risk analysis to identify the need for risk mitigation strategies and to design an HF validation study that adequately evaluates the risk mitigation strategies. In circumstances where, based on the use-related risk analysis and other information, a sponsor determines that an HF validation study is not needed, the sponsor may submit the use-related risk analysis and other information, together with the justification for not conducting a HF validation study, for review under the IND.

B. Human Factors Validation Study Protocol

Sponsors should include the following elements in the submission:

1. Background

- Description of intended product users, uses, use environments, and training (if applicable)
- Graphical depiction and written description of product user interface (see Appendix C for example), including the intend-to-market ***labels*** and ***labeling*** that will be evaluated in the HF validation study
 - For Instructions for Use (IFUs), in addition to an intended commercial printed layout version, sponsors should provide a Word version to facilitate the exchange of labeling comments and revisions between the sponsor and FDA.¹⁶
- Summary of known use problems with previous or similar products¹⁷
- Summary of preliminary analyses and evaluations, including formative evaluations; a discussion of key findings; and any changes made to the user interface (e.g., device constituent part design change, labeling changes), as well as a discussion of how the sponsor used the formative evaluation results and findings to update the product user interface and use-related risk analysis

¹⁶ Submitting the IFU document in a Word version is consistent with recommendations to submit labeling content to FDA as part of a marketing application; see draft guidance *SPL Standard for Content of Labeling Technical Qs & As*. 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 Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹⁷ In certain circumstances, there may be post-marketing experience that is relevant to the product under consideration. Such information might include known use problems with previous models of the subject product or known use problems with similar products.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
2. Analysis of **hazards** and risks associated with use of the product in a use-related risk analysis
 3. **HF validation testing** details
 - a. Study objective(s)
 - b. Type of testing (**simulated-use** vs. actual use)¹⁸
 - c. Test environment and conditions¹⁹
 - d. Training provided to participants and rationale for how it corresponds to real-world training and **training decay** (if applicable)
 - e. Distinct user groups by number and type of test participants²⁰
 - f. User task description and categorization (e.g., critical)²¹ and a description of use scenarios that include critical tasks
 - g. Definition of successful performance or failure of each test task
 - h. Description of data (e.g., data collected from observational tasks, knowledge tasks, and subjective interview) to be collected and methods for documenting
 - i. Methods for root cause analysis of all use errors, difficulties, and **close calls**²²
 - j. Moderator script

¹⁸ See draft guidance for industry and FDA staff *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (Combination Products Human Factors Draft Guidance), available at <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>, for further discussion of simulated vs. actual use studies. When final, this guidance will represent the FDA's current thinking on this topic.

¹⁹ A rationale for how the testing environment and conditions of testing is representative of real-world use is helpful. In identifying conditions of testing, sponsors should consider aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, in dim lighting, or in noisy situations.

²⁰ When describing study participants and how they represent distinct user populations (groups), it is helpful to describe the characteristics that distinguish the groups and that can affect user interaction with the product (e.g., limited hand dexterity, cognitive deficit).

²¹ The selection of user tasks can be derived from the comprehensive use-related risk analysis. Tasks that could lead to harm (e.g., underdose or overdose), including those requiring the user to respond to alerts or alarms, should be categorized as critical and prioritized for testing. A task requiring comprehension of warnings, caution statements, or contraindications in the product labels or labeling would generally be considered a critical knowledge task. See *Combination Products Human Factors Draft Guidance*, available at <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>, for definition of critical tasks.

²² While close calls and difficulties may not manifest into use errors/task failures, they are good sources of data in terms of providing potential user interface inadequacies that should be further evaluated.

Contains Nonbinding Recommendations

Draft — Not for Implementation

207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241

4. Product samples (5 samples of product that will be tested in the HF validation)²³

C. Human Factors Validation Study Report²⁴

Sponsors should include the following elements in their submission:

1. Summary of findings and conclusions
 - a. Conclusions based on HFE process²⁵
 - b. Brief summary of validation study results
 - c. Discussion of whether additional risk mitigation measures are necessary
 - i. If additional mitigation measures are needed, the study report should include a description of the additional mitigation measures and justify whether additional validation testing is not warranted. However, if additional validation testing is needed, the results should be submitted within the report.
 - d. Discussion of *residual use-related risks* versus benefits of the product
2. Background²⁶
 - a. Brief summary of *Human Factors Engineering* processes applied throughout the development of the product
 - b. Descriptions of intended product users, uses, use environments, and training (if applicable)
 - c. Graphical depiction and written description of user interface (see Appendix C), including the intend-to-market labels and labeling that were evaluated in the HF validation study

²³ FDA recognizes that in some circumstances, the ability to provide the requested quantity of samples may not be feasible. In this instance, we recommend you contact FDA for further guidance.

²⁴ The contents of the HF validation study report are intended to be equivalent to the contents outlined in Appendix A of the guidance *Applying Human Factors and Usability Engineering to Medical Devices*.

²⁵ If the HFE process identifies no use errors or problems that could result in harm, the sponsor should discuss how the validation study results supports a conclusion of safe and effective use by the end user. Otherwise, the sponsor should include a discussion of why the existing mitigations are effective and why the Agency should find the residual risks acceptable in the report. The discussion should incorporate findings from the entire HFE process.

²⁶ If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 242 d. Summary of known use problems with previous products or similar products
243
244 e. Summary of preliminary analyses and evaluations, including formative
245 evaluations
246
247 i. The summary should include a discussion of key findings and any
248 changes made to the product design and its labeling based on key
249 findings, and should explain how the sponsor used the formative
250 results and findings to update the product user interface and risk
251 analysis.
252
253 f. Reference to previous HF validation study protocol submission, description
254 of changes made to the protocol after prior feedback from the FDA, and
255 description of any protocol deviations that occurred during the study
256
257 3. Analysis of hazards and risks associated with use of the product in a use-related
258 risk analysis²⁷
259
260 4. HF validation testing details
261
262 a. Study objective(s)
263
264 b. Rationale for test type selected (simulated-use or actual use)²⁸
265
266 c. Test environment and conditions of use
267
268 d. Training provided to test participants and how it will correspond to real-world
269 training levels and training decay (if applicable)
270
271 e. Distinct user groups broken out by number and type of test participants
272
273 f. ***User tasks*** description and categorization and a description of use scenarios
274 that include critical tasks
275
276 g. Definition of successful performance or failure of each test task
277
278 h. Test results and analysis (see example in Appendix D)
279
280 i. Observations of task performance, including occurrences and
281 description of use errors, close calls, and use difficulties

²⁷ If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

²⁸ See Combination Products Human Factors Draft Guidance for further discussion of simulated vs. actual use studies. When final, this guidance will represent the FDA's current thinking on this topic

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 282 ii. Documentation of subjective data from study participants regarding
- 283 product use, use errors, close calls and use difficulties.
- 284 iii. Root cause analysis of all use errors, difficulties, and close calls and
- 285 discussion of risk mitigation strategies

- 286
- 287 5. Product samples (5 samples of intend-to-market product) ²⁹
- 288

D. Threshold Analyses

289 Threshold analyses generally are utilized in comparing two drug products. For these analyses,
290 sponsors should include the following elements in their submission:

- 291 1. Labeling comparison (a side-by-side, line-by-line comparison between the
- 292 proposed product and the product it references that includes the full prescribing
- 293 information, instructions for use, container labels and carton labeling, and
- 294 descriptions of the products)
- 295
- 296 2. Comparative task analysis³⁰ (a comparative task analysis of the proposed product
- 297 and the product it references)
- 298
- 299 3. Physical comparison of the device constituent part(s) (e.g., examine, through a
- 300 visual or tactile examination, the physical features of the product that it plans to
- 301 reference and compare them to those of the proposed product)
- 302
- 303 4. Sponsor's determination of whether design differences exist and, if so, whether
- 304 they are characterized as minor design differences or other design differences,³¹
- 305 and the rationale for each characterization
- 306
- 307
- 308
- 309

²⁹ FDA recognizes that in some circumstances, the ability to provide the requested quantity of samples may not be feasible. In this instance, we recommend you contact FDA for further guidance.

³⁰ To conduct a comparative task analysis, sponsors should systematically dissect the use process for each product (i.e., for both the proposed product and the product it references) and analyze and compare the sequential and simultaneous manual and cognitive activities for end-users interacting with each product. FDA recommends that sponsors analyze the differences with the goal of characterizing the potential for use error. See the Association for the Advancement of Medical Instrumentation/American National Standards Institute HE75: 2009-Human factors engineering—Design of medical devices, available at: http://my.aami.org/aamiresources/previewfiles/HE75_1311_preview.pdf. Presenting this information in a side-by-side comparison table can help to facilitate FDA evaluation of this information.

³¹ For further discussion on identifying design differences and characterizing design difference(s), see Comparative Analyses Draft Guidance, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf> and draft guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>. When final, these guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

310 5. Product samples (5 samples each of the proposed product and the product it
311 references)³²

312

E. Comparative Use Human Factors Study Protocol³³

314

315 Sponsors should include the following elements in their submission:

316

317 1. Background, including description of the intended product users, uses, and use
318 environments

319

320 2. Threshold analyses (see section IV.D, above)³⁴

321

322 3. Comparative use HF testing details

323

324 a. Study objective(s)

325

326 b. Type of testing (simulated-use vs. actual use)³⁵

327

328 c. Statistical analysis plan (SAP) and sample size considerations (including
329 proposed analyses and all assumptions, as well as literature references or other
330 justification supporting the methods or assumptions)

331

332 d. Test environment and conditions of testing

333

334 e. Distinct user groups broken out by number and type of test participants

335

336 f. User task description and categorization (e.g., critical)³⁶ and a description of
337 use scenarios that include critical tasks

338

339 g. Definition of successful performance or failure of each test task

340

341 h. Description of data (e.g., data collected from observational tasks, knowledge
342 tasks, and subjective interview) to be collected and methods for documenting

343

³² FDA recognizes that in some circumstances, the ability to provide the requested quantity of samples may not be feasible. In this instance, we recommend you contact FDA for further guidance.

³³ Potential applicants intending to submit a drug-device combination product under an ANDA are strongly encouraged to discuss the results of the threshold analyses with the Agency via the controlled correspondence or pre-ANDA submission pathways, or both, prior to conducting comparative use human factors studies.

³⁴ If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

³⁵ See Combination Products Human Factors Draft Guidance for further discussion of simulated vs. actual use studies.

³⁶ In some instances, it may be appropriate to focus the selection of user tasks on the critical tasks related to the external critical design attributes found to be different between the proposed product and the product it references.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 344 i. Methods for evaluating error rates
345
346 j. Moderator script
347 4. Product samples (5 samples each of the proposed product and the product it
348 references that will be tested in the comparative use HF study)³⁷
349

F. Comparative Use Human Factors Study Results Report

350
351
352 Sponsors should include the following elements in the submission:

- 353
354 1. Summary of study findings and conclusions
355
356 ▪ Conclusions³⁸
357
358 ▪ Brief summary of study results
359
360 2. Background³⁹
361
362 a. Descriptions of intended product users, uses, and use environments
363
364 b. Reference to previous protocol submission, description of changes made to
365 the protocol after prior feedback from the FDA, and description of any
366 protocol deviations that occurred during the study
367
368 3. Threshold analyses (see section IV.D, above)⁴⁰
369
370 4. Comparative use HF testing details
371
372 a. Study objective(s)
373
374 b. Rationale for test type selected (simulated-use or actual use)⁴¹
375

³⁷ FDA recognizes that in some circumstances, the ability to provide the requested quantity of samples may not be feasible. In this instance, we recommend you contact FDA for further guidance.

³⁸ A comparative use human factors study should be designed to provide sufficient data to confirm that the use error rate for the critical task(s), as impacted by the differing external critical design attribute of the device constituent part(s) for the proposed generic combination product, is not worse than the corresponding use error rate for the RLD when used by patients and caregivers in representative use scenarios and use environments consistent with the labeled conditions of use. See Comparative Analyses Draft Guidance for further discussion.

³⁹ If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

⁴⁰ If previously submitted, cross-reference the prior submission and include the eCTD sequence number and date of submission. Sponsors should not resubmit the electronic files when referencing that document.

⁴¹ See Combination Products Human Factors Draft Guidance for further discussion of simulated vs. actual use studies.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- c. SAP and sample size considerations (including analyses and all assumptions, as well as literature references or other justifications supporting the methods or assumptions)
- d. Test environment and conditions of use
- e. Distinct user groups broken out by number and type of test participants
- f. Critical tasks and use scenarios included in testing
- g. Definition of successful performance or failure of each test task
- h. Test results and analysis
 - i. Use error rates and analysis
 - ii. Observations of task performance, including occurrences of use errors

V. WHERE TO SEND A THRESHOLD ANALYSIS OR HUMAN FACTORS SUBMISSION

Generally, FDA expects that sponsors will submit threshold analyses or HF submissions consistent with the respective regulatory pathway. Sponsors should submit an HF validation study protocol and questions regarding the protocol to the IND. For proposed generic products, sponsors should submit threshold analyses, device assessments, and questions via the controlled correspondence or pre-ANDA submission pathways, or both, as appropriate. Comparative use HF study protocols should be submitted within a specific pre-ANDA meeting request.

It is recommended that all sponsors plan their development timelines to allow for Agency feedback on protocols prior to initiation and conduct of the appropriate HF study. In addition, sponsors should submit HF validation study results reports or comparative use HF study results reports in their application for FDA review (i.e., NDA, BLA, or ANDA).

Submissions to a Commercial IND, NDA, BLA, or ANDA must be made in Electronic Common Technical Document (eCTD) format.⁴² Submissions to a Research IND⁴³ may be in paper or electronic format. For paper submissions, sponsors should submit 3 copies to the appropriate address below.

⁴² See guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (Using eCTD Specifications Guidance); see also section 745A(a) of the FD&C Act (21 U.S.C. 379k-1(a)).

⁴³ See FDA's web page on Investigational New Drug (IND) Application at <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454

A. Drug Products, Including Biologics, and Combination Products, That Are the Subject of an IND Paper Submission

1. Human Factors Submissions for Prescription or Nonprescription Drugs, Including Biologics, That Are the Subject of an IND Reviewed by CDER

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

2. Human Factors Submissions for Prescription or Nonprescription Biologics That Are the Subject of an IND Reviewed by CBER

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
Bldg. 71, Rm. G112
Silver Spring, MD 20993-0002

B. Drug-Device Combination Products Under Development for Submission Under ANDA

1. Controlled Correspondence

Sponsors seeking FDA’s feedback on a specific element in the development of a drug-device combination product (e.g., identification and assessment of identified differences between the user interface of a proposed generic combination product and its reference listed drug) should submit the correspondence through the process outlined in FDA’s draft guidance *Controlled Correspondence Related to Generic Drug Development*.⁴⁴ This will facilitate prompt consideration of and response to the controlled correspondence by the appropriate discipline.

2. Pre-ANDA Meeting

A request for a product development or pre-submission meeting for complex products that may be submitted in an ANDA should be sent through the process outlined in FDA’s draft guidance for industry [*Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*](#) (Generic Drug User Fee Act). The meeting request should clearly identify in the subject line that the prospective applicant is requesting a product development or pre-submission

⁴⁴ We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

455 meeting and should include adequate information for FDA to assess the potential utility of the
456 meeting and identify the appropriate staff that should attend the meeting.

457

C. Electronic Submissions

459

460 The sponsor should place the request for HF submission review in Module 1.2 and associated
461 documents (e.g. use-related risk analysis, protocols, reports) in Module 5, section 5.3.5.4 – Other
462 Study Reports and Related Information in eCTD.

463

464 The eCTD leaf title of the document should be clear, concise, and indicative of the content.

465 Examples include:

466

467 • HF - REQUEST FOR HUMAN FACTORS VALIDATION STUDY PROTOCOL
468 REVIEW

469

470 • HF - AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION STUDY
471 PROTOCOL REVIEW

472

473 • HF - REQUEST FOR HUMAN FACTORS VALIDATION STUDY REPORT REVIEW

474

475 • HF - AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION STUDY
476 REPORT REVIEW

477

478 • HF-REQUEST FOR HUMAN FACTORS VALIDATION OTHER REVIEW⁴⁵

479

480 • HF-AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION OTHER
481 REVIEW

482

483 The sponsor should also provide the eCTD location of the contents of the HF submission on the
484 cover letter and, if possible, include cross-document links or external bookmarks to the
485 information. This approach will help ensure that the information can be accessed quickly and
486 easily. For further information on providing leaf titles and study results reports (including file-
487 tags) in eCTD, see the eCTD Technical Conformance Guide.⁴⁶

488

489

VI. REVIEW TIMELINE

490
491

⁴⁵ For the purposes of the eCTD, there are three options: protocols, reports, or other. “Other” includes use-related risk analyses and threshold analyses.

⁴⁶ The eCTD Technical Conformance Guide is available at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

492 The Agency intends to review and comment on HF validation study protocol submissions in
493 accordance with PDUFA VI performance goals.⁴⁷ The review clock for the performance review
494 goals begins when the Agency receives a ***complete submission***. FDA will:

- 496 • By fiscal year (FY) 2019, review 50% of HF protocol submissions and provide the
497 sponsor with written comments within 60 days
- 498
- 499 • By FY 2020, review 70% of HF protocol submissions and provide the sponsor with
500 written comments within 60 days
- 501
- 502 • By FY 2021, review 90% of HF protocol submissions and provide the sponsor with
503 written comments within 60 days
- 504

505 If, after submitting an HF validation study protocol, a sponsor submits additional questions,
506 unsolicited revisions to the protocol, or a lengthy or complex response to an FDA question, or
507 amends original submission materials with new information for any reason, FDA ordinarily will
508 not respond to the original questions and will consider the original protocol submission
509 withdrawn. FDA will consider submission of a revised protocol, or revised or additional
510 supporting materials, to be a new submission with a new 60-day timeline for response.

511
512 FDA will review all threshold analyses or comparative use HF submissions consistent with good
513 review management principles and practices, as applicable, and in a timeframe to support any
514 applicable performance goals under FDA's various user fee programs, taking into consideration
515 the specific circumstances (e.g. breakthrough designation) surrounding the individual
516 application.

VII. HOW TO OBTAIN ADDITIONAL INFORMATION

521 FDA encourages industry to meet with the Agency when appropriate⁴⁸ to obtain Agency advice
522 during product development. Meetings should not be used to obtain Agency review of HF
523 validation study protocols or reports.

524
525 Prior to submitting an ANDA for a generic combination product, sponsors are encouraged to
526 submit a controlled correspondence⁴⁹ or pre-ANDA meeting package, or both,⁵⁰ when
527 appropriate.

⁴⁷ PDUFA VI reauthorization performance goals and procedures for fiscal years 2018 through 2022, Section I.1.5.e, available at: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>.

⁴⁸ Please refer to Guidance for Industry *Formal Meetings between FDA and Sponsors or Applicants*, available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>.

⁴⁹ Draft guidance for industry, *Controlled Correspondence Related to Generic Drug Development*, available at: <https://www.fda.gov/downloads/drugs/guidancecomplianceinformation/guidances/ucm583436.pdf>. 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 Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁵⁰ Please refer to draft guidance for industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*, available at

Contains Nonbinding Recommendations

Draft — Not for Implementation

528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568

VIII. REFERENCES

Applicable guidance documents relating to HF, product design, requesting meetings with the Agency, and providing electronic submissions include those listed below:

- A. Guidance documents related to HF
- Draft Guidance on [*Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*](#)
 - Draft guidance for industry [*Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*](#)
 - Draft guidance for industry [*Considerations in Demonstrating Interchangeability With a Reference Product*](#)
 - Guidance for industry and FDA staff [*Applying Human Factors and Usability Engineering to Medical Devices*](#)
- B. Guidance documents related to product design
- Guidance for industry [*Safety Considerations for Product Design to Minimize Medication Errors*](#)
 - Draft guidance for industry [*Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*](#)
- C. Guidance on requesting meetings with Agency
- Draft guidance for industry [*Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*](#)
 - Draft guidance for industry, [*Controlled Correspondence Related to Generic Drug Development*](#)
 - Draft guidance for industry, [*Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*](#)

<https://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm578366.pdf>. 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 Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 569
- 570
- 571
- 572
- 573
- 574
- 575
- 576
- 577
- 578
- Guidance for industry and review staff [*Best Practices for Communication Between IND Sponsors and FDA During Drug Development*](#)
 - D. Guidance on providing electronic submissions
 - Guidance for industry [*Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*](#)

Contains Nonbinding Recommendations

Draft — Not for Implementation

GLOSSARY

579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623

Applicant or sponsor: The entity that submits proposed Threshold Analyses or HF submissions for the following types of products:

- Prescription drug products (including biologics) that are the subject of an NDA (21 CFR 314.3(b)), a BLA (21 CFR 601.2), or an ANDA (21 CFR 314.92), or that are currently the subject of an IND (21 CFR 312.3(b)) in anticipation of the submission of a marketing application
- Nonprescription drug products that are the subject of an IND, NDA, or ANDA

Close calls: Instances in which a user almost makes a use error that could result in harm, but the user takes an action to “recover” and prevent the use error from occurring.

Comparative Use Human Factors Study Protocol: A study protocol for a proposed combination product that describes the design and methodology for a comparative use human factors study.

Comparative Use Human Factors Study Results Report: A study report that provides the results of a comparative use human factors study.

Complete submission: The information FDA identifies for a sponsor to include to ensure that the Agency can conduct a complete review of a proposed Human Factors Validation Study Protocol.

Critical task: A user task which, if performed incorrectly or not performed at all, may cause harm to the patient or user, where “harm” includes compromised medical care.

Formative evaluation: The process of assessing, at one or more stages during the product development process, a user interface or user interactions with the user interface in order to identify the interface’s strengths and weaknesses and to identify potential use errors that would or could result in harm to the patient or user.

Hazard: A potential source of harm.

Human Factors Engineering: The application of knowledge about human behavior, abilities, limitations, and other characteristics of medical device users when designing medical devices, including mechanical and software-driven user interfaces, systems, tasks, user documentation, and user training, to demonstrate and enhance safe and effective use. HF engineering and usability engineering can be considered synonymous.

Human Factors Validation Study Protocol: A study protocol that describes the design and methodology for a human factors validation study.

Contains Nonbinding Recommendations

Draft — Not for Implementation

624 **Human Factors Validation Study Results Report:** A study report that provides the results of a
625 human factors validation study.

626
627 **Human factors validation testing:** Testing conducted at the end of the product development
628 process to assess user interactions with a product user interface and to identify use errors that
629 may result in serious harm to the patient or user. Human factors validation testing is also used to
630 assess the effectiveness of risk management measures. Human factors validation testing
631 represents one portion of design validation.

632
633 **Label:** As defined in section 201(k) of the FD&C Act (21 U.S.C. 321(k)), the term *label* means
634 “a display of written, printed, or graphic matter upon the immediate container of any article.”

635
636 **Labeling:** As defined in section 201(m) of the FD&C Act (21 U.S.C. 321(m)), the term *labeling*
637 means “all labels and other written, printed, or graphic matter (1) upon any article or any of its
638 containers or wrappers, or (2) accompanying such article.” Labeling includes outside containers
639 or wrappers and package liners.

640
641 **Medication error:** The National Coordinating Council for Medication Error Reporting and
642 Prevention describes *medication error* as any preventable event that may cause or lead to
643 inappropriate medication use or patient harm while the medication is in the control of the health
644 care professional, patient, or consumer. Such events may be related to professional practice,
645 health care products, procedures, and systems, including prescribing; order communication;
646 product labeling, packaging, and nomenclature; compounding; dispensing; distribution;
647 administration; education; monitoring; and use.⁵¹

648
649 **Residual use-related risks:** The risks that remain after risk control measures have been taken.

650
651 **Simulated-use testing:** Testing of a product under conditions of use that mimic real-world use
652 conditions without administering the actual therapy to patients.

653
654 **Task:** An action or set of actions performed by a user to achieve a specific goal.

655
656 **Task Analyses:** A systematic breakdown of device use process into discrete sequences of
657 tasks.⁵²

658
659 **Threshold analyses:** Conducted to identify differences (if any) that may exist between the
660 proposed combination product’s user interface and the product it references. Consist of labeling
661 comparison, comparative task analysis, and physical comparison of the device constituent
662 part(s).⁵³

663

⁵¹ National Coordinating Council for Medication Error Reporting and Prevention web page, available at:
<http://www.nccmerp.org/aboutMedErrors.html>.

⁵² See an example of a task analysis in Guidance for Industry and FDA Staff titled “Applying Human Factors and Usability Engineering to Medical Devices,” available at <https://www.fda.gov/downloads/MedicalDevices/.../UCM259760.pdf>.

⁵³ See Comparative Analyses Draft Guidance.

Contains Nonbinding Recommendations

Draft — Not for Implementation

664 **Training decay:** The time elapsed between receiving training and first product use.

665

666 **Use environment:** The environment(s) in which the product will be used. This may include a
667 variety of settings, such as clinical settings or home settings.

668

669 **Use error:** A user action, or lack of action, that was different from that expected by the
670 manufacturer and that caused an outcome that (1) was different from the result expected by the
671 user, (2) was not caused solely by product failure, and (3) did or could result in harm.

672

673 **Use-related risk analysis:** An analytical method to identify use errors associated with each use
674 step, and then the hazards/risks and clinical significance of those hazards/risks. The use-related
675 risk analysis includes a comprehensive and systematic evaluation of all the steps involved in
676 using the product (e.g., based on a task analysis), the errors that users might commit or the tasks
677 they might fail to perform (considering known problems for similar products), the potential
678 negative clinical consequences of use errors and task failures, the mitigation strategies, and
679 methods for validating the risk mitigation strategies.

680

681 **User:** A person who interacts with (i.e., operates or handles) the product.

682

683 **User interface:** All components of the product with which the user interacts, including the
684 device constituent part(s) of the product and any associated controls and displays, as well as
685 product labels, labeling, and packaging.

686

Contains Nonbinding Recommendations

Draft — Not for Implementation

APPENDIX A

EXAMPLE OF STATEMENTS TO INCLUDE IN THE COVER LETTER

- 1) For use-related risk analysis reviews, include the statement “**REQUEST FOR USE-RELATED RISK ANALYSIS REVIEW**” in bold capital letters.
- 2) For amendments to use-related risk analysis reviews, include the statement “**AMENDMENT TO REQUEST FOR USE-RELATED RISK ANALYSIS REVIEW**” in bold capital letters.
- 3) For HF protocol reviews, include the statement “**REQUEST FOR HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW**” in bold capital letters.
- 4) For amendments to HF protocols, include the statement “**AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW**” in bold capital letters.
- 5) For HF study results reports, include the statement “**REQUEST FOR HUMAN FACTORS VALIDATION STUDY REPORT REVIEW**” in bold capital letters.
- 6) For amendments to HF study results reports, include the statement “**AMENDMENT TO REQUEST FOR HUMAN FACTORS VALIDATION STUDY REPORT REVIEW**” in bold capital letters.
- 7) For comparative use HF threshold analyses reviews, include the statement “**REQUEST FOR THRESHOLD ANALYSES REVIEW**” in bold capital letters.
- 8) For amendments to comparative use HF threshold analyses reviews, include the statement “**AMENDMENT TO REQUEST FOR THRESHOLD ANALYSES REVIEW**” in bold capital letters.
- 9) For comparative use HF protocol reviews, include the statement “**REQUEST FOR COMPARATIVE USE HUMAN FACTORS PROTOCOL REVIEW**” in bold capital letters.
- 10) For amendments to comparative use HF protocol reviews, include the statement “**AMENDMENT TO REQUEST FOR COMPARATIVE USE HUMAN FACTORS PROTOCOL REVIEW**” in bold capital letters.
- 11) For comparative use HF study results report reviews, include the statement “**REQUEST FOR COMPARATIVE USE HUMAN FACTORS REPORT REVIEW**” in bold capital letters.

Contains Nonbinding Recommendations

Draft — Not for Implementation

733
734
735
736
737
738
739
740
741
742

- 12) For amendments to comparative use HF study results report review, include the statement “**AMENDMENT TO REQUEST FOR COMPARATIVE USE HUMAN FACTORS REPORT REVIEW**” in bold capital letters.

APPENDIX B


EXAMPLE OF USE-RELATED RISK ANALYSIS

Task No.	Use task description	Description of potential use errors	Potential hazards/harm and severity ⁵⁴	Critical task (Yes/No)	Risk mitigation measure for each use error	Evaluation method in HF validation study
4	Press green button and hold for 10 seconds	Button is held for less than 10 seconds	Full dose is not injected; leads to patient death	Yes	Redesign product to eliminate the need to hold for 10 seconds	Evaluated in HF validation study in use scenario 1: Administration of Drug, task 4

743
744
745
746
747
748

APPENDIX C

EXAMPLE OF DESCRIPTION OF USER INTERFACE

Interface Item	Written description of the user interface	Graphical depiction of the user interface
Inspection Window	The user inspects the window to ensure that the drug color is clear and drug solution does not have any particulates	

749
750

⁵⁴ Describe potential hazard/harm and severity for each potential use error.

Contains Nonbinding Recommendations

Draft — Not for Implementation

APPENDIX D

HYPOTHETICAL EXAMPLE OF HF VALIDATION DATA

751
752
753
754
755
756
757
758
759
760

A hypothetical example of the results of analyzing human factors validation study data are shown in the table below. Analysis of human factors validation study data should focus on any problems found during the testing. The study data should be analyzed to determine which part of the user interface was involved and how the user interaction could have resulted in the use error or problem.

Description of Tasks (denote C for critical)	Number of use errors and description of use errors	Number of close calls and use difficulties ⁵⁵ and description of close calls and use difficulties	Study participant's subjective feedback ⁵⁶	Sponsor's Root cause analysis ⁵⁷	Sponsor's Discussion of Mitigation strategies ⁵⁸
Task 4: Press green button and hold for 10 seconds (C)	1 use error. The user did not press the green button for 10 seconds, he only held it for 5 seconds.	0 close calls or use difficulties	The user heard a second click and stopped pressing the button because he thought the injection was complete based on the click.	Root cause analysis showed that the user interface has audible cues that do not coincide with the labeled hold time and contribute to confusion.	Product was redesigned to align the audible cues to the "hold time" needed to deliver the drug. This change impacts a critical task for drug delivery. Thus, the change was evaluated in another validation study conducted to demonstrate the effectiveness of this change to the user interface.

761

⁵⁵ While close calls and difficulties may not manifest into actual use errors/failures, they are good source of data in terms of providing potential user interface inadequacies that should be further evaluated.

⁵⁶ What the participant(s) say about the use errors/close calls/use difficulties from their perspective.

⁵⁷ This should incorporate the sponsor's analysis of the subjective data obtained from study participants clarifying why or how the use errors and failures occurred from the participant's perspective. Some questions to consider: What did study participants say about the errors/failures? Did they say how/why the errors/failures occurred? Did they comment on any aspect of the user interface that may have influenced their behavior/action while they were performing the task? Did they note any suggested user interface improvements?

⁵⁸ This should address whether additional product modifications, risk mitigations, or risk mitigation validation should be implemented as necessary.