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DRAFT GUIDANCE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
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Center for Biological Evaluation and Research
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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 [1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

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

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

The FDA guidance document, *"Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products"* provides general recommendations for the technical and scientific information to be included in marketing applications for a range of injectors for various uses.[4] In that document the reliability of the injector in delivering the drug 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.

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

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

II. SCOPE

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

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

[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 Developmen*t, 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.

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).

regulations call for ongoing assessment of systems and the implementation of corrective actions where appropriate."[11]

IV. BACKGROUND ON RELIABILITY

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

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

- 21 CFR 820.30(c) states that "[e]ach manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient."

- 21 CFR 820.30(d) states that "[e]ach manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements. Design output procedures shall contain or make reference to acceptance criteria and shall ensure that those design outputs that are essential for the proper functioning of the device are identified."

- 21 CFR 820.30(f) states that "[e]ach manufacturer shall establish and maintain procedures for verifying the device design. Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF." Moreover, 21 CFR 820.30(g) states that "[e]ach manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents. 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.

uses and shall include testing of production units under actual or simulated use conditions."

- 21 CFR 820.30(h) states that "[e]ach manufacturer shall establish and maintain procedures to ensure that the device design is correctly translated into production specifications."

- 21 CFR 820.30(i) states that "[e]ach manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation."

- 21 CFR 820.100 states that "each manufacturer shall establish and maintain procedures for implementing corrective and preventive action."

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

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

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

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

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

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

Establishing reliability

Establishing reliability is an iterative process in which the design controls should focus on emergency-use injector attributes determined to be essential for achieving the emergency-use injector's intended use.[13] The level of reliability necessary to manufacture a safe and effective combination product directly correlates to the level of risk associated with an unreliable emergency-use injector. Because reliability as a mathematical model is defined as $R(t) = 1 - F(t)$, where $F(t)$ represents the cumulative distribution function of failure, the goal should be to define the point at which that distribution, $F(t)$, is adequately controlled. The reliability specification(s), $R(t)$, 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.

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

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

- Identification of the reliability requirements and specifications;
- Risk analysis;
- Design verification and validation of the reliability requirements and specifications; and
- Design transfer of the reliability specification to the correct production specifications.

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

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

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

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

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

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

V. RELIABILTY REPORT DEVELOPMENT AND CONTENT RECOMMENDATIONS FOR PREMARKET SUBMISSIONS

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

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

1. Design Inputs and Design Outputs Necessary[18] for Ensuring Reliability

As described in Section IV, specifications for how reliably the emergency-use injector functions and the use condition of the patient or caregiver need to be identified.[19] The design inputs necessary for ensuring reliability should be identified and developed into specified design outputs. Selecting design inputs that may not be relevant to the reliable function of the emergency-use injector could result in an inability to meet the manufacturer's established reliability specifications. To assist in identifying design input requirements, manufacturers 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).

- 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:
  - Use tasks, which may include unpacking, preparation, administration and disposal of the combination product; and
  - Use conditions and environments of use.
- Use-condition factors[20] 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:
  - Use environment (e.g., school, work, public transportation vehicle, harsh climates, first responder chaotic conditions) and associated risks to reliability; and
  - User characteristics (e.g., self- injection with cognitive or physical impairment associated with the disorder being treated) and associated risks to reliability.

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

(See next page for Table-1.)

[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.

Table-1: Emergency-Use Injector Design Reliability Development Considerations[22]	
Consideration Category	**Examples**
Protective Packaging	• 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	• Force to remove caps or needle shields • Force to deactivate safety mechanism
Activation Force	• Force to initiate the injection mechanism
Needle Insertion	• Needle bevel specifications • Needle material of construction • Needle Insertion Forces (e.g., penetrating clothing, skin, etc.) • Needle resistance to bending and fracture
Needle Patency	• Particulates
Injection Depth	• 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	• 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	• Needle does not retract before intended dose is delivered • Audible, visual, or tactile feedback does not prematurely signal a completed injection
Dose Accuracy	• Intended dose delivered to intended injection site or depth

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.

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

2. Definition of Emergency-Use Injector Reliability Specifications

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

For the reliability specification analysis, failure to inject should be the primary endpoint. This should be the top-level failure mode of the fault tree analysis as described in Section V.3.[23] The reliability analysis and testing should include emergency-use injector performance requirements based on the assessment of the design (see Section V.1). In general, FDA recommends that these include dose accuracy, extended needle length, activation force, and injection time be included as part of emergency-use injector reliability.[24] However, manufacturers should assess the specific emergency-use injector design to determine if additional performance attributes are considered to be essential for completing a successful injection. For example, a specific design may have a cap that must be removed to initiate injection and the manufacturer may determine that cap removal is essential to completing a successful injection.

3. Fault Tree Analysis

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

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

- The probability data for each basic event[25] should be included in the fault tree;
- The analysis should consider potential common cause failures and whether assumptions of independence of events are supportable;
- Any risk analyses (e.g., such as design and process failure modes effects analysis)[26] used to support the fault tree analysis should be included in the reliability report;
- Once the fault tree analyses are completely developed, data should be provided to support that the reliability specification for the top-level failure mode is verified and validated (e.g., the probability data for each basic event should be supported with evidence); and,
- The basic events in the fault tree analysis should be linked to appropriate design and/or manufacturing controls.

Based on standard fault tree analysis quantification methods, the reliability of each basic event within the fault tree analysis should be assessed through a cumulative analysis to determine whether the reliability specification for the top-level failure mode is adequately supported. The statistical methods utilized to demonstrate the reliability of each basic event within the fault tree analysis should inform the test sample size necessary for reliability testing of the final finished combination product. To assess the potential for the basic event failure mode of the emergency-use injector, it is important to use a statistical tolerance interval[27] method in which the limits of each individual component are analyzed (e.g., dimensions, geometry, material strength, etc.),[28] both by itself and in conjunction with its associated components (i.e., stack-up analysis). To effectively use the tolerance interval method, the critical measurable elements of each component contributing to the basic event should be clearly stated and the statistical tolerance limit[29] identified. Data to support the tolerance interval methodology should be provided and may include process validation data for individual components. The resultant *k* factor[30] for each basic event should be used to calculate the necessary sample size of the reliability study based on the desired reliability specification and confidence interval.

An example of acceptable use of the statistical tolerance interval methodology is one 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 statistic 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

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

4. Reliability Testing

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

a. Use Conditions and Preconditioning Recommendations

To identify the reliability test conditions to ensure achievement of the reliability specification at the end of use-life,[32] it is important to define the combination product's use conditions and preconditioning steps. This ensures that the testing program has adequately challenged the ability of the emergency-use injector to withstand stressors that are likely to occur or to which the product will be exposed during the use-life. Combination product-specific use-life factors to consider for preconditioning steps that influence shelf-life may include the following preconditions:

- Shipping;
- Aging;
- Storage orientation and conditions;
- Vibration;
- Shock (e.g., resistance to impacts, such as being dropped); and
- Environmental factors:
  - Temperature (extremes and cyclic);
  - Altitude and pressure effects (e.g., airplane, submarine, or other above/below sea-level effects); and
  - Air particulates (dust/sand).

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

- Validation data to ensure that the accelerated methods accurately model the time-dependent failure mechanisms of the emergency-use injector;
- Results of testing at various time points to identify any trends in emergency-use 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.

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

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

b. Testing

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

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

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

5. Total Product Life Cycle Reliability

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

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

[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.

- 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

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.

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

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

VI. RELIABILITY REPORT FORMAT CONSIDERATIONS

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

Section	Content
1.	Combination Product Definition • 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

When submitting this information to an NDA or BLA, we recommend including the information with other device constituent part information located in eCTD module 3.2.P.7.[37]

VII. WHERE TO FIND ADDITIONAL INFORMATION

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

These meetings can include requests for clarification on the reliability information discussed in this document. For applicants with emergency-use delivery systems that are not emergency-use injectors, these meetings could be used for early consideration of the principles identified in this document. All meeting requests should be submitted to the lead center in accordance with its procedures and should identify the requested participants (e.g., the lead center, CDRH, Office of Combination Products). FDA intends to use its Inter-Center Consult Review Process[38] for the assessment of the scientific and technical questions described in this document. The following guidance documents provide procedural information on requesting meetings with FDA and general information on combination products.

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

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

- Guidance for Industry and FDA Staff - *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with 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

- 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

- For general information on combination products see 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

VIII. APPENDIX: FAULT TREE EXAMPLE

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

- Basic Event: A failure mode event or state that cannot be further developed.

- Failure to successfully inject: Failure of an emergency-use injector to successfully inject occurs when one or more functional failure modes result in the emergency-use injector failing to deploy the needle or failing to complete drug delivery when or as intended. This could include circumstances where the emergency-use injector prematurely activates or does not activate when intended.

- Failure Mode: The manner in which a failure occurs.

Fault Tree Analysis:

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

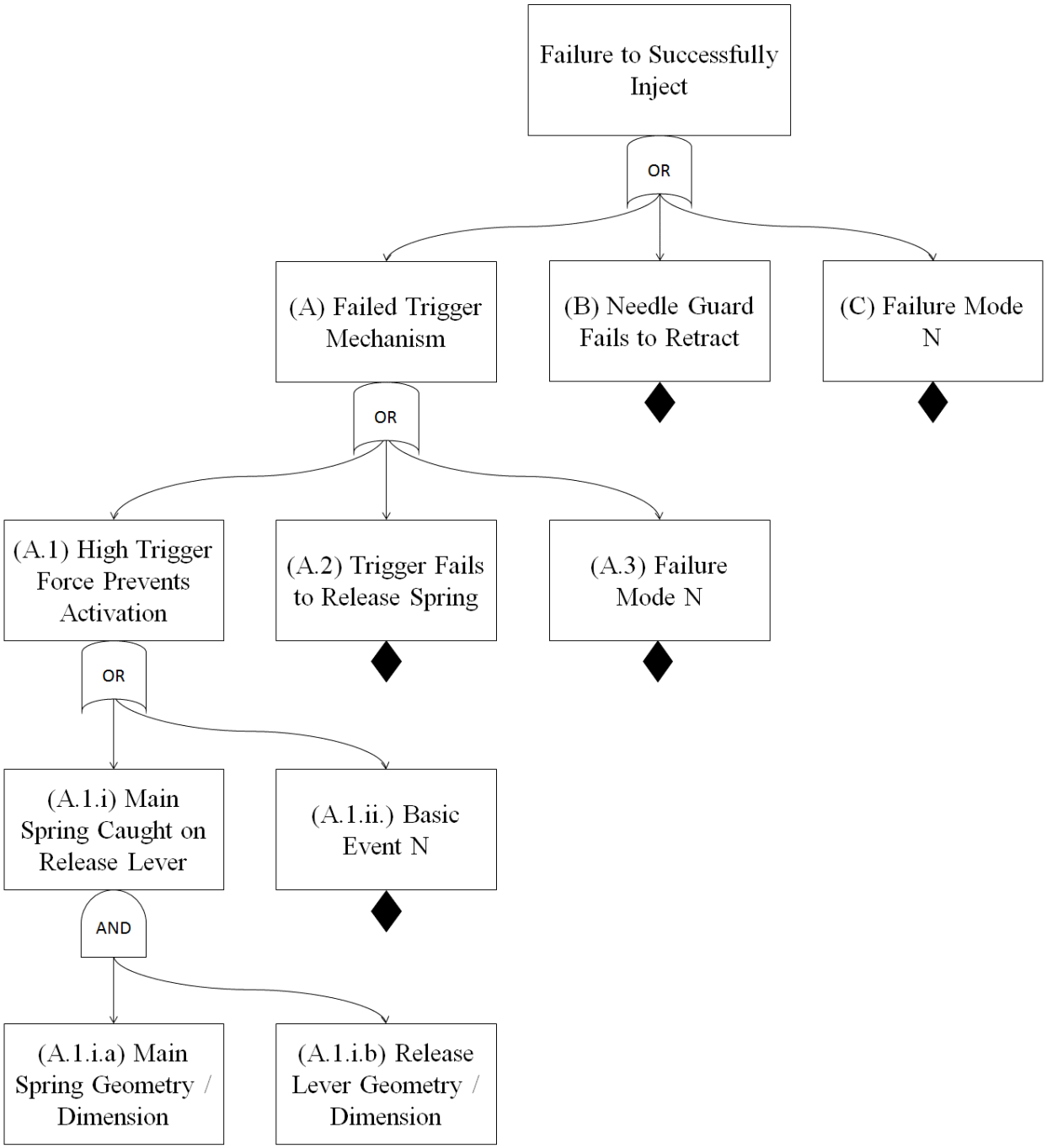
- Definition of the scope of the analysis;
- Familiarization with the design, functions and operation of the system;
- Definition of the top event;
- Construction of the fault tree;
- Analysis of the fault tree logic; and,
- Reporting on results of the analysis;

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

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

(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.


Failure to Successfully Inject
OR
(A) Failed Trigger Mechanism
(B) Needle Guard Fails to Retract
(C) Failure Mode N
OR
(A.1) High Trigger Force Prevents Activation
(A.2) Trigger Fails to Release Spring
(A.3) Failure Mode N
OR
(A.1.i) Main Spring Caught on Release Lever
(A.1.ii.) Basic Event N
AND
(A.1.i.a) Main Spring Geometry / Dimension
(A.1.i.b) Release Lever Geometry / Dimension

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