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VIA ELECTRONIC SUBMISSION

June 22, 2020

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-D-5573; Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA: Draft Guidance for Industry and FDA Staff

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to provide comments on FDA's "Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA: Draft Guidance for Industry and FDA Staff" dated April 22, 2020 (the "Draft Guidance").

The CPC recognizes the need for emergency-use delivery devices that must be exceptionally reliable in order to achieve their full life-saving benefit in treating critical patients. The CPC greatly appreciates FDA's efforts to provide needed guidance on the Agency's recommendations for demonstrating reliability of injectors and is pleased to see this topic being addressed across all three Centers and OCP. Technical considerations for demonstrating reliability for emergency-use delivery devices have been conveyed to combination product applicants in FDA product review correspondence in the past, and consistent FDA guidance, with industry input, will be of great assistance to developers of these products.

The CPC finds the regulatory framework and Design Control discussion provided in the Draft Guidance to be supportive of this expected use. However, the analysis of reliability, based on risk assessments and extensive design verification testing evidence, will continue to be a development challenge that may discourage companies from seeking these markets. In addition, many of the recommendations in the Draft Guidance will raise inherent regulatory uncertainty for applicants

[1] The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad, and unique perspective to these issues.

(if requirements are strictly imposed in FDA NDA/BLA review correspondence late in development). Further, some of the practices recommended in the Draft Guidance do not appear to be practical, and the use of a quantitative Fault Tree Analysis ("FTA") to the "base component level" for most components or to their assembly poses a challenge to realistically assess or estimate extremely remote probabilities that would be additive in the fault tree for a top level 99.999% reliability with 95% confidence.[2]

The CPC has carefully evaluated FDA's Draft Guidance and we ask that the Agency consider our major points of concern discussed below, as well as our line-specific comments, which are provided in Appendix A.

Major Comments:

The Draft Guidance is premised on a required reliability (99.999% acceptable frequency or probability of failure with 95% confidence) of an injector covered by the document (see Major Comment #3) to perform a defined function based on a specified harm to the patient. This combination, frequency or probability of occurrence and harm, defines the acceptable risk of failure. The frequency or probability has been clearly specified, however, in order for this to be of value, both a clear description of the failure that is to be held to the reliability expectation and the patient harm to be avoided, must be provided. Furthermore, the Draft Guidance only refers to the probability level, but lacks the description of the associated confidence level.

It is also important to note that none of the drugs that would be delivered by these injectors are 100% effective at addressing the condition or preventing the harm for which they are intended. As such, while it is desirable to minimize the potential for failure of the device, even if 99.999% reliable, the drug delivered may still not provide acceptable treatment or prevention of harm.

1. <u>Parameter(s) That Must Meet Minimum 99.999% Reliability</u> – The Draft Guidance is unclear about which parameter is the "single critical parameter" that establishes and confirms the reliability expectation of 99.999%. On the one hand, the Draft Guidance states that "for the reliability specification analysis, failure to inject should be the primary endpoint," and that "[t]his should be the top-level failure mode of the fault tree analysis" (lines 356-357). This implies that successfully "initiating actuation" of a functioning automated delivery mechanism is the key parameter for establishing a reliability expectation of 99.999%.

   On the other hand, FDA recommends that "reliability analysis and testing should include e*mergency-use injector performance requirements* based on the assessment of the design (see Section V.1)" (emphasis added) (lines 358-359); in general, FDA recommends dose accuracy, extended needle length, activation force and injection time be considered as part of emergency-use injector reliability, but also calls on manufacturers to determine whether "additional performance attributes are *considered to be essential for completing a successful injection*" (emphasis added) (lines 362-364). This implies that it is a "*successful injection*" that is the top-level criteria for the reliability specification. In addition, elsewhere in the Draft Guidance, FDA

[2] Note that, throughout the document, all references to 99.999% or other reliability specifications are at 95% confidence.

implies that "injection," "activation and drug delivery functions," or each and every, individual Essential Performance Requirement ("EPR") (e.g., specified volume delivered, needle extension to specified depth, etc.) are the parameters that must meet the specified 99.999% reliability.

The CPC recommends restricting the expectation of 99.999% reliability to **instances of a complete failure to operate**, supported by a combination of testing results, engineering analyses, and estimation of failure rates generated through a risk-based assessment. All other performance specifications or requirements that are statistically verified through testing, including EPRs, should be held to a lower reliability expectation. Further, FDA should clearly confirm that the complete failure to operate is the single critical parameter that would drive all analysis and conclusions with respect to the FTA.

It would seem that different reliability specifications for other functions at other time points and conditions may be implied in the document. This would be supported by the suggestion that fault tree analyses for the EPRs can be separated from the fault tree as provided in lines 370-374 ("The information described in the preceding sections [(related to design inputs/outputs and reliability specifications)] 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)."). Placing these other performance criteria in the same fault tree would require that they be held to the same, and likely a higher reliability specification. The CPC recommends that the Draft Guidance be revised to specifically state that EPRs and other performance criteria can be held to reliability specifications that are different, and possibly lower than, the top-level failure, or complete failure to operate.

2. Patient Harm That Would Require Stated Reliability – The Draft Guidance provides some conditions (e.g. anaphylaxis, opioid overdose, poisoning, or severe hypoglycemia) that are to be addressed by the injectable drugs for which this Draft Guidance, and stated reliability level (99.999%), would apply. However, in order for this Draft Guidance to be consistently applied, the harm must be defined, not the condition. Most companies categorize harm and severity into a set of defined levels. The most severe harms, usually defined as catastrophic, are restricted to those failures that could result in patient death. In line with the intent of the Draft Guidance, FDA should clarify that the types of drugs delivered and conditions addressed that would be held to the highest level of reliability (99.999%) would only be those where the failure (see Major Comment #1 as to the failure that should be covered) can directly result in patient death.

3. Type of Devices in Scope of the Draft Guidance – In the Introduction section of the Draft Guidance, FDA states that the guidance covers emergency-use injectors submitted under a biologics license application ("BLA"), new drug application ("NDA"), or abbreviated new drug application ("ANDA"). This implies that the term "emergency-use injector" means a single entity combination product injector marketed with an emergency-use drug. However, in the Scope section of the Draft Guidance, FDA suggests that the recommendations for reliability assessment for an emergency-use injector could be "useful" for the demonstration of reliability

for other emergency-use products (lines 52-55). The examples provided by FDA of such "other emergency-use products" are simple, user-actuated devices where reliability has not been an issue (e.g., manually-operated syringes, topical cutaneous sprays that are dependent on user application, and transdermal systems, also manually applied and rarely relevant to rescue use). The CPC is also concerned that FDA's recommendations for reliability testing and analysis detailed in the Draft Guidance could spill over to many other combination products where there may be potential for patient harm, even for severe harm, but no significant risk of patient death.

Recent FDA feedback, where the Agency has provided a reliability target of 99.999% or other recommendations provide in this Draft Guidance, that impose new, burdensome requirements on applicants which are not necessarily appropriate or practical, suggests that these concerns are valid.

Accordingly, the CPC believes that the Draft Guidance (including its title) should be revised to clarify that its scope and recommendations only apply to *emergency-use injectors used in a non-clinical setting where an automated mechanical actuation, independent of operator intervention, is relied on for the rescue product delivery, and where the failure to operate can result in patient death.*

Additionally, the Draft Guidance focuses on injectors being used by lay users outside of a controlled clinical environment where there is heavy dependence on the device functioning reliably in that one opportunity the patient has to self-inject. However, the CPC would like to highlight that there are other emergency-use combination products that may be used by skilled professionals, in a controlled environment, where there may be opportunities to resolve potential issues (e.g., by using a back-up device or alternative treatment). While reliability is certainly still applicable to such products, the CPC believes that the Agency should not mandate a reliability level as high as 99.999% for products used under these conditions (or other conditions where there is a different user profile and/or use environment than contemplated in the Draft Guidance). This is consistent with Major Comment #6 on probability of harm.

Hence, the CPC recommends that FDA add language to the Draft Guidance that advises sponsors developing products that fall outside the specific scope of the Draft Guidance to interact with FDA during the development process to identify a suitable reliability level.

4. Point at Which Specified Reliability Must Be Met – As written, Section V.4 of the Draft Guidance ("Reliability Testing") could be interpreted to mean that the product must meet the *reliability specification* at the end of life, which is, as dictated in this section, after worst case conditioning at the expiration date. The number of samples that would need to be stored to expiration and tested to demonstrate a probability of failure at less than 1 in 100,000 would be astronomical. Further, the probability that a single product will be used at the last day of life after being subjected to extreme conditions is already exceptionally low. The CPC agrees that the product should be reliable at the end of its life based on functional stability testing. However, the Draft Guidance should clearly state that the expectation for functional stability (worst-case testing), reliability of successful injection is acceptable, with test data, at a much lower level, and perhaps that the performance of the device at all stages of testing can be used

in support of the justification that the device meets the reliability specification over its useful life.

5. Correlation of 99.999% Reliability Specification as Equal to a 1/100,000 Potential for Failure – The Draft Guidance states that 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. Throughout the Draft Guidance, FDA suggests that this will be achieved through establishing 99.999% reliability for the performance of the device. However, these two concepts, 99.999% reliability at 95% confidence and <1/100,000 failures, are NOT the same. Establishing 99.999% reliability at 95% confidence for a successful injection (no failures to operate) would require a test demonstrating zero events in 299,572 units, or less than 1 failure in 299,572 operations. For a test allowing a 1/100,000 failure rate, the reliability at 95% confidence would be 99.995%, requiring almost 200,000 less samples. The CPC recommends that FDA revise the top-level reliability target stated in the Draft Guidance to 99.995%, which would allow for statistical consistency with a predicted maximum failure rate of less than 1/100,000.

6. Reliability is ***Not*** Probability of Harm – The Draft Guidance relies upon ISO 14971 to explain that, for an emergency-use injection, a 1/1,000,000 probability of device failure (i.e. improbable) would be burdensome and difficult to demonstrate, and a 1/10,000 probability of failure (i.e., probable) would not be sufficient - finally justifying a 1/100,000 probability of failure (i.e., remotely probable) and specifying a fixed failure rate of 99.999% with a 95% confidence (see Major Comment #5 regarding the equality of these terms). However, the ISO standard suggests that semi-quantitative probability levels should be based on "probability of harm per use," or "probability of harm per device," and not necessarily on probability of failure (i.e., strict device failure rates). The probability of occurrence of harm is the product of the probability of a hazardous situation occurring (e.g., occurrence of the failure) and the probability of the harm as a result of that failure. There are many factors that would need to be considered in determining a probability for harm, such as the degree of anaphylaxis or other conditions (e.g., hypoglycemia), whether other treatments can also be applied, and whether human (use) errors resulting in failed treatment can ever achieve this reliability level. For example, partial delivery of a dose may still be effective, and needle insertion depth is unlikely to be a critical parameter in many treated patients. The user profile may also impact the potential for harm; for example, if the device is intended for use by a clinician, such as an emergency first responder (e.g., EMT or school nurse), who will have back-up supplies.

   The CPC's concern is that a fixed reliability criterion assumes that every device failure would have a catastrophic outcome (death), and that meeting a reliability criterion of slightly less would be unacceptable and un-approvable, i.e., have no public health benefit in emergency-use treatments. The fixed reliability requirement also implies that a quantitative FTA must require even higher reliability levels for baseline component events based on a tolerance interval assessment which may be impracticable or difficult to justify. The CPC recommends that the fixed reliability level specified in the Draft Guidance be reserved for catastrophic failures (complete failure to operate) in use cases where the death of the user could be unavoidable.

7. Draft Guidance Can Be Streamlined by Focusing on the Expectations Applicable to Only Emergency-Use Injectors – The Draft Guidance mixes general design control activities with the additional activities needed for emergency-use combination products. Although it is understood that the Design Control Regulation justifies establishing reliability requirements for these injectors, the CPC recommends that FDA remove information from the Draft Guidance that is part of usual design controls and streamline the document to specifically identify relevant information and reliability expectations for those emergency-use injectors in scope, including how they can be met through appropriate design and manufacturing controls. The CPC also recommends that FDA remove routine design validation and corresponding references from the Draft Guidance to improve the clarity and focus of the document.

8. Recommendations Will Result in Very Large Sample Sizes – The Draft Guidance recognizes that *k* factors should be used for each failure event, but the *k* factors for establishing sample sizes or used as acceptance criteria for individual performance tests, solely for the purposes of meeting a top level reliability criterion of 99.999%, may be difficult to achieve without significant testing of large samples. For instance, reference to a *k* factor of 4.265 captures 99.999% of a distribution, assuming it is normal and able to be tested using variable data. The *k* factor above is not adjusted for a given confidence level; to do so would require the Agency to specify a sample size as well as the desired population capture. If the test of interest required attribute data (pass/fail), the sample size required to meet this 99.999% reliability at a 95% confidence level becomes ln(0.05)/ln(0.99999) or 299,572 units.

9. Draft Guidance Lacks Clarity Regarding Expectations for Assembly Process and Control Strategies – While the Draft Guidance recommends that assembly processes and control strategies be considered in meeting the proposed reliability recommendation, in most cases, 100% inspection of correctly assembled parts using validated automated inspection technology (machine vision) would meet that assurance level and it is not clear in the Draft Guidance what techniques beyond this activity would be required. The fault tree analysis is more useful if its focus is on design faults. We ask that FDA provide additional detail on its expectations here.

10. Probability of Failure for Components – The Draft Guidance recommends use of a statistical tolerance interval method in the fault tree for each individual component's limits (e.g., dimensions, geometry, material strength, etc.), both alone and in conjunction with its associated components (i.e., stack-up analysis), to clearly state the critical measurable elements of each component contributing to its basic fault event, and to provide data in support of the tolerance interval methodology, including, potentially, process validation data for individual components. When assessing these basic faults, manufacturers would have to assess and justify these basic faults as having even lower probability of failure than the top-level injection failure probability for the quantitative (additive) justification of the overall injector reliability criterion. We ask that FDA provide additional guidance on how these lowest probability scores can practically be achieved using engineering justifications in addition to tolerance interval assessment.

    In addition, most suppliers who provide platform injector technologies to pharmaceutical companies do not typically provide component level data to applicants for inclusion in NDA/BLAs, instead providing master files (DMF/MAF) of this confidential information to be

referenced for these submissions. The Draft Guidance should advise how the reliability requirement should be met with holders of master files. Our preference would be for the Draft Guidance to not address component level testing other than such testing the marketing applicant could conduct itself (e.g., acceptance testing).

11. Expectations for Procedure Submissions – The Draft Guidance does not clarify whether the Total Product Life Cycle Reliability section proposed for the Reliability Report requires the submission of the numerous procedures listed therein for NDA/BLA approval, or whether activities listed this section are implied as, or would become, post approval commitments. The Draft Guidance should clarify whether it is acceptable to provide a summary of these procedures in lieu of the actual procedures, and whether this review can be a cGMP inspection activity.

* * *

The CPC recognizes that it is critical for emergency-use injectors to be as reliable as possible and agrees with many of the principles and recommended practices outlined in the Draft Guidance. However, we would appreciate additional clarity in the final guidance based on the feedback we have provided above, which would pave the way for more practical assessments of reliability. We appreciate the opportunity to provide input on the Draft Guidance and welcome any questions or further discussion.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Appendix A: Line-Specific Comments

Section #, Line #	Text in Guidance	Proposed Comment and Recommended Edit	Rationale for Change
Section IV, 103-111 & 154-162	"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." "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	The Agency's points in the first paragraph cited in the left hand column regarding the use environment and users (lay) is important for reliability requirements for emergency-use injectors. The Agency should also consider that there are other emergency-use combination products that may be for use only in clinics and used only by qualified healthcare professionals. Hence, we recommend the Agency include the following text, after both of the paragraphs cited in the left hand column, to enable early discussions to identify an appropriate "clinically-relevant" reliability level for other types of emergency-use combination products: "...**The Agency acknowledges that there are other types of emergency-use combination product scenarios as well, such as single use, emergency-use products that may be for use only in-clinic by qualified healthcare professionals in a controlled environment or potentially where the user has more than one opportunity to successfully use the product. The approach for identifying an appropriate clinically relevant reliability level for such products would need to take into consideration elements of use environment and intended users. Reliability approaches for such products should be discussed with the Agency early in the product development process.**"	Provide clarity and further guidance on reliability expectations for broader types of emergency-use combination products.

Section #, Line #	Text in Guidance	Proposed Comment and Recommended Edit	Rationale for Change
	function (e.g., the morbidity or mortality associated with untreated anaphylactic shock)."		
Section IV, 135-141	"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 uses and shall include testing of production units under actual or simulated use conditions.'"	While design validation is an important element of design controls per 21 CFR 820.30, its relevance for inclusion in the text of the Draft Guidance is not clear. As the reliability requirements are more focused on the functionality of the device constituent part of the combination product, demonstrated via design verification testing, the CPC recommends removing design validation references from the Draft Guidance to avoid confusion.	The process of testing products for reliability is more akin to Design Verification, rather than validation. Consistency is needed throughout the document regarding design validation not being in scope of reliability.
Section IV,	N/A (general comment on approach)	The need of an emergency use device to function when needed, is unquestionable. This Draft Guidance however is unlikely to fulfil this purpose, even if fully implemented, as it requires a (costly) analysis and test program, based on statistical models that are known to have limited scientifically validity within the very small outer ends of the normal distribution of 99.999%. At the same time, this document does not provide the opportunity or option to use other scientifically and historically well-founded 'reliability engineering' methodologies, such as HASS HALT (highly accelerated lifecycle testing) testing and FMEA analysis.	If the purpose of this Draft Guidance is to prevent malfunctions of devices, caused by a long "shelf life" in pockets or car compartments, then a more effective and less burdensome approach would be to require an accelerated or HALT test combined with the ordinary worst case testing. If the purpose is to prevent malfunctions caused by variation in manufacture and distribution, a more effective and less burdensome approach would be to require an ISO14971 compliant

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			process to include possible errors in manufacture, assembly, pack, and distribution.
Section IV, 160-162	"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)."	A "reliability specification consistent with the level of risk" is not a productive way for using risk management for reliability. We suggest using the framework of ISO14971, which is well-established in the industry and recognized by FDA, rather than inventing a new process, the effectiveness of which may be questioned, i.e., use risk analysis to identify which component and assembly errors may impact reliability, and to control risk by e.g.,100% screening of these assembly steps, and to verify the effectiveness of these measures. Recommended edits: Replace the expectation of a risk-based reliability specification with one of a "risk management process ensuring that risk related to reliability is controlled to an acceptable level during design, development, manufacture and distribution."	Change recommended to align with and leverage the established risk management framework.
Section IV, 170	"…test conditions were representative of how the product would be exposed up to expiry."	Limiting testing to only "representative conditions" will lead to prohibitive costs that will prevent access to treatment. Methods which accelerate the testing should be allowed.	If testing is to be used, then accelerated or HASS-HALT methods may be appropriate.

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Section IV, 164-170	"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."	Regarding (2), the Agency's implication is not clear on how design validation ensures reliability targets are met. As indicated in Section II, Footnote 6, it is mentioned that, "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." Accordingly, it is not clear why (2) is included in this statement and we ask that it be removed to avoid confusion.	To allow for consistency throughout the document regarding design validation not being in scope of reliability.
Section IV, 176-180	"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."	These two concepts are not the same. 99.999% reliability for a successful injection (no failures to operate) would require zero-events in 299,572 units, or less than 1 failure in 299,572 operations. For a test allowing a 1/100,000 failure rate, the reliability at 95% confidence would be 99.995%, requiring almost 200,000 less samples.	If the desire is to limit the failures to less than 1/100,000, then the reliability should be set at a minimum of 99.995%.
Section IV, 184-189	"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."	ISO 14971:2019 does not currently include examples for "semi-quantitative analysis that identifies probable, remote, and improbable events rates" nor does it provide a scale for probability as an example; however, it is recognized that this information may have been moved to ISO/TR 24971, which is expected to be published in 2020, but is not available as of the date of these comments. Recommended edits: "…~~In~~ **Within** the **context of the** standard, **an** example~~s are provided~~ for semi-quantitative analysis **of probability includes identifying**~~ies~~ probable,	Recommendation included to align with currently published version of the standard and the associated technical report.

Section #, Line #	Text in Guidance	Proposed Comment and Recommended Edit	Rationale for Change
		remote, and improbable events rates. **~~In the standard,~~ As an example,** events occurring in the range of 1/10,000 detection rate are considered to be probable."	
Section IV, 224-226	"The reliability specification(s), R(t), represents the probability that the emergency-use injector will perform as intended, without failure, for a given time interval under specified conditions."	We ask that FDA clarify that "t" not be restricted to time to failure. Historically, reliability was often expressed as a mean time to failure. Using time as the variable is not applicable for single use devices as the mission life of the device is short, e.g., seconds. An emergency-use device normally exists in a standby mode and must be able to perform its intended function on an as-needed basis. Recommended edits: "The reliability specification(s), R(t), represents the probability that the emergency-use injector will perform as intended, without failure, **when needed ~~for a given time interval~~** under specified conditions."	Recommended edits for clarity.
Section IV, 222-227	"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, 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."	Recommend removing the time function "t" in the reliability specification(s) (R(t); F(t)).	Use of the time function "t" is more relevant to a product or system that is operating continuously and does not seem to be appropriate for a single use device that operates only once, with a relatively short duration. Otherwise, it could be interpreted that the reliability specification is somehow related to the storage time, or expiration date, which cannot be the case.

Section #, Line #	Text in Guidance	Proposed Comment and Recommended Edit	Rationale for Change
Section IV, 237	"• Design verification and validation of the reliability requirements and specifications"	Recommended edits: "• Design verification **~~and validation~~** of the reliability requirements and specifications"	To allow for consistency throughout the document regarding design validation not being in scope of reliability.
Section V, 291-295	"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."	Recommended edits: "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."	To allow for consistency throughout the document regarding design validation not being in scope of reliability.
Section V.1, 302–341	The first paragraph of the section states: "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." The last paragraph of the section states: "The preceding tabular considerations are to assist in identifying the emergency-use injector performance characteristics that inform the design inputs and outputs."	This entire section is confusing as it switches between design inputs, design outputs, development considerations and performance characteristics. The second paragraph cited in the column to the left implies that performance characteristics precede and inform inputs and outputs, when design inputs always precede the determination of performance specifications.	This section needs to be rewritten to focus ONLY on the performance characteristics that may be considered for reliability. We also recommend eliminating the design control terminology as it is not helpful here.
Section V.1, Table 1	Table-1: Emergency-Use Injector Design Reliability Development Considerations	This table lists numerous product characteristics categories as examples for consideration of reliability and many are relevant to appropriate specification setting, risk analyses and reliability assessment. However, several listed examples are more descriptive in nature (e.g., body habitus, skin and tissue	Please consider adding appropriate context to this table or discussing how each of these items are relevant to reliability.

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		characteristics, anatomical location(s) for injection, audible, visual, or tactile feedback does not prematurely signal a completed injection), are not determined or controlled by the drug manufacturer (e.g., needle bevel specifications, needle material of construction) and/or are not highly relevant to reliability and its quantification (needle injection depth). In many cases, some of these examples would problematic too, as the Draft Guidance advises that it is important to "clearly define the difference between acceptable and unacceptable emergency-use injector performance to determine appropriate design inputs" (lines 338-340) based on these listed examples. Also, some of the examples listed in Table-1 are design inputs but may not need to be directly controlled to a degree necessary to achieve a reliability of 99.999% with a 95% confidence level. Some quantitative design specifications are determined by human factors considerations to estimate a reasonable acceptance criterion that may not be directly related to the automated mechanical function of an injector, and many of these have been designated by FDA as Essential Performance Requirements ("EPRs"). However, when attempting to achieve a fixed reliability of an EPR to a confidence interval (95%), the analysis of risk should predominate rather than reliability. The tolerance of injection depth (i.e., needle removal force, force to deactivate a safety mechanism, and activation force are not as critical as the singular occurrence of the automated mechanical injection. In reliability testing of individual EPRs, a single "out of specification result" or a wider standard deviation in test results for individual product lot could jeopardize a 99.999% reliability claim when the incremental added risk of actual harm is negligible.	

Section #, Line #	Text in Guidance	Proposed Comment and Recommended Edit	Rationale for Change
Section V.1, 312-315	• "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"	This point does not align with the information in footnote 6 and footnote 20 which indicate that the user/interface and human factors are not part of the reliability level identification and verification. The text in Lines 317 to 323 adequately captures the importance of use condition factors. We recommend remove this cited text for consistency and to avoid confusion.	To allow for consistency throughout the document regarding user interface and human factors not being in scope of reliability.
Section V.2, Footnote 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."	Recommended edits: "The acceptance criteria for the performance attributes in **Table-1** ~~**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."	Correction of typographical error.
Section V.2, 359-362	"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."	Injection Time is not included in Table 1. We recommend adding Injection Time and relevant information in Table 1 for consistency.	Update requested for consistency.
Section V.3, 398-408, & Footnotes 28 and 30	"To assess the potential for the basic event failure mode of the emergency-use injector, it is important to use a statistical tolerance interval 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	ISO 16269 provides tolerance intervals for only normal and non-normal data. There are over 20 different data distributions that can be applied to model development data. Using these widely accepted reliability distributions allow the calculation of reliability without having to use non-normal tolerance intervals. Non-normal tests at a 99.9% tolerance interval at a 95% level of confidence would require a 2,995 sample size; a 99.99% interval, 62,956 samples and 99.999%, 3,141,477 samples. Removing the restriction on using only the normal distribution will allow the data to be analyzed based on the most appropriate distribution model with sample sizes appropriate for reliability statistics. Accordingly, we recommend that the Agency add verbiage to the Draft Guidance to allow probability distributions other than	Recommendation to provide clarity to industry on ISO 16269 applicability and use of probability distributions other than the Normal Distribution to be considered in the determination of reliability.

Section #, Line #	Text in Guidance	Proposed Comment and Recommended Edit	Rationale for Change
	reliability study based on the desired reliability specification and confidence interval."	the Normal Distribution to be considered in the determination of reliability.	
Section V.3, 398-408, Footnote 28 and 30	"To assess the potential for the basic event failure mode of the emergency-use injector, it is important to use a statistical tolerance interval 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)."	Recommended edits: "To assess the potential for the basic event failure mode of the emergency-use injector, it is important **to apply an appropriate statistical technique. One example of a statistical technique that can be utilized is** use of a ~~**statistical**~~ tolerance interval method in which the limits of each individual component are analyzed (e.g., dimensions, geometry, material strength, etc.), both by itself and in conjunction with its associated components (i.e., stack-up analysis)."	Specifically recommending statistical tolerance intervals is too restrictive / prescriptive.
Section V.4, 462-464	"Reliability verification testing should be conducted on the final finished combination product…"	Testing or modules and use of a surrogate in lieu of drug product can be appropriate when properly justified as performance "representative" of the finished product. Recommended edits: "Reliability verification testing should be conducted on the final finished combination product **or a surrogate representative of the final finished combination product**…"	Add allowance for the use of surrogate test fluids and for modular testing as long as the testing is representative of the performance of the finished product.
Section VIII, Appendix 625-626	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.	In lines 601-609, definitions for basic event, failure to successfully inject and failure mode are included. To provide additional clarity, we ask that the Agency add a clear definition of "fault" and describe how it fits into the Fault Tree Analysis example provided.	Definition requested for further clarity.