

Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA: Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Food and Drug Administration
Center for Devices and Radiological Health
Center for Drug Evaluation and Research
Center for Biological Evaluation and Research
Office of Combination Products in the Office of the Commissioner
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1 **Technical Considerations for Demonstrating Reliability of**
2 **Emergency-Use Injectors Submitted under a BLA, NDA, or ANDA**
3 **Guidance for Industry and Food and Drug Administration Staff**¹
4

5 *This draft guidance, when finalized, will represent the current thinking of the Food and Drug*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

10
11
12 **I. INTRODUCTION**
13

14 This guidance covers emergency-use injectors submitted under a biologics license application
15 (BLA), new drug application (NDA), or abbreviated new drug application (ANDA). The term
16 “emergency-use injector” means injectors marketed with an emergency-use drug² as a prefilled
17 single entity combination product under 21 CFR 3.2(e)(1) or as a co-packaged combination
18 product under 21 CFR 3.2(e)(2). Emergency-use injector includes pen injectors, autoinjectors, or
19 on-body-wearable delivery systems for drugs for emergency treatment of conditions such as
20 anaphylaxis, opioid overdose, poisoning, or severe hypoglycemia.

21
22 For injectable drug or biological products that are intended to treat emergent, life-threatening
23 conditions, it is essential to ensure that the emergency-use injector will reliably deliver the drug
24 as intended. Failure of the injector may prevent adequate delivery of a life-saving drug to a
25 patient. In this context, reliability is defined as the probability that the injector will perform as
26 intended, without failure, for a given time interval under specified conditions.³
27

28 The FDA guidance document, “*Technical Considerations for Pen, Jet, and Related Injectors*
29 *Intended for Use with Drugs and Biological Products*” provides general recommendations for
30 the technical and scientific information to be included in marketing applications for a range of
31 injectors for various uses.⁴ In that document the reliability of the injector in delivering the drug
32 product is listed as one of the functional elements FDA assesses in premarket review. This

¹ This guidance has been prepared by the Center for Devices and Radiological Health in cooperation with the Center for Drug Evaluation and Research, the Center for Biologic Evaluation and Research, and the Office of Combination Products in the Office of Medical Products and Tobacco/ Office of Clinical Policy and Programs/ Office of the Commissioner at the Food and Drug Administration.

² For purposes of this guidance, unless otherwise stated, the term drug applies to human drug and biological products.

³ Reliability definition source: IEC 61078:2016 - Reliability Block Diagrams. Some Agency guidance documents use the term robustness to convey the reliability concept.

⁴ The FDA guidance *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* is accessible at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-pen-jet-and-related-injectors-intended-use-drugs-and-biological-products>.

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33 document describes additional information and data that FDA recommends be included in
34 marketing applications to demonstrate that an emergency-use injector is reliable.

35
36 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
37 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
38 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
39 the word *should* in Agency guidances means that something is suggested or recommended, but
40 not required.

41 42 II. SCOPE

43
44 This guidance’s focus is emergency-use injectors marketed with the emergency-use drug as a
45 prefilled single entity combination product or as a co-packaged combination product.⁵ The
46 recommendations in this guidance are applicable to combination products intended to treat
47 emergent, life-threatening conditions, when it is essential to ensure that the injector will reliably
48 deliver the drug as intended.⁶ Such products are marketed as combination products assigned to
49 the Center for Drug Evaluation and Research (CDER) or the Center for Biological Evaluation
50 and Research (CBER) with market authorization under an approved NDA, ANDA, or BLA.⁷

51
52 Although this guidance contains specific recommendations of ways to demonstrate the reliability
53 of emergency-use injectors,⁸ the recommendations would also be useful in considering how to
54 demonstrate the reliability of other emergency-use drug delivery devices; e.g., intranasal sprays,
55 inhalation devices, topical cutaneous sprays, syringes, or transdermal systems. Questions
56 regarding whether these recommendations would apply to a specific emergency-use drug
57 delivery system and proposed methods to demonstrate the reliability should be discussed with
58 the Agency early in the product development process.⁹

59

⁵ See 21 CFR part 3. Combination products are comprised of differently regulated articles; i.e., a drug-device, device-biological product, drug-biological product, or a combination of a drug, device, and biological product. See 21 CFR 3.2(e)(1) and (2) for definitions of single entity and co-packaged combination products.

⁶ The reliability data discussed within this guidance document is limited to assessing functional performance of the device and does not address human factors/user interface considerations. For information on human factors see FDA guidance: *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-factors-studies-and-related-clinical-study-considerations-combination-product-design-and>; or FDA guidance *Applying Human Factors and Usability Engineering to Medical Devices*, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices>.

⁷ See 21 CFR 3.4. Combination Products are assigned to a lead center based on the primary mode of action (PMOA). In this instance, the drug or biological product is considered to be the PMOA and the combination products are assigned to CDER or CBER. For additional information contact the Office of Combination Products at combination@fda.gov.

⁸ Throughout this document the term emergency-use injector applies to the device constituent part of the combination product.

⁹ Applicants developing an emergency-use injector or similar product for an ANDA should request Agency feedback on the potential applicability of the recommendations in this guidance document.

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III. REGULATORY FRAMEWORK

Combination products are subject to 21 CFR Part 4, which sets forth current good manufacturing practice (CGMP) requirements for combination products. The constituent parts of a combination product retain their regulatory status (as a drug or device, for example) after they are combined. The CGMP requirements that apply to each of the constituent parts apply to the combination product they constitute.

For single-entity combination products and co-packaged combination products, such as those covered in this guidance, part 4 identifies two ways to demonstrate compliance with CGMP requirements. Under the first option, manufacturers demonstrate compliance with all CGMP regulations applicable to each of the constituent parts included in the combination product. Under the second option, manufacturers implement a streamlined approach for combination products that include both a drug and device by demonstrating compliance with either the drug CGMPs (21 CFR parts 210 and 211) or the device Quality System (QS) regulation (21 CFR part 820) and also demonstrating compliance with specified provisions from the other two sets of CGMP requirements.

Under the streamlined approach described in 21 CFR 4.4(b), manufacturers of drug-led, drug-device combination products,¹⁰ such as those that are the subject of this guidance, may meet the requirements of both the drug CGMPs and device QS regulation by designing and implementing a CGMP operating system that demonstrates compliance with the drug CGMPs and the following provisions from the device QS regulation in accordance with 21 CFR 4.4(b)(1) (drug CGMP-based streamlined approach):

- 21 CFR 820.20 Management responsibility
- 21 CFR 820.30 Design controls
- 21 CFR 820.50 Purchasing controls
- 21 CFR 820.100 Corrective and preventive action
- 21 CFR 820.170 Installation
- 21 CFR 820.200 Servicing

As explained in the FDA guidance for *“Current Good Manufacturing Practice Requirements for Combination Products*, “the core requirements embedded in these regulations provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. This includes establishing a strong quality management system, using appropriate quality raw materials, establishing robust manufacturing and control procedures based on sound design principles, and detecting and investigating product quality deviations. In addition, these

¹⁰ A biological product regulated under section 351 of the Public Health Service Act is also, by definition, a drug or a device. Accordingly, for combination products that include a biological product, in addition to complying with the drug CGMP and device QS regulation requirements as applicable in accordance with 21 CFR part 4, manufacturers of such products must comply with the CGMP requirements in 21 CFR parts 600 through 680 that would apply to the biological product if it were not part of a combination product. 21 CFR 4.4(b)(3).

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98 regulations call for ongoing assessment of systems and the implementation of corrective actions
99 where appropriate.”¹¹

100 IV. BACKGROUND ON RELIABILITY

101
102
103 Emergency-use injectors such as those for treatment of anaphylaxis typically are used by the
104 patient, caregiver, or first responder outside of a health care environment. For the patient
105 experiencing the emergency or their assisting lay caregivers, there may be only one opportunity
106 to use the product and for that one opportunity the emergency-use injector needs to successfully
107 inject the drug at that time. Further, because these emergency-use injectors are for a single use,
108 the functional performance cannot be verified before the injector is used. Therefore, to ensure
109 safe and effective use of the emergency-use injector, FDA recommends using the reliability
110 engineering methods described in this guidance to ensure that the injector will function as
111 intended within its expiration date. Designing the combination product to achieve its identified
112 functional performance (reliability) is consistent with the combination product good
113 manufacturing practice design control requirements provisions (see 21 CFR 4.4(b)(1)(ii) and
114 4.4(b)(1)(iv)).

115
116 Although the requirements of both the drug CGMPs and device QS regulation must be met, as
117 described in Section III above, several aspects of the design requirements identified in 21 CFR
118 4.4(b)(1)(ii) are particularly important in the development and reliability of an emergency-use
119 injector. For example,

- 120
121 • 21 CFR 820.30(c) states that “[e]ach manufacturer shall establish and maintain
122 procedures to ensure that the design requirements relating to a device are appropriate and
123 address the intended use of the device, including the needs of the user and patient.”
- 124
125 • 21 CFR 820.30(d) states that “[e]ach manufacturer shall establish and maintain
126 procedures for defining and documenting design output in terms that allow an adequate
127 evaluation of conformance to design input requirements. Design output procedures shall
128 contain or make reference to acceptance criteria and shall ensure that those design
129 outputs that are essential for the proper functioning of the device are identified.”
- 130
131 • 21 CFR 820.30(f) states that “[e]ach manufacturer shall establish and maintain
132 procedures for verifying the device design. Design verification shall confirm that the
133 design output meets the design input requirements. The results of the design verification,
134 including identification of the design, method(s), the date, and the individual(s)
135 performing the verification, shall be documented in the DHF.” Moreover, 21 CFR
136 820.30(g) states that “[e]ach manufacturer shall establish and maintain procedures for
137 validating the device design. Design validation shall be performed under defined
138 operating conditions on initial production units, lots, or batches, or their equivalents.
139 Design validation shall ensure that devices conform to defined user needs and intended

¹¹ See Section II.B accessible at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products>.

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140 uses and shall include testing of production units under actual or simulated use
141 conditions.”

- 142
- 143 • 21 CFR 820.30(h) states that “[e]ach manufacturer shall establish and maintain
144 procedures to ensure that the device design is correctly translated into production
145 specifications.”
 - 146
 - 147 • 21 CFR 820.30(i) states that “[e]ach manufacturer shall establish and maintain
148 procedures for the identification, documentation, validation or where appropriate
149 verification, review, and approval of design changes before their implementation.”
 - 150
 - 151 • 21 CFR 820.100 states that “each manufacturer shall establish and maintain procedures
152 for implementing corrective and preventive action.”
 - 153

154 FDA considers that “the needs of the user and patient” (21 CFR 820.30(c)) in an emergency-use
155 context would be that, for the patient experiencing the emergency or his/her assisting lay
156 caregiver, there is only one opportunity to use the product and, thus, FDA has found emergency-
157 use injectors acceptable if they would successfully inject the drug on the first try. In this
158 instance, the design input requirements would provide functional measures for performance
159 characteristics, specifications for how reliably the emergency-use injector functions, and the use
160 condition of the patient or caregiver. This would include identification of a reliability
161 specification that is consistent with the level of risk to the patient if the emergency-use injector
162 does not function (e.g., the morbidity or mortality associated with untreated anaphylactic shock).

163

164 In addition, FDA interprets the requirements under 21 CFR 820.30(f) and (g) to mean that a
165 manufacturer of an emergency-use injector must verify and validate the design of the injector to
166 ensure that it works in “one opportunity” situations. These requirements can be met, for
167 example, if available documentation demonstrates that (1) the emergency-use injector has met its
168 design input requirements within the specified reliability targets at expiry and (2) design
169 validation has been conducted on finished products to ensure reliability targets are met and that
170 test conditions were representative of how the product would be exposed up to expiry.

171

172 The preceding design control requirements are intended to ensure that the emergency-use
173 injector performance is as reliable as possible. Consistent with this purpose, FDA has found
174 emergency-use injectors to be acceptable if they would successfully inject on the first try in “one
175 opportunity” (or emergency) situations. This reliability concept has an inherent feasibility
176 consideration. FDA recommends that emergency-use injectors include design control
177 specifications for successful injection reliability of 99.999% with a 95% level of confidence. As
178 FDA has found such specifications to be acceptable under applicable standards. This prospective
179 99.999% target is equivalent to post-market detection of failure to successfully inject in
180 1/100,000 injection attempts. This reliability level was found to balance appropriately the
181 objective of ensuring the emergency-use injector performance is as safe and reliable as possible
182 with considerations on feasibility.

183

184 As part of determining an acceptable level of reliability, FDA has considered available
185 information for risk assessment. Specifically, the FDA-recognized standard, ISO 14791 -

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186 *Application of risk management to medical devices*, provides insight regarding probabilities of
187 occurrence.¹² In the standard, examples are provided for semi-quantitative analysis that
188 identifies probable, remote, and improbable events rates. In the standard, events occurring in the
189 range of 1/10,000 detection rate are considered to be probable. In FDA review experience, this
190 probable failure rate is likely associated with unacceptable rates of adverse events for
191 emergency-use injectors that may result in product recalls. In the standard, events occurring less
192 than a 1/1,000,000 detection rate are considered to be improbable. Although the lowest possible
193 failure rates are desirable, FDA believes that based on the standard rates and current technology,
194 that the improbable rate of less than 1/1,000,000 detection rate could result in drug shortage or
195 delayed product availability. In contrast to both of the preceding rates, events occurring within
196 1/100,000 to 1/1,000,000 detection rate are considered as a remote probability of occurrence.
197 Therefore, based on the ISO standard, FDA believes the detection of failure to successfully inject
198 in 1/100,000 injection attempts is an appropriate risk management target for ensuring successful
199 injection and treatment when there is only one opportunity to inject. Further, FDA review of
200 recent marketing applications demonstrates that the reliability target of 99.999% with a 95%
201 level of confidence (i.e., 1/100,000 failure to successfully inject rate) is achievable for these
202 emergency-use injectors.

203
204 The following information provides the details of an example of what FDA currently believes
205 would be an acceptable approach for the mathematical model, statistics, fault tree analysis, and
206 use of combination product current good manufacturing design control requirements provisions
207 (21 CFR 4.4(b)(1)(ii) and 4.4(b)(1)(iv)) to establish reliability of the emergency-use injector.
208 FDA recognizes that as an alternative to the approach discussed in this guidance, applicants may
209 propose other reliability specifications methodologies. For example, based on considerations
210 such as product design, drug being delivered, for emergent unmet medical needs, counter-
211 terrorism considerations, or conditions of use, alternative reliability specifications may be
212 appropriate. During emergency-use injector development FDA encourages applicants to seek
213 FDA meetings to discuss their proposals and rationale (e.g., context of use, risk/benefit, shortage,
214 and supportive data).

215 216 Establishing reliability

217
218 Establishing reliability is an iterative process in which the design controls should focus on
219 emergency-use injector attributes determined to be essential for achieving the emergency-use
220 injector's intended use.¹³ The level of reliability necessary to manufacture a safe and effective
221 combination product directly correlates to the level of risk associated with an unreliable emergency-
222 use injector. Because reliability as a mathematical model is defined as $R(t) = 1 - F(t)$, where $F(t)$
223 represents the cumulative distribution function of failure, the goal should be to define the point at
224 which that distribution, $F(t)$, is adequately controlled. The reliability specification(s), $R(t)$,
225 represents the probability that the emergency-use injector will perform as intended, without failure,

¹² ISO 14971:2007/R(2016) *Medical Devices - Application of risk management to medical devices*; Section 3.4.2
Semi-quantitative analysis.

¹³ For more information on design controls for a combination product see 21 CFR Part 4 Subpart A, and related
FDA guidance *Current Good Manufacturing Practice Requirements for Combination Products* accessible at
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products>.

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226 for a given time interval under specified conditions. This level of risk should be identified in the
227 risk analysis conducted as part of device design controls activities.¹⁴

228
229 This assessment is specific to the combination product's intended use because the risks are likely
230 to be impacted by the condition being treated, environments of use, emergency-use injector
231 technology, drug, user characteristics, etc. The emergency-use injector reliability analysis, in
232 addition to the traditional development activities, should incorporate the following device design
233 control activities as applicable to the emergency-use injector:

- 234
- 235 • Identification of the reliability requirements and specifications;
 - 236 • Risk analysis;
 - 237 • Design verification and validation of the reliability requirements and specifications; and
 - 238 • Design transfer of the reliability specification to the correct production specifications.
- 239

240 As described in Section IV Background on Reliability, after transfer of the design into
241 production, the manufacturing controls must be adequate to produce reliable emergency-use
242 injectors as specified.¹⁵ These controls should, among other required activities, include the
243 following to ensure the design specifications and tolerances that must be achieved during
244 production and that all sources of potential quality problems are analyzed:

- 245
- 246 • Adequate manufacturing in-process controls and release activities to ensure the final
247 finished emergency-use injector conforms to its specifications;
 - 248 • Adequately defined acceptance activities for the supplied components to ensure that the
249 manufactured combination product has the required design attributes to ensure the
250 reliability specifications are achieved; and
 - 251 • Establish and maintain procedures for implementing corrective and preventive action
252 (CAPA) activities (e.g., post-market complaints) to ensure that all sources of quality data
253 are analyzed and, where necessary, preventive or corrective actions are taken.¹⁶
- 254

255 In addition to providing assurance of the emergency-use injector reliability, the advantages of a
256 well-constructed reliability analysis include the following life-cycle management benefits in the
257 linkage between the design and manufacturing controls.

- 258
- 259 • The least reliable design elements or manufacturing controls of an emergency-use
260 injector can be identified prior to commercialization of the combination product. This
261 can further inform potential improvements in manufacturing controls, tracking or
262 trending limits of part rejects, and future investigations of failed combination products;
 - 263 • Future changes to either design or manufacturing processes can be evaluated against the
264 reliability analysis to assess the potential impact to the emergency-use injector reliability;
 - 265 • Post-market emergency-use injector failure investigations can directly link to the
266 emergency-use injector reliability analysis to readily identify gaps or deficiencies in the
267 emergency-use injector's design and/or manufacturing controls; and

¹⁴ See 21 CFR 820.30(g).

¹⁵ See 21 CFR 820.30(h).

¹⁶ See 21 CFR 820.100.

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- 268 • Once the results of those specific design elements or manufacturing controls are
269 understood within the context of the overall reliability analysis, if the reliability analysis
270 is implemented early in the development cycle, reliability improvements can be made by
271 making changes to the emergency-use injector design or manufacturing processes or
272 controls.

273
274 Section V below provides an example of an acceptable way to demonstrate the reliability of the
275 emergency-use injector and define failure to successfully inject.

276

277 V. RELIABILITY REPORT DEVELOPMENT AND CONTENT 278 RECOMMENDATIONS FOR PREMARKET SUBMISSIONS

279

280 As discussed in Section IV, achieving the necessary reliability specification is based on
281 knowledge of the design, manufacture, and use of the combination product. Generally, the
282 highest risk is failure to successfully inject (e.g., activation and drug delivery functions). This
283 occurs when one or more functional failure modes result in the emergency-use injector failure to
284 deploy the needle to the target site or failure to complete drug delivery as intended. As described
285 in Section IV Background on Reliability, FDA has found emergency-use injectors to be
286 acceptable if they would successfully inject in “one opportunity” (or emergency) situations. As
287 stated above, FDA has found emergency-use injectors to be acceptable under the applicable
288 standards when they include design control specifications for successful injection reliability of
289 99.999% with a 95% level of confidence.

290

291 To establish the emergency-use injector’s safe and effective injection performance, the
292 marketing application should include information to verify and validate that the emergency-use
293 injector achieves its reliability specifications and related information. The following sections
294 identify examples of acceptable activities for developing the verification and validation data. If
295 applicants submit such information, FDA recommends that the applicants provide these data in
296 the form of an emergency-use injector reliability report to facilitate efficient review.¹⁷ The
297 following subsections provide examples of the type of information to provide in the reliability
298 report. Section VI of this guidance provides a reliability report format example.

299

300 1. Design Inputs and Design Outputs Necessary¹⁸ for Ensuring Reliability

301

302 As described in Section IV, specifications for how reliably the emergency-use injector
303 functions and the use condition of the patient or caregiver need to be identified.¹⁹ The design
304 inputs necessary for ensuring reliability should be identified and developed into specified
305 design outputs. Selecting design inputs that may not be relevant to the reliable function of
306 the emergency-use injector could result in an inability to meet the manufacturer’s established
307 reliability specifications. To assist in identifying design input requirements, manufacturers
308 should consider the following information:

¹⁷ Throughout the remainder of this document the term “reliability report” applies to the emergency-use injector reliability report.

¹⁸ See 21 CFR 820.30(c) and 820.30(d).

¹⁹ See 21 CFR 820.30(c).

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- Intended use and associated risks;
 - Emergency-use injector risk analysis, including the drug constituent part characteristics;
 - Use-related issues to the extent that they could impact the reliability of the combination product, including:
 - o Use tasks, which may include unpacking, preparation, administration and disposal of the combination product; and
 - o Use conditions and environments of use.
 - Use-condition factors²⁰ to consider include all users of the emergency-use injector, where they are using it, and the possible circumstances under which the emergency-use injector may be used, including:
 - o Use environment (e.g., school, work, public transportation vehicle, harsh climates, first responder chaotic conditions) and associated risks to reliability; and
 - o User characteristics (e.g., self- injection with cognitive or physical impairment associated with the disorder being treated) and associated risks to reliability.

325 Table -1 provides an example of emergency-use injector design considerations for
326 emergency-use injector reliability only.²¹

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328

329

330 (See next page for Table-1.)

331

²⁰ The use condition factors discussed within this guidance document are limited to assessing functional performance of the emergency-use injector and do not address human factors/user interface considerations. For information on human factors see FDA guidance: *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (Draft 2016)*, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-factors-studies-and-related-clinical-study-considerations-combination-product-design-and-> or *Applying Human Factors and Usability Engineering to Medical Devices*, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices>.

²¹ Other types of input or output considerations for the safe and effective use of the emergency-use injector should continue to be part of the combination product development. For more information see FDA guidance *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* accessible at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-pen-jet-and-related-injectors-intended-use-drugs-and-biological-products>.

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Table-1: Emergency-Use Injector Design Reliability Development Considerations²²	
Consideration Category	Examples
Protective Packaging	<ul style="list-style-type: none"> • Packaging ability to prevent emergency-use injector damage during shipping, daily carry, etc. • Removal from packaging or carrying case (e.g., force to remove)
Removal / Deactivation of Safety Mechanisms	<ul style="list-style-type: none"> • Force to remove caps or needle shields • Force to deactivate safety mechanism
Activation Force	<ul style="list-style-type: none"> • Force to initiate the injection mechanism
Needle Insertion	<ul style="list-style-type: none"> • Needle bevel specifications • Needle material of construction • Needle Insertion Forces (e.g., penetrating clothing, skin, etc.) • Needle resistance to bending and fracture
Needle Patency	<ul style="list-style-type: none"> • Particulates
Injection Depth	<ul style="list-style-type: none"> • Target tissue for drug delivery • Body habitus, skin and tissue characteristics • Anatomical location(s) for injection • Types of garments to be injected through • Exposed needle length
Drug Delivery Initiates as Intended	<ul style="list-style-type: none"> • Needle reaches intended injection depth • Drug delivery begins when needle is at intended injection depth • Drug fluid properties (e.g., viscosity)
Drug Delivery Stops as Intended	<ul style="list-style-type: none"> • Needle does not retract before intended dose is delivered • Audible, visual, or tactile feedback does not prematurely signal a completed injection
Dose Accuracy	<ul style="list-style-type: none"> • Intended dose delivered to intended injection site or depth

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The preceding tabular considerations are to assist in identifying the emergency-use injector performance characteristics that inform the design inputs and outputs. Based on such considerations the applicant should develop the design inputs and outputs that are essential for ensuring reliability of the applicant’s proposed product. The reliability report should define all the design inputs and outputs determined to be necessary for achieving reliability. It is important to clearly define the difference between acceptable and unacceptable emergency-use injector performance to determine appropriate design inputs that will inform

²² For more information on development design controls for a combination product see 21 CFR Part 4 Subpart A, and see related FDA guidance *Current Good Manufacturing Practice Requirements for Combination Products* accessible at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products>.

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340 the design outputs. If the design outputs are not correctly defined, then the overall reliability
341 analysis may also be inadequate.

342

343 2. Definition of Emergency-Use Injector Reliability Specifications

344

345 As noted in the preceding discussion on design inputs and outputs, there are multiple design
346 specifications that should be considered with respect to the reliability of the emergency-use
347 injector. Using the mathematical expression identified in Section IV, $R(t) = 1 - F(t)$, the
348 reliability specification is defined as the probability distribution, $R(t)$. An example of
349 acceptable reliability specifications is those that are developed in accordance with the risk
350 assessment as described in Section V.3 – Fault Tree Analysis of this document and, through
351 this analysis, linked to the appropriate manufacturing controls to ensure the reliability of the
352 final finished combination product. The specifications may be one or two-sided depending
353 upon the risk associated with the failure (e.g., risk of overdose and under-dose exists for a
354 two-sided dose-accuracy reliability specification).

355

356 For the reliability specification analysis, failure to inject should be the primary endpoint.
357 This should be the top-level failure mode of the fault tree analysis as described in Section
358 V.3.²³ The reliability analysis and testing should include emergency-use injector
359 performance requirements based on the assessment of the design (see Section V.1). In
360 general, FDA recommends that these include dose accuracy, extended needle length,
361 activation force, and injection time be included as part of emergency-use injector
362 reliability.²⁴ However, manufacturers should assess the specific emergency-use injector
363 design to determine if additional performance attributes are considered to be essential for
364 completing a successful injection. For example, a specific design may have a cap that must
365 be removed to initiate injection and the manufacturer may determine that cap removal is
366 essential to completing a successful injection.

367

368 3. Fault Tree Analysis

369

370 The information described in the preceding sections could be used to develop a model of the
371 reliability using fault tree analysis. The fault tree analysis would focus on failure to achieve
372 the reliability specifications. An example of an acceptable analysis is one that also includes
373 additional fault trees to address other emergency-use injector performance requirements
374 determined to be essential for reliability (e.g., dose accuracy, extended needle length).

375 Manufacturers should consider the following for their fault tree analyses:

376

- 377 • Design and manufacturing elements should be considered for the fault tree analysis
378 for the purposes of establishing the reliability of the emergency-use injector to
379 perform as intended, without failure, for a given time interval under specified
380 conditions;

²³ For more information of fault tree analyses see IEC 61025:2006 – Fault Tree Analysis (FTA); NASA Fault Tree Handbook with Aerospace Applications, 2006.

²⁴ The acceptance criteria for the performance attributes in Table-2 should be established based on relevance to clinical performance (i.e., established as design inputs), and not based on manufacturing capability or to facilitate meeting the reliability target.

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- 381 • The probability data for each basic event²⁵ should be included in the fault tree;
- 382 • The analysis should consider potential common cause failures and whether
- 383 assumptions of independence of events are supportable;
- 384 • Any risk analyses (e.g., such as design and process failure modes effects analysis)²⁶
- 385 used to support the fault tree analysis should be included in the reliability report;
- 386 • Once the fault tree analyses are completely developed, data should be provided to
- 387 support that the reliability specification for the top-level failure mode is verified and
- 388 validated (e.g., the probability data for each basic event should be supported with
- 389 evidence); and,
- 390 • The basic events in the fault tree analysis should be linked to appropriate design
- 391 and/or manufacturing controls.

392

393 Based on standard fault tree analysis quantification methods, the reliability of each basic
394 event within the fault tree analysis should be assessed through a cumulative analysis to
395 determine whether the reliability specification for the top-level failure mode is adequately
396 supported. The statistical methods utilized to demonstrate the reliability of each basic event
397 within the fault tree analysis should inform the test sample size necessary for reliability
398 testing of the final finished combination product. To assess the potential for the basic event
399 failure mode of the emergency-use injector, it is important to use a statistical tolerance
400 interval²⁷ method in which the limits of each individual component are analyzed (e.g.,
401 dimensions, geometry, material strength, etc.),²⁸ both by itself and in conjunction with its
402 associated components (i.e., stack-up analysis). To effectively use the tolerance interval
403 method, the critical measurable elements of each component contributing to the basic event
404 should be clearly stated and the statistical tolerance limit²⁹ identified. Data to support the
405 tolerance interval methodology should be provided and may include process validation data
406 for individual components. The resultant *k* factor³⁰ for each basic event should be used to
407 calculate the necessary sample size of the reliability study based on the desired reliability
408 specification and confidence interval.

409

410 An example of acceptable use of the statistical tolerance interval methodology is one
411 described above.³¹ An acceptable methodology should evaluate both design and

²⁵ The basic event is a failure mode event or state that cannot be further developed; i.e., the lowest level failure mode that cannot be further subdivided.

²⁶ ISO 14971 Second edition 2007-Medical devices - Application of risk management to medical devices; and IEC 60812:2006 - Analysis techniques for system reliability - Procedure for failure mode and effects analysis (FMEA). (FDA recognized standards.)

²⁷ Statistical tolerance interval is an interval determined from a random sample in such a way that one may have a specified level of confidence that the interval covers at least a specified proportion of the sampled population per ISO 3534-1:2006. (FDA recognized standards.)

²⁸ ISO 16269-6 Second edition 2014 – Statistical interpretation of data - Determination of statistical tolerance intervals. (FDA recognized standards.)

²⁹ Statistical tolerance limit is the statistic representing an end-point of a statistical tolerance interval per ISO 3534-1:2006. (FDA recognized standards.)

³⁰ The *k* factor is the variable used to determine the limits of a statistical tolerance interval per ISO 16269-6:2014.

³¹ There are other methods that may also be appropriate to support the fault tree analysis and overall reliability specifications. If a manufacturer intends to use a method not described in this guidance document, the FDA

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412 manufacturing risks associated with the emergency-use injector such that the fault tree
413 analysis is assessing reliability of the final, finished combination product. (See Section VIII -
414 Appendix for a fault tree analysis template example.)

415

416 4. Reliability Testing

417

418 FDA recommends that a reliability analysis include verifying and validating the adequacy of
419 the data used to support the reliability specifications, and that the data support the reliability
420 specification over the combination product expiry period. The following subsections
421 describe information recommendations for preconditioning and testing reliability samples.

422

423 a. Use Conditions and Preconditioning Recommendations

424

425 To identify the reliability test conditions to ensure achievement of the reliability
426 specification at the end of use-life,³² it is important to define the combination product's
427 use conditions and preconditioning steps. This ensures that the testing program has
428 adequately challenged the ability of the emergency-use injector to withstand stressors that
429 are likely to occur or to which the product will be exposed during the use-life.

430 Combination product-specific use-life factors to consider for preconditioning steps that
431 influence shelf-life may include the following preconditions:

432

433 • Shipping;

434 • Aging;

435 • Storage orientation and conditions;

436 • Vibration;

437 • Shock (e.g., resistance to impacts, such as being dropped); and

438 • Environmental factors:

439 o Temperature (extremes and cyclic);

440 o Altitude and pressure effects (e.g., airplane, submarine, or other above/below
441 sea-level effects); and

442 o Air particulates (dust/sand).

443

444 FDA recommends that the reliability report include the following information to help
445 establish the acceptability of the use of accelerated testing to generate supporting data:

446

447 • Validation data to ensure that the accelerated methods accurately model the time-
448 dependent failure mechanisms of the emergency-use injector;

449 • Results of testing at various time points to identify any trends in emergency-use
450 injector performance; and

encourages the manufacturer to request a meeting to discuss the validity of the proposed approach for supporting the reliability specification.

³² Use-life begins when the product manufacture is complete and ends on the date when the product cannot function as intended (the expiration date). For the combination product, the expiration date also may be described as shelf life or end of use-life of the drug-device combination product.

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- 451
- A statistical justification to ensure that the sample size at the final time point is
452 adequate to support the pre-specified reliability and confidence interval goals.
453 FDA recommends that the tolerance interval method discussed in Section V.3 be
454 used to provide the sample size justification.

455

456 The report should also describe the use conditions that are important for the emergency-
457 use injector’s reliability and should define the bounded specifications for each condition
458 (e.g., a temperature range).

459

460 b. Testing

461

462 Reliability verification testing should be conducted on the final finished combination
463 product after considering the appropriate preconditioning and use conditions laid out in
464 Section IV.4.a. A reliability report should include the test protocol with validated test
465 methods.

466

467 The sample size for reliability verification testing should be justified with an appropriate
468 statistical method as discussed in Section V.3 and based on the emergency-use injector
469 reliability specifications described in Section V.2. If multiple test groups are included in
470 the manufacturer’s protocol, such as aged and non-aged test groups, then the sample size
471 should ensure adequate statistical results from each group.

472

473 All test failures should undergo root cause analyses which directly link to the fault tree
474 analysis. The fault tree analysis may need to be updated based on any previously
475 unknown failure modes discovered during reliability verification testing. If there is a
476 failure, the reliability testing may need to be redone depending on the conclusions of the
477 root cause analyses.

478

479 5. Total Product Life Cycle Reliability

480

481 Throughout the life cycle of the combination product, manufacturers may become aware
482 of potential emergency-use injector malfunctions, nonconformance or other related
483 quality problems. In these cases, manufacturers must investigate the potential cause and
484 identify any actions that may be needed to correct and prevent recurrence.³³

485

486 An example of an acceptable reliability report is one that documents the manufacturer’s
487 plan for maintaining emergency-use injector reliability throughout the product life cycle
488 as part of compliance with 21 CFR part 4 current good manufacturing practice
489 requirements for combination products.³⁴ An example of an acceptable plan is a plan that
490 includes the following:

491

³³ 21 CFR 820.100.

³⁴ See 21 CFR Part 4 Subpart A, and related FDA guidance *Current Good Manufacturing Practice Requirements for Combination Products* accessible at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products>.

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- Procedures that include requirements for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned combination product, and other sources of quality data to identify existing and potential causes of nonconformance, or other quality problems;³⁵
 - As part of defect and/or failure investigations, the procedures use the reliability data and fault tree analysis as part of the root cause analysis;
 - Procedures for when, during complaint investigations and related CAPA activities, it is appropriate to image the emergency-use injector internally or physically open the emergency-use injector to inspect, measure, and test assemblies or individual components and compare results with the specifications and data identified in the reliability analysis;
 - Appropriate steps for linking the reliability data to the appropriate acceptance activities, including the specific emergency-use injector attributes that are evaluated, evaluation methods, and acceptability criteria that should be considered in the context of the emergency-use injector’s reliability;
 - Detailed descriptions of the in-process control and release test sampling plans to ensure that the reliability specification is maintained for each released lot;
 - Established action limits for significant increases in rejections of the emergency-use injector and its components due to incoming inspection, in-process control, or release test failures;
 - The activities triggered by exceeding an action limit should include 1) the need for implementing CAPA, 2) a root cause investigation, and 3) an associated risk analysis of the failure. The reliability data and fault tree analysis are consulted as part of the root cause investigation;
 - Procedures for updating the reliability data when new information is obtained (e.g., previously unidentified failure modes); and
 - A section that addresses disposition of non-released emergency-use injector or combination product pending analysis and mitigation of newly identified failures.

6. Activities when Implementing Emergency-Use Injector Design or Manufacturing Modifications

531

532

533

534

An example of an acceptable reliability report is one that includes a plan for the activities to be completed when implementing an emergency-use injector design or manufacturing modification. After completing the initial reliability report, future design changes and

³⁵ 21 CFR 820.100.

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535 manufacturing process changes may occur that necessitate re-evaluation of reliability to
536 ensure emergency-use injector reliability.³⁶ To determine when the reliability data may
537 need to be updated, the impact of the change should be evaluated based on the existing
538 reliability model.

539

540 Manufacturers should consider if the change impacts the design output specifications of
541 the emergency-use injector or the basic events of the fault tree analysis. If it is
542 determined that the change does impact these aspects, creates new design outputs, or
543 creates new risks, then the emergency-use injector reliability report should be updated
544 with data regarding the changes and included within your premarket submission.

545

546 VI. RELIABILITY REPORT FORMAT CONSIDERATIONS

547

548 To facilitate the data assessment, the reliability report should be provided in the following
549 format:

550

Section	Content
1.	Combination Product Definition <ul style="list-style-type: none">• Drug Type• Indications for Use• Emergency-Use Injector Technical and Functional Description• Design Inputs and Design Outputs Necessary for Reliability
2.	Emergency-Use Injector Reliability Specifications
3.	Fault Tree Analysis
4.	Reliability Test Plan and Data
5.	Total Product Life Cycle Reliability Plan
7.	Conclusions
8.	Appendices Containing Supporting Data Reports or Risk Analyses

551

552 When submitting this information to an NDA or BLA, we recommend including the information
553 with other device constituent part information located in eCTD module 3.2.P.7.³⁷

554

555 VII. WHERE TO FIND ADDITIONAL INFORMATION

556

557 As noted in Section II, the drug-delivery emergency-use injectors addressed by this guidance are
558 designed as combination products with a CDER or CBER lead. These combination products are
559 submitted under an IND, NDA, ANDA, or BLA pathway (including supplements). To address
560 any uncertainties for the emergency-use injector reliability development process, FDA strongly
561 encourages early development meetings (e.g., Pre-IND or Pre-ANDA to discuss the initial
562 combination product) as well as subsequent IND meetings throughout the development process.

³⁶ See 21 CFR 820.30(i) and 820.70(b).

³⁷ See section-5 in the FDA eCTD Technical Conformance Guide: Technical Specifications Document: Guidance for Industry *Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, December 2019 accessible at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ectd-technical-conformance-guide>.

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563 These meetings can include requests for clarification on the reliability information discussed in
564 this document. For applicants with emergency-use delivery systems that are not emergency-use
565 injectors, these meetings could be used for early consideration of the principles identified in this
566 document. All meeting requests should be submitted to the lead center in accordance with its
567 procedures and should identify the requested participants (e.g., the lead center, CDRH, Office of
568 Combination Products). FDA intends to use its Inter-Center Consult Review Process³⁸ for the
569 assessment of the scientific and technical questions described in this document. The following
570 guidance documents provide procedural information on requesting meetings with FDA and
571 general information on combination products.

572

573 • Guidance for Industry - *Formal Meetings Between the FDA and Sponsors or Applicants*
574 *of PDUFA Products*; [https://www.fda.gov/regulatory-information/search-fda-guidance-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry)
575 [documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry)
576 [guidance-industry](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry)

577

578 • *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under*
579 *GDUFA – Guidance for Industry (DRAFT)*; [https://www.fda.gov/regulatory-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry)
580 [information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry)
581 [applicants-complex-products-under-gdufa-guidance-industry](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry)

582

583 • Guidance for Industry and FDA Staff - *Technical Considerations for Pen, Jet, and*
584 *Related Injectors Intended for Use with Drugs and Biological Products*;
585 [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-pen-jet-and-related-injectors-intended-use-drugs-and-biological-products)
586 [considerations-pen-jet-and-related-injectors-intended-use-drugs-and-biological-products](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-pen-jet-and-related-injectors-intended-use-drugs-and-biological-products)

587

588 • eCTD Technical Conformance Guide: Technical Specifications Document: “Guidance
589 for Industry *Providing Regulatory Submissions in Electronic Format —Certain Human*
590 *Pharmaceutical Product Applications and Related Submissions Using the eCTD*
591 *Specifications*” December 2019 accessible at [https://www.fda.gov/regulatory-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ectd-technical-conformance-guide)
592 [information/search-fda-guidance-documents/ectd-technical-conformance-guide](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ectd-technical-conformance-guide)

593

594 • For general information on combination products see
595 <https://www.fda.gov/CombinationProducts/default.htm>

³⁸ For more information on the Inter-Center Consult Review process see
<https://www.fda.gov/media/81927/download>

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596 VIII. APPENDIX: FAULT TREE EXAMPLE

597

598 The following is a template example of a fault tree analysis for an emergency-use injector. The
599 example uses the following key terms.³⁹

600

- 601 • Basic Event: A failure mode event or state that cannot be further developed.
- 602
- 603 • Failure to successfully inject: Failure of an emergency-use injector to successfully inject
604 occurs when one or more functional failure modes result in the emergency-use injector
605 failing to deploy the needle or failing to complete drug delivery when or as intended. This
606 could include circumstances where the emergency-use injector prematurely activates or
607 does not activate when intended.
- 608
- 609 • Failure Mode: The manner in which a failure occurs.

610

611 Fault Tree Analysis:

612

613 For the emergency-use injector, each final element of the fault tree (e.g. A.1.i.a) should directly
614 link to probability data supporting the overall reliability of the product. The steps for fault tree
615 analysis include the following. See the preceding sections of this document for guidance for
616 information on the completion of these steps, conduct of the analysis, and data submission.

617

- 618 • Definition of the scope of the analysis;
- 619 • Familiarization with the design, functions and operation of the system;
- 620 • Definition of the top event;
- 621 • Construction of the fault tree;
- 622 • Analysis of the fault tree logic; and,
- 623 • Reporting on results of the analysis;

624

625 The template defines the top event as the Failure to Successfully Inject. The fault tree should be
626 broken down into all reasonable, identified faults and failure modes that could lead to a Failure-
627 to-Inject event. The lowest level in the example fault tree illustrates how individual components
628 are incorporated into the fault tree.

629

630 This fault tree example is not prescriptive. The actual number of levels and total amount of
631 failure modes identified in a manufacturer's fault tree will depend on the specific design and
632 manufacturing of that emergency-use injector.

633

634

635

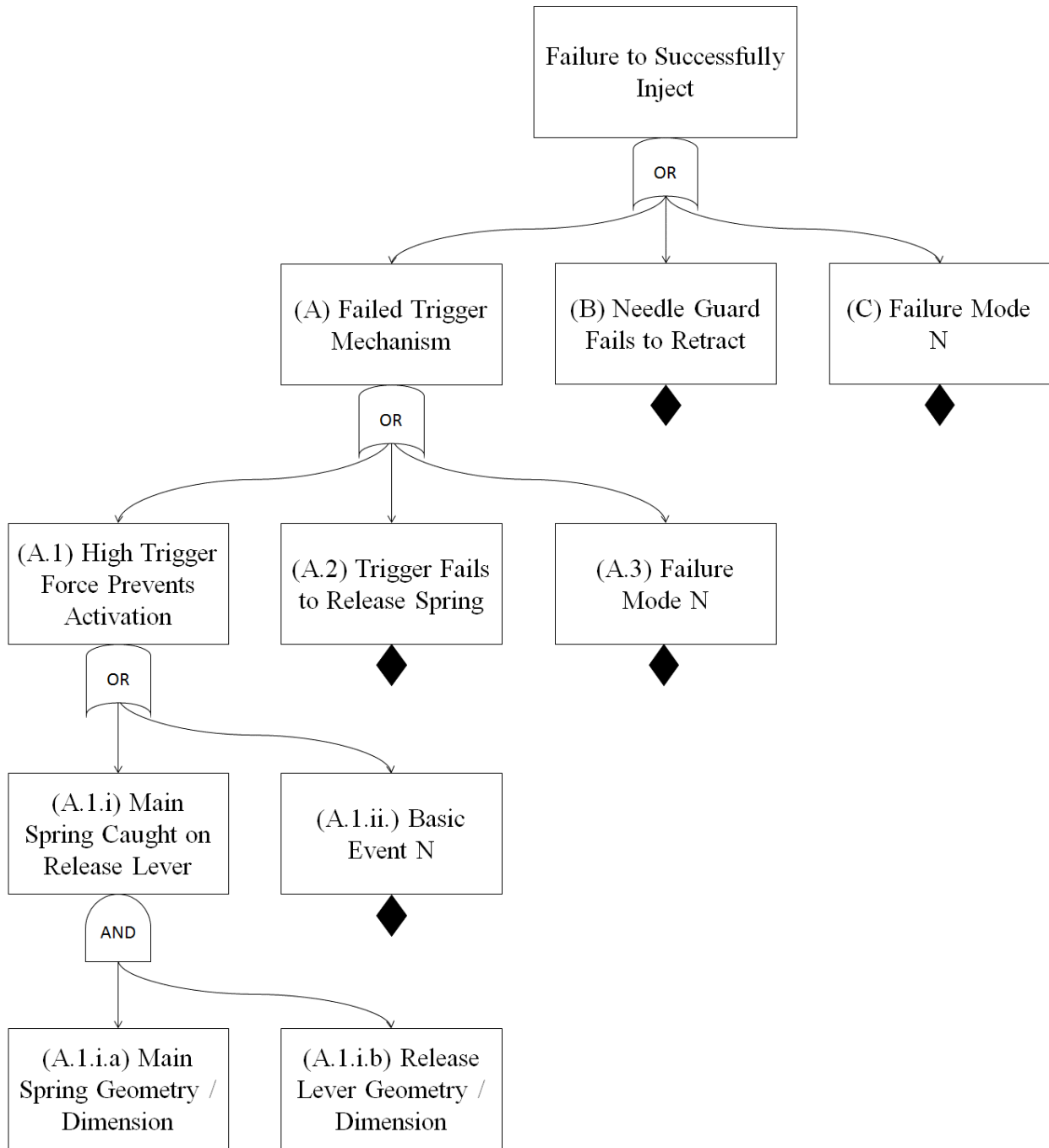
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(See next page for example of flow diagram.)

³⁹ For a more complete glossary and more information see ISO 61025:2006 – Fault tree analysis and the NASA Fault Tree Handbook with Aerospace Applications, 2006.

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