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IPAC-RS Comments on FDA Draft Guidance
"*Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products*"[1]

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) is an international association of companies focusing on orally inhaled and intranasal products. IPAC-RS seeks to advance the science, and especially the regulatory science, through joint research, consensus building, development of best practices, and collaborations among stakeholders.

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IPAC-RS would be open to discussing these comments further, e.g., in a workshop.

Please do not hesitate to contact us if you have any questions.

[1] Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products | FDA OCP/CBER/CDRH/CDER June 2024

GENERAL COMMENTS

General Comments Regarding Overall Process and Clarification of Terminologies and Application

1. The key concern with this draft Guidance is with respect to the lack of consistency relative to other FDA requirements, and internally contradictory recommendations, which cause confusion and potential misapplication of this guidance document. IPAC-RS would respectfully request that this draft Guidance be brought in line with the other existing FDA Guidances and international standards, such as ISO and ICH. Specific suggestions are provided in the comments below.

2. This draft Guidance describes a framework of Design Outputs but does not provide narrative regarding the link from Design Inputs – which is inherently flawed and incongruent with existing guidance. "User requirements", on the other hand, is something that feeds into the Design Inputs. Note, however, that User Requirements are NOT controlled as Design Outputs are. Design Input requirements are a critical foundation in determining the essential Design Outputs, where functional requirements are established for the drug delivery device, and result in the Design Outputs for subsequent verification and validation. Design Outputs are the results of the design process, which is based on Design Inputs. Thus, it is logical that identification of Essential Design Inputs (EDIs) would serve as the basis to ensure the EDOs are appropriately identified per 21 CFR 820.30 (d).

    a. Examples given throughout the guidance as outputs e.g. glide force, cap removal force, dose accuracy are considered Design Inputs, and it is the subsequent specification that arises from these Design Inputs which becomes a Design Output. Suggestion to include detail on the expectations and a footnote explaining that in the generic examples, specific details have been omitted for the hypothetical device or include in hypothetical values to clarify input vs output.

    b. Furthermore, examples of 'system level design outputs' listed on Lines 801-803 of the draft Guidance for a prefilled syringe include cap removal force, deliverable volume, injection depth, and injection forces; however, these are classically considered to be design requirements / performance characteristics of the device (i.e. Design Input requirements) and do not meet the definition of Design Outputs per existing Design Controls regulations and existing FDA Guidance. This is demonstrated by the final FDA Guidance on cGMP Requirements for Combination Products, Section V.A.2.b.i – Design inputs and outputs for Prefilled Syringe

which lists delivered dose, delivery rate (i.e. injection forces), and drug delivery method (i.e. injection depth) as design inputs / user needs for the pre-filled syringe:

i. Design inputs and outputs

The table below includes illustrative examples of design inputs and user needs and related design outputs for this prefilled syringe.

Design Input/User Needs	*Design Output*
Required minimum/maximum dose delivery for drug	Drawing/specification for syringe dimensions, markings, etc.
Drug viscosity and desired/required delivery rate	Drawing/specification for needle bore, glide force, etc.
Expected use condition (e.g., expected user experience/education level)	Content and reading level for the prefilled syringe's labeling
Maximum and minimum allowable temperature for prefilled syringe	Packaging/labeling specifications for the prefilled syringe
No degradation of drug or syringe over the expected shelf-life as a result of contact with one another	Specifications for drug-contacting syringe materials
Expected shipping method and appropriate storage conditions	Design drawings/specifications for primary and secondary packaging, labeling for acceptable storage conditions
Drug delivery method (e.g., needle or needleless delivery)	Drawing/specification for needle and/or other associated syringe components

3. Overall, the guidance does not provide enough definition of terminologies. The terminology surrounding Design Inputs, EDDOs, Essential Performance Requirements, and Primary Functions should be clearly defined to ensure there are no discrepancies in application, and to provide clarity versus existing FDA requirements and definitions.

    a. It may be useful to include definitions for these terms, in addition to CQAs and Design Outputs, to show the link between these items and how they can—or cannot—be used interchangeably. Consider incorporating some of the information in the notes within the body of the guidance itself. Examples where further definition is required: Lines 167-170 where the title of the paragraph is 'Design Outputs' but the content is about design inputs. Also note 8 on Page 1 could be incorporated into the body itself.

    b. Further, when it comes to CQAs and EDDOs, drug and device still seem to be considered separately. It would be beneficial to have further narrative/process as to the linkages between these characteristics, including acknowledgement that CQAs and

EDDOs may overlap and therefore when implementing the control strategy CQAs and EDDOs may be satisfactorily controlled through one test/inspection for both.

c. Institution of the term EDDO and relationship with terminology in other guidance, e.g. CQA in "ICH Q8 (R2): Pharmaceutical Development" and "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products- Quality Consideration" (2018 draft guidance) and EPR in "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". Is it acceptable to continue to use the CQA and EPR terminology in design control and submission documentation if the specific CQAs and EPRs are clarified as EDDOs in some way (e.g. footnote, cross reference or similar).

d. Line 350 - downstream controls. For higher risk products, upstream = in process, downstream = lot release. In the Appendix, in process controls are mentioned rather than release.

4. It is not clearly stated throughout the guidance document that acceptance standards, for example, may be found within other guidance documents (product specific or general). It would be beneficial to have a table or list of relevant standards to the guidance document within the document, in order to enable linkage through the process and ensure alignment on acceptance standards, processes and terminologies.

    a. Consider including specific references to relevant Standards e.g. ISO 11608 series for needle-based injection systems for medical use, ISO 20072 Aerosol drug delivery device design verification, IEC 60601-1 for Medical electrical equipment general requirements for basic safety and essential performance — Requirements and test methods, etc. And guidance such as ICH.

    b. Would like feedback on relationship with other effective or draft guidance for industry such as "ICH Q8 (R2): Pharmaceutical Development" or "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".

5. It is unclear if the new concepts and terminology introduced in the draft Guidance (e.g., Drug Delivery Design Outputs, System Level Design Outputs, Device Dependent Design Outputs, Essential Drug Delivery Outputs) are intended to be implemented as part of formal cGMP Requirements / Quality System Regulations that must be available during facility inspections for drug-device Combination Product

manufacturers. This is referenced without a full explanation on Line 80, Footnote 21, and Lines 470-473 of the draft Guidance. Currently, the final rule on cGMP Requirements for Combination Products only refers to the identification of "design outputs that are essential for the proper functioning of the device" as part of 21 CFR 820 (d) Design Outputs, and does not make reference to the new terminology / concepts introduced in this draft Guidance.

a. As it is currently written, the draft Guidance has the potential to significantly increase the level of evidence required for clinical and marketing applications for drug delivery products, including requests for copies of device development artifacts. The level of information suggested by the Guidance runs counter to the principles outlines in M4Q, ICH Q12, and FDA's eCTD Technical Conformance Guide where only summary information of CMC processes and specifications is provided for Health Authority review. This is further supported by the existing FDA draft Guidance on ICH Q12: Implementation Considerations for FDA-Regulated Products Guidance for Industry issued May 2021, which clearly states that ICH Q12 and the corresponding FDA Guidance applies to combination products with device constituent parts. Requesting this level of documentation evidence also runs counter to the understood principles of why the EDDO concept exists, which has been suggested as a means for the Agency to focus on what is important and essential to the review of the product.

b. Section VIII.A describes what should be included in an IND application. Consider updating associated guidance e.g. "Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products" and "INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information" as these do not contain guidance on what information to include on the device for drug device combination products.

6. Most of the draft guidance seems to have been written with injectors in mind. Some of the approaches are indeed generalizable to other drug-device combination products, such as orally inhaled and nasal drug products (OINDPs), but other concepts are not applicable to OINDPs.

7. The organization of the draft Guidance is extremely confusing. There are two instances of table 1 (in lines 855 and 939) and two tables without a number (lines 828 and 846). Please give numbers to all tables, consecutively, as tables 1-9, or at least unambiguously, (e.g., Table D-1 if it occurs in Appendix D).

Comments Regarding Design Validation of EDDOs

8. As mentioned above, the draft Guidance appears to confuse important terms with respect to design inputs and design outputs as a consequence of the initial conflation of input/output terminology. An important example of this includes repeated references to 'validating EDDOs' within the draft Guidance (see Section VI, Lines 215, 225, 375, 386, 399-400, 427, 564, etc.), which is a misapplication of the term 'validation' given that design outputs are not validated. Design Verification confirms that design outputs meet design input requirements (i.e. device meets performance requirements), while Design Validation confirms that devices conform to user needs and intended use(s) (i.e. devices meet user requirements which are included as part of the definition of Design Inputs). Therefore, it is clear from 21 CFR definitions and existing FDA Guidance that it is inaccurate to say that manufacturers must 'validate design outputs' when in fact design validation confirms that the final finished device meets user needs as part of design inputs, not design outputs.

    a. Would like clarification on the relationship between EDDOs and design verification/validation. If the example EDDOs are desired to be validated, can FDA describe the Design Input that feeds into that EDDO to be verified/validated.

    b. The draft Guidance includes Section VI.B – Design Validation for EDDOs, which includes references to different forms of data to 'validate EDDOs' including clinical studies, PK/PD studies, literature, simulated bench testing, and anthropometric data. No simulated use testing (i.e. human factors engineering) is referenced in the draft Guidance's section on design validation. However, manufacturers of drug delivery devices routinely achieve design validation solely through human factors validation studies without any bespoke clinical studies associated with the commercial device presentation. This approach is supported by existing FDA Guidance that states that Human Factors validation testing can represent design validation (e.g., Applying Human Factors and Usability Engineering to Medical Devices Guidance for Industry and Food and Drug Administration Staff issued February 2016, Content of Human Factors Information in Medical Device Marketing Submissions Draft Guidance for Industry and Food and Drug Administration Staff issued in December 2022, and Bridging for Drug-Device and Biologic-Device Combination

Products Guidance for Industry issued in December 2019). The primary means by which drug delivery devices' intended use / user needs are validated is via simulated use studies (e.g. Human Factors Validation Studies) or use in drug-led clinical studies in which the primary endpoints are safety/efficacy of the drug product delivered via the drug delivery device. In addition, Section VI.B of the draft Guidance also incorrectly lists examples of design validation data (e.g., anthropometric data, simulated bench testing, etc.) that are more regularly utilized by manufacturers as sources of information to justify design input requirements (e.g. injection depth, activation force, etc.). Literature on patient populations, simulated bench testing, and anthropometric data are not used by manufacturers to validate the user needs / intended use of the device, but rather these types of data are utilized to provide rationale / justification for acceptance criteria associated with design inputs so that design input requirements are set appropriately for the intended user / patient populations. Examples of design validation activities may include Human Factors Validation studies, clinical testing, animal testing, compilation of relevant scientific literature on the subject drug delivery device, and device functionality testing in which verification activities are leveraged for design validation purposes. As such, Section VI.B of the draft Guidance should be re-written to properly reflect the appropriate methods of design validation for drug delivery devices, and the sources of data used to support design requirements' acceptance criteria should be removed as methods of validation.

9. We question the recommendation to provide a side-by-side comparison of EDDOs or EDDO performance for an ANDA submission or a BLA submitted under section 351(k) of the PHS act for a combination product. *See* Line 404 - *Additional Validation Considerations for ANDA Submissions and BLAs Submitted under Section 351(k) of the PHS Act for Combination Products*. Recognizing that EDDOs will be subject to design validation, design validation of EDDOs for ANDA submissions and BLAs submitted under section 351(k) of the PHS act for combination products can also be confirmed as per the processes described in Section B, 'Design Validation of EDDOs', as opposed to providing a side-by-side comparison. Design validation by other means than a side-by-side comparison, in combination with provision of a threshold/comparative analysis and any adherence to product specific guidance, would be sufficient for an ANDA submission to demonstrate equivalence and/or comparative performance.

Comments Regarding the EDDO Identification Process – Further Clarification Required

10. It is noted that preparatory steps involved in dose delivery are to be considered in the identification of EDDOs. It is recommended that the scope be clarified such that EDDOs apply to devices and device constituent parts only, and that further packaging (pouches, cartons etc.) are out of scope. Further clarification as to the definition of preparatory steps is also required to support the determination of EDDOs for devices whereby there are numerous preparatory steps, for example, vial kits for reconstitution.
11. Product Preparation – Appendix C gives EDDO example of 'cap removal force' under product preparation stage. Previously this was detailed as including a secondary function for RNS removal in autoinjectors. Would a 'simple' cap removal (such as nozzle cap on a nasal spray), also be defined as an EDDO without any critical secondary function?
12. There are concerns with inconsistency across dosage forms and the examples included in the appendices e.g. categorizing audible and visual feedback as EDDOs (Appendix B, Table 1). Although this type of feedback is required for performance (in terms of allowing the User to determine the status of drug delivery and thus verified as a Design Output) they are not essential in achieving drug delivery and no harm would come to the User if the audible/visual aspect of the design failed to operate. This distinction is important to avoid any ambiguity between what is considered an Essential Drug Delivery Output versus a Design Output.

Comments Regarding Testing/Device Control Strategy

13. It is appreciated that FDA has provided the following clarifications within the draft Guidance:
    a. Manufacturers can rightfully justify upstream testing/evaluation as part of a device control strategy such that not all device functions are required to be tested on release
    b. Manufacturers should not need to conduct product stability, device shelf-life, or release testing on device parameters (such as component dimensions) that should not be expected to change over time
    c. Manufacturers can leverage accelerated aging data to support product shelf-life claims within marketing applications
    d. Manufacturers of non-emergency use products should not be expected to conduct sequential preconditioning as part of design verification testing

Comments Regarding Risk Management

14. **Fault Tree Analysis (FTA)** – There are multiple sections where Fault Tree Analysis would seem an appropriate method of determining component level outputs from system level (eg pg 7); could the FTA standard be recommended as is done in the '..Reliability of Emergency-Use Injectors..' guidance?
15. **'EDDO related risks'** – pg.16 - expected to have separate call out in Risk Management activities – or expecting an FTA for each of the EDDOs?

SPECIFIC LINE-BY-LINE COMMENTS

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 17-19		Please use consistent terminology within the guidance.	It is stated that the expression "**drug delivery devices**" will be used as short for all types of devices, products and parts that are listed on p1, row 17-19, but later in the guidance text, longer expressions are used, e.g. p4, row 78 "**drug delivery devices and combinations products**" and p15, row 504 "**device or device constituent part**". It would be clearer and more concise if the short expression "drug delivery devices" was used consistently, as stated at p 1.
Line 19 Footnote 6	intended for delivery of a human 18 drug, including a biological product5 (herein referred to as *drug delivery devices*).6 (6.For the purpose of this guidance, the terms *drug* and *drug constituent part* are used interchangeably.)	Revise, delete or clarify the footnote.	Footnote 6 talks about "drug constituent parts," while the text which it is footnoting is talking about "drug delivery devices" in line 19. How does that footnote apply?

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 73	In accordance with this provision, manufacturers shall ensure that EDDOs are identified and approved before release (21 CFR 820.30(d)).	In accordance with this provision, manufacturers shall ensure that EDDOs are identified and approved before release or transfer to the next design phase or production (21 CFR 820.30(d)).	To add further clarification as to the term 'release', as discussed in questions on 820.30(d).
Line 77-80	EDDO-related information, including verification and validation data, is provided in investigational and marketing applications for drug delivery devices and combination products with drug delivery devices to demonstrate that the drug delivery device appropriately delivers the intended drug dose to the intended delivery site. In addition to being part of design control activities, the EDDO processes discussed in this guidance can also be used for defining a control strategy.	EDDO-related information, including summaries of verification and validation activities if applicable, is provided in investigational and marketing applications for drug delivery devices and combination products with drug delivery devices to demonstrate that the drug delivery device appropriately delivers the intended drug dose to the intended delivery site. In addition to being part of design control activities, the EDDO processes discussed in this guidance can also be used for defining a control strategy for the device.	It is important to emphasize that summaries of verification and validation activities may be provided in investigational and marketing applications. It is important to note that design validation activities may not be completed or fully initiated at the time of investigational applications. Important to emphasize that EDDOs may contribute to the device part's control strategy for a drug-device combination product, but would not be sufficient to dictate and entire combination product control strategy, including the drug product.

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 106-116	Similar to the CQA concept, as noted above, EDDOs are essential for the appropriate functioning of the device, and in some instances, an applicant could expand CQAs to include device drug-delivery function features for a combination product. Likewise, a quality target product profile (QTPP), which is similar to design inputs (see 21 CFR 820.3(f) and 820.30(c)), may assist an applicant in identifying CQAs, including those for drug delivery. As appropriate, studies conducted to verify that the CQAs are met may address EDDO verification and validation. Applicants may be able to leverage CQA information to support EDDO identification, control, and maintenance processes. When the EDDO is amenable to verification and validation through analytical methods (see section VI), the chemistry, manufacturing, and controls (CMC) information may address these design control requirements.	Similar to the CQA concept, as noted above, EDDOs are essential for maintenance of the appropriate quality and functioning of the device, and in some instances, an applicant could expand CQAs to include EDDOs for a combination product. Likewise, a quality target product profile (QTPP), which is similar to design inputs (see 21 CFR 820.3(f) and 820.30(c)), may assist an applicant in identifying CQAs, including those for drug delivery. For combination products, FDA acknowledges that the EDDOs could be interpreted as analogous to ICH Q12 Established Conditions (ECs) of a device constituent of a drug-device combination product as outlined in Module 8 of the ICH Q12 Training Materials 'Drug-Device Combination Products that meet the Definition of a Pharmaceutical or Biological Product Example for ICH Q12'. Based on ICH Q12, selection of ECs for the device constituent involves assessing the "characteristics of the product that are essential for its safe and proper use" (primary characteristics) and identifying the ECs associated with these primary characteristics based on a predefined intended use of the product.	See General Comment regarding ICH Q12 Established Conditions It is important to properly align the concept of EDDOs with ICH Q12 in alignment with FDA Guidance and ICH Q12 training materials for drug-device combination products, which was co-developed with FDA and industry. Deleted lines associated with 'EDDO verification and validation activities' due to improper use of design control terminology – see General Comment Reference link: Module 8 of the ICH Q12 Training Materials 'Drug-Device Combination Products that meet the Definition of a Pharmaceutical or Biological Product Example for ICH Q12'.
Line 123-124	Ensuring the appropriate device design attributes and manufacturing process steps are evaluated during lifecycle changes	Ensuring the appropriate device design attributes and manufacturing process steps are evaluated during lifecycle changes **(e.g., identification of design outputs as Established Conditions);** and	Important to emphasize that identification of Established Conditions in line with ICH Q12 principles is a streamlined way to evaluate lifecycle changes of drug delivery devices

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 135-143	• **Identification** of the EDDO defines the device drug-delivery function of the product and focuses design and development efforts to ensure appropriate drug delivery. • **Control** of the EDDO ensures the product meets the device drug-delivery function quality standards. See section VII for information on control strategy. • **Maintenance** of the EDDO ensures that any changes to the product made during clinical development or post-market that could adversely impact the EDDO are evaluated to help preserve the quality of the drug-delivery function.	• **Identification** of the EDDO defines the necessary drug-delivery function requirements of the device and streamlines submission content as part of the product's clinical and marketing applications. • **Control** of the EDDO ensures the product meets the device drug-delivery function quality standards. See section VII for information on control strategy. • **Maintenance** of the EDDO ensures that any changes to the product made during clinical development or post-market that could adversely impact the EDDO are evaluated to help preserve the quality of the drug-delivery function. The process of identifying EDDOs follows the principles of identifying Established Conditions for device constituents of drug-device combination products in ICH Q12.	Identification – Important to emphasize that the primary goal of EDDO identification is to streamline FDA submission content • Maintenance – important to emphasize the relationship between EDDOs and ICH Q12 Established Conditions when discussing lifecycle changes to drug-device combination products
Line 165-171	(1) **Design Outputs** – Begin by defining the proposed intended use, consider, e.g., the indications for use, population, and condition and frequency of use, and design inputs (e.g., user requirements, design specifications, route of administration, drug characteristics, dosage form, and delivery volume). This information should be used to identify the design outputs.	1. **Design Inputs** – Begin with all design input requirements for the device that address the intended use of the device, including the needs of the use and patient. Sources of design input requirements include desired performance characteristics, risk, biocompatibility, human factors, sterility, user/patient preferences, etc.	See General Comments These recommended changes are in alignment with FDA / CDRH Guidance on Design Controls and FDA inspection plain language guidance
Line 173-175	**Drug Delivery Design Outputs** – Identify those design outputs related to the delivery of the drug (e.g., related to the intended dose; delivery to target site; method of delivery; product preparation; and the initiation, progression, and completion of dose delivery).	**Essential Design Inputs** – Identify any design input requirement essential to the safe and/or proper functioning of the device (e.g., the intended dose; delivery to target site; method of delivery; product preparation; and the initiation, progression, and completion of dose delivery).	These recommended changes are in alignment with FDA / CDRH Guidance on Design Controls and FDA inspection plain language guidance

Line 177-180	**System Level Design Outputs** – Identify the drug delivery design outputs that are system level design outputs (i.e., design outputs that are the functions necessary for the performance of the final finished product). For more information, see the discussion below following step 4 and in Figure 2.	**Essential Device Functions (EDFs)** – Identify the system-level Essential Design Inputs (EDIs) that are dependent on the device design and necessary to achieve drug delivery in the context of the risk profile of the product. . Examples of EDFs could include delivered volume, injection time, injection forces, etc. For more information, see the discussion below and in Table A of . Examples of EDI / EDF considerations for an autoinjector: • Delivered volume / dose accuracy is an EDF because it is a functional EDI directly associated with drug delivery • Biocompatibility is not an EDF because it is a non-functional EDI • Container closure integrity is not an EDF because it is non-functional and requires no interaction between the user and the device • Cap removal force may be an EDF depending on the risk profile of the product. It is not directly associated with drug delivery, but rather a preparatory step and as such would not be considered an EDF. However, if a delay in delivery of the drug could pose a high severity of harm, then cap removal force may be considered an EDF as it is an essential function for on-time delivery of the drug. • Plunger breakloose force is not an EDF for an autoinjector because it is a functional requirement that contributes to other system-level drug delivery requirements of the device (e.g., delivered volume and injection time). Plunger breakloose force is an EDI for an autoinjector.	These recommended changes are in alignment with FDA / CDRH Guidance on Design Controls and FDA inspection plain language guidance

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 182-186	(4) Device Dependent Design Outputs – Identify the system level drug delivery design outputs that are independent of the user and dependent on the device design. This step is to assure that design and manufacture of the product are adequately controlled. (This step is not intended to address usability because drug delivery performance that depends on the user is not an EDDO).		We would appreciate further clarity on the term 'independent of the user'. Is this intended to mean that EDDO performance is independent of human factors/ validation (i.e. effectiveness of the feature)?
Line 188-191	As described in step 3, an EDDO is a system level design output. We note that there are other design outputs known as component level outputs that are different from system level outputs. Component level outputs work together to achieve a system level output and are not EDDOs. Component level outputs support, but are subordinate to, system level outputs (see Figure 2).	As described in step 3, an EDDO is directly associated with a function of the device necessary in achieving the intended use of drug delivery. We note that there are other EDIs that will not meet this threshold, but will still result in the identification of EDDOs to assure that the design and manufacture of the product are adequately controlled (see Figure 3 – new, below).	See General Comments
Line 193 Figure 2	Component level output > needle > needle length/diameter	Add one more dashed section in the image, to separate the component from the component level output	The third column should be the outputs
Line 204-208	See Appendix A for a narrative illustration of the process concepts for identifying EDDOs for a PFS. Appendix B illustrates the distinction between EDDOs and other design outputs for an autoinjector. In addition, this document provides examples of design outputs for common combination products with drug delivery devices that are likely to be considered EDDOs (see Appendix C).	See Appendix A for a narrative illustration of the process concepts for identifying Essential Device Functions (EDFs) for a PFS. Appendix B illustrates the distinction between EDFs and other design inputs for an autoinjector. In addition, this document provides examples of design inputs for common combination products with drug delivery devices that are likely to be considered EDFs (see Appendix C).	See General Comments

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 221-225	In addition to the storage and shipping stressors, there are stressors associated with the use environments (e.g., health care facility, school, home, first response environment). Verification and validation test reports provided in a submission should provide information on how the tests conducted, including the conditions and methods selected, are adequate to verify and validate the EDDOs.	In addition to the storage and shipping stressors, there are stressors associated with the use environments (e.g., health care facility, school, home, first response environment) that may be considered for validation activities. Verification and validation information provided in a submission should provide information on how the tests conducted, including the conditions and methods selected, are adequate to verify and validate the drug delivery device.	Important to clarify that use environment stressors relate to design validation activities such as human factors studies. Important to clarify that summary design verification and validation information is sufficient for submission content and individual test reports are not always necessary for submissions. Important to clarify that design outputs are not verified / validated. Design verification confirms design input requirements are met, and design validation confirms user needs / intended uses are met.
Line 235	It is important that prior to initiation of any clinical studies (or any in vivo bioequivalence studies, as applicable) or commercial distribution, applicants verify the performance of the product	It is important that prior to initiation of any clinical studies (or any in vivo bioequivalence studies, as applicable) or commercial distribution, applicants verify the performance of the product to an appropriate level in line with the development stage	Verification requirements ahead of a Phase I in clinic study may be less than those required for a Phase III at home study, therefore the applicant should verify appropriate to the development stage
Line 237	How applicants conduct design verification testing is dependent on device design, intended use, and applicable regulations, standards, and guidances	How applicants conduct design verification testing is dependent on device design, intended use, and applicable regulations, standards, and guidances. Applicants may leverage test methods, acceptance criteria, and statistical analysis techniques from recognized standards	Addition of this language to the beginning of this section will clarify that using existing Standards applies to **all** elements of Design Verification Testing (DVT) rather than specific parts of it, i.e. lines 259-261 is currently only in 'Preconditioning' section

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 237		It is important that prior to initiation of any clinical studies (or any *in vivo* bioequivalence studies, as applicable) or commercial distribution, applicants verify the performance of the product to ensure the device is safe for use and will meet design requirements.	Important to emphasize the primary goal of any design verification testing to support use of a device in clinical studies is to establish safe use
Lines 257 to 259	Because of the risk to the patient should the device fail, sequential preconditioning is generally expected for emergency-use injectors, and applicants should identify the sequence in which the preconditions should be applied.	Revise, clarify, or delete	FDA Draft Guidance for Industry, 'Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA" does not mention sequential preconditioning.
		Because of the risk to the patient should the device fail, sequential preconditioning is generally expected for single-dose emergency-use injectors, and applicants should identify the sequence in which the preconditions should be applied.	Important to clarify that multi-dose drug delivery devices may not be required to meet the same sequential preconditioning recommendations as other single-dose emergency use products. For example, rescue metered-dose inhalers are often multi-dose products that have a significantly different risk profile as it relates to first-dose failure as compared to single-dose emergency-use autoinjectors.
Lines 316-319	… the protocol should enable assessment of the impact of actual preconditions associated with use (e.g., repeat use following the instructions for use including any reprocessing steps) and verification that the EDDO is maintained following preconditioning.	… the protocol should enable assessment of the impact of actual **preconditioning** associated with use (e.g., repeat use following the instructions for use including any reprocessing steps) and verification that the EDDO is maintained following preconditioning.	This would be the normal/standard/expected use of the term *precondition*.
Line 318	..verification that the EDDO is maintained following preconditioning.	… verification that the EDDO is met following preconditioning.	Clarify that design verification confirms design inputs are met (not maintained)

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 333	A design verification testing protocol should include a statistical sampling plan with the number of lots to be tested and acceptance criteria.	A design verification testing protocol should include a statistical sampling plan with the lot(s) to be tested and acceptance criteria.	Clarify that multiple lots are typically not necessary for design verification testing (multiple lots are typically used for product stability testing)
Line 334	The tested lots should be manufactured using principles that are representative of the commercial process (e.g., materials and methods of manufacture)	The tested lots should be manufactured using representative commercial processes (e.g., materials and methods of manufacture) or final finished product as appropriate for the design and development stage	Adding this wording allows flexibility for the manufacturer to define what is appropriate to use depending on the development stage. It is also then consistent with line 623
Line 341	For a combination product, such data can be derived from design verification shelf-life testing, stability testing, or both	For a combination product, such data can be derived from design verification shelf-life testing, product stability testing, or both.	Clarify that stability testing is intended for the product and not just the device
Line 362	As appropriate, accelerated aging data may be used to establish the shelf life. When used, accelerated aging data should be confirmed by real-time aging data.	As appropriate, accelerated aging data may be used to establish the shelf life. When used, accelerated aging data **shall** be confirmed by real-time aging data.	"Shall" is mandatory, which is the case for shelf-life assignment
Lines 366	B. Design Validation for EDDOs	B. Design Validation for Drug Delivery Devices To ensure appropriate design validation, the applicant must ensure that devices conform to defined user needs and intended uses. As mentioned above, design validation is a process that inherently assesses the entirety of the device including all functions, materials, and interface elements. However, in the context of premarket reviews for drug delivery devices, the Agency intends to focus review of design validation aspects on EDDOs.	Important to clarify that design validation information provided in submissions will focus on aspects of EDDOs
Lines 372 to 373	The most appropriate method may depend on the application type, stage of development, and EDDO.	Revise, clarify or delete.	Can the Agency clarify when it is appropriate to undertake validation within a development program rather than upon completion of development?

Location	Original Text	Proposed Changes	Rationale/Comment(s)
374-375	For certain application types, examples of methods available to validate the EDDO specifications may include the studies identified below.	REPLACE with "Methods for the validation of the EDDO specifications may be included as parts of the clinical studies or the PK/PD or bioequivalence/bioavailability studies"	The meaning of the original sentence in the draft guidance is unclear.
Line 439 onward		**VII. CONTROL STRATEGIES FOR ESSENTIAL DRUG DELIVERY FUNCTIONS**	See General Comments Also, Section VI states control strategies are risk based. It would be useful to understand whether there is a spectrum of criticality within the EDDO classification and whether there are specific criteria as to whether certain EDDOs can qualify for upstream controls.
Line 441	After completion of the design verification and validation processes described in section VI…	After completion of the design verification and validation activities described in section VI,…	Clarify wording to focus on activities and not processes
Line 451-452	Therefore, the number and types of controls implemented, and the amount of information regarding the control strategy to include in an application should correspond to the product risks.	Therefore, the number and types of controls implemented should correspond to the product risks.	Suggest to remove text that discusses submission content given discussion in Section VII – Information to Provide in Applications

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Lines 452-457	For a lower risk product with less complex manufacturing processes, certain EDDOs may be adequately controlled with downstream controls. A possible example is release testing of glide force and breakloose force on a PFS with a non-emergency use drug for administration by a health care provider. In contrast, for a higher risk product, a combination of upstream and downstream controls may be needed to ensure consistent EDDO performance.		The current text in Section VII lines 452-457 does not seem to be in alignment in terms of potential control for downstream and upstream controls. A lower risk product seems only to be permitted to be controlled via downstream controls, whilst a higher risk product may be controlled via a combination of upstream and downstream controls. The example used in Appendix D, whilst referring to needle extension length for an autoinjector (in itself potentially a higher risk product), indicates that upstream controls may be effective at the supplier level as they are not subject to change after assembly and filling or over the shelf life of the autoinjector. Depending on the product risk, it seems reasonable to determine that upstream controls alone may be sufficient to demonstrate control in certain circumstances.
Line 536-539	Provide a description of the device design, including any novel features and functionalities, including engineering drawings or diagrams of the device with all dimensions labeled, descriptions of the individual device components, or any other available information to explain the device design.	Provide a description of the device design, including any novel features and functionalities, including engineering drawings or diagrams of the device, descriptions of the individual device components, or any other available information to explain the device design.	Clarify that this level of detail is not necessary for original submission content and is rather available upon request / inspection if necessary

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 546-550	Device safety – Identify EDDOs that are necessary for patient safety during the study. For example, a device may cause harm if the dose accuracy performance is not adequate (e.g., by delivering a larger dose than intended). For safety-related EDDOs, provide verification and validation data prior to the start of a clinical study. See Performance data for data recommendations.	Device safety – Identify EDDOs that are necessary for patient safety during the study. For example, a device may cause harm if the dose accuracy performance is not adequate (e.g., by delivering a larger dose than intended). For safety-related EDDOs, provide verification data prior to the start of a clinical study. See *Performance data* for data recommendations.	Clarify that clinical study submissions should not be expected to include design validation data at this stage
Line 561	The following considerations apply when the clinical study results are part of the EDDO validation:	The following considerations apply when the clinical study results are part of the design validation for a drug delivery device:	Reword for accuracy
Line 564-570	If the clinical study is intended to obtain data to validate one or more EDDOs, it is appropriate for the clinical study protocol to include endpoints relevant to the performance of the device (e.g., infusion rate, dose range, injection time). Where possible, to support provision of evaluable EDDO data, applicants should submit such protocols for Agency feedback on the EDDO validation endpoints in a formal meeting or communication with FDA (see section IX). Also, such clinical studies should be conducted with the final finished drug delivery device.	If the clinical study is intended to obtain data to support design validation of a drug delivery device, applicants should submit such protocols for Agency feedback in a formal meeting or communication with FDA (see section IX). Also, such clinical studies should be conducted with the final finished drug delivery device.	Remove reference to endpoints related to device performance in clinical study protocols as this is often not the case for drug delivery devices in which the devices are used in drug-led clinical studies that only contain product related safety/efficacy endpoints

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 623	Performance data – Include acceptance criteria and performance data verifying and validating the final finished product.	-	Guidance is not consistent throughout on the requirement of using devices that are either representative of the commercial product or FFF. This line states FFF is required for verification, whereas line 334 requires only representative product to be used in verification activities.
Line 625	Provide the following data:	Examples of the information include the following:	Clarify that these are examples of information that could be provided but may not be required (e.g. design verification reports vs summary data)
Line 652	When verifying and validating the EDDO(s), include the EDDO(s) in the following evaluations, when applicable as discussed in sections VI and VII:	When verifying EDDO(s), include the EDDO(s) in the following evaluations, when applicable as discussed in sections VI and VII:	Clarification that the activities listed in Section 8.B.3 are not related to design validation activities

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 663-671	Control strategy – Provide a control strategy based on the product risk profile that ensures that the final finished product maintains its EDDO(s). Include a summary of the controls implemented (upstream and/or at release), including a justification describing how the controls are sufficient to assure the quality of the EDDO is achieved. In the control strategy description, include supporting evidence such as engineering drawings, tolerance stack-up analysis, and manufacturing flow diagrams. FDA may request additional specific documentation referenced in the control strategy during the review. Applicants can consult with the appropriate product office for questions regarding control documentation to include in a submission.	(c) Control strategy – Provide a summary of the device control strategy based on the product risk profile that ensures that the final finished product maintains its EDDO(s). Include a summary of the controls implemented (e.g., upstream and/or at release), including a justification describing how the controls are sufficient. FDA may request additional specific documentation referenced in the control strategy during the review. Applicants can consult with the appropriate product office for questions regarding control documentation to include in a submission.	Important to emphasize that a summary of the device control strategy should be provided in marketing applications, not the entirety of the control strategy (which would be available upon inspection) Give this table an appropriate, consecutive number
Line 677-680	When modifying the product design or manufacturing process of an approved or cleared product, applicants should evaluate whether there are any new EDDOs and verify and validate the new EDDOs, as appropriate. Applicants should also perform an analysis of the impact of the change on the verification and validation of the previously identified EDDOs.	When modifying the product design or manufacturing process of an approved or cleared product, applicants should evaluate whether there are any new EDDOs and re-verify and re-validate the drug delivery device, as appropriate. Applicants should also perform an analysis of the impact of the change on the verification and validation of the previously identified EDDOs. Also, please add footnote to this text to allow the utilization of CQA and EPR terminology as appropriate with EDDO clarification in an appropriate manner (e.g. footnote, cross reference or similar).	Wording clarification Also, add a footnote because for post-market submissions these are likely to be pre-existing (before the inclusion of the EDDO within guidance) therefore it is desired to have consistency of terminology with the pre-existing package and the appropriate link to the EDDO which is directed by this new guidance.

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 717	…to shift outside the validated specifications over time or…	…shift outside the specifications over time or…	Specifications are not 'validated', the user needs / intended uses are validated per design control definitions
Line 726-728	If the specifications are changing, provide new EDDO validation data or a rationale for why the validation from the original application can be leveraged (e.g., tightening a specification).	If the specifications are changing, provide new **verification** / validation data or a rationale for why the **verification** / validation data from the original application can be leveraged (e.g., tightening tolerance of an EDDO acceptance criteria).	Clarify that verification data may be appropriate to support new specifications, not validation data. Correct terminology used in example.
Line 761-764	These meetings would include discussion of the proposed control strategy and the proposed approach and timing of EDDO validation (e.g., type of studies and completion before beginning the pivotal clinical studies).	These meetings would include discussion of the proposed control strategy and the proposed approach and timing of EDDO verification and validation activities (e.g., type of studies and completion in relation to pivotal clinical studies and marketing submissions).	Important to clarify that validation activities may not be completed prior to initiation of clinical studies
Appendix A			Appendix A provides an example of expected EDDOs for a Pre-Filled Syringe (PFS). Appendix C also provides an example table of expected EDDOs for a PFS however the two examples do not match (Appendix C includes needle length and withdrawal force). We would request that the content is aligned between the two Appendices to avoid potential confusion and disparity.
Line 774-776	During development, the applicant considers the design inputs in identifying the design outputs and identifies which design outputs are essential drug delivery outputs (EDDOs).	During development, the applicant identifies the design inputs, and subsequently which of those inputs are essential. Specifications determined for the essential design inputs are subsequently essential drug delivery outputs (EDDOs).	See General Comments

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 778-783	**Step 1 – Identify Design Outputs** The applicant first identifies the device design outputs as part of design control activities. Design output requirements include all attributes of the device necessary to meet intended user needs and include, for example, specifications for deliverable volume, clarity of the barrel, biocompatibility, sterility, color of plunger rod, markings on the barrel, material performance characteristics, needle safety activation force, and needle guard characteristics.	**Step 1 – Identify Design Inputs** The applicant first identifies the device design inputs as part of design control activities. Design input requirements include all attributes of the device necessary to meet intended user needs and include, for example, requirements for deliverable volume, biocompatibility, sterility, color of plunger rod, markings on the barrel, needle safety activation force, break loose and glide force, and needle length.	See General Comments
Line 785-789	**Step 2 – Identify Drug Delivery Design Outputs** As design outputs are being developed, the applicant analyzes the tasks needed to deliver the intended drug dose with the PFS to the intended delivery site, including the successful product preparation and the initiation, progression, and completion of dose delivery, and identifies design outputs related to these tasks. These are the drug delivery design outputs.	**Step 2 – Identify Essential Design Inputs** As design inputs are being developed, the applicant analyzes the requirements necessary to safely deliver the intended drug dose with the PFS to the intended delivery site, including the successful product preparation and the initiation, progression, and completion of dose delivery, and identifies design inputs related to these tasks. These are the essential design inputs (EDIs) for the safe and/or proper functioning of the device.	See General Comments

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 794-799	**Step 3 – Identify System Level Design Outputs** The applicant analyzes the drug delivery outputs to identify system level drug delivery outputs. For example, the applicant determines that glide force is a system level drug delivery output because it is necessary for the progression and completion of the dose. (See Figure 2 for an illustrative example of the relationship between system level and component level design outputs.)	**Step 3 – Identify Essential Device Functions** The applicant analyzes the drug delivery inputs to identify the EDIs that are system level functions dependent on the device design and necessary to achieve drug delivery in the context of the risk profile of the product. For example, the applicant determines that glide force is a system level function necessary for drug delivery because it is necessary for the progression and completion of the dose.	See General Comments
Line 796 (and throughout examples)	the applicant determines that glide force is a system level drug delivery output because it is necessary for the progression and completion of the dose.	the applicant determines that glide force of x +/- y N is a system level drug delivery output because it is necessary for the progression and completion of the dose.	Outputs should be measurable and include tolerances; “glide force” alone is not an output.

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 801-823	After assessing the device, the applicant identifies the following system level drug delivery outputs: cap removal force, deliverable volume, injection depth, and injection forces (breakloose force, glide force, needle safety activation force).	After assessing the device, the applicant identifies the following system level EDIs: deliverable volume, and injection forces (breakloose force, glide force, needle safety activation force). The specification to subsequently control the EDI is EDDO. The applicant determines that while the target injection site is subcutaneous tissue and the PFS is prestaked with a 12 mm needle, the user controls the injection depth through the injection technique. Therefore, the injection depth is dependent on the user and not a function of the device of the device; therefore, it is not an EDI. The applicant determines that while the cap removal force is necessary to prepare the PFS for dose delivery (i.e. proper functioning), the risk profile of the PFS product is such that a delay in dose would not cause harm to the patient. Therefore, the cap removal force is not considered an EDI since the it is not a device function whose failure would result in harm to the user and/or patient.	No Step 4 necessary – recommend streamlining the process and removing further burden from manufacturers Important to clarify that due to the risk profile of the product, cap removal force would not be considered an EDI
Line 828		Table 1 (or Table A-1)	Give a number to this table for ease of reference.
Line 828		Based on these assessments, the applicant determines that the following are EDIs for the PFS product. For this illustrative example, the EDIs are categorized in the table by the different aspects of drug delivery (top row) to which they are related. Delivery of intended dose: Deliverable volume Delivery to the target site: N/A Product preparation: N/A Initiation of dose delivery: Breakloose force Dose delivery progression: Glide force Dose delivery completion: Glide force, Needle safety activation force	Edits based on comments above

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 833-845	As an illustrative example of the distinction between essential drug delivery outputs (EDDOs) and other design outputs, the table below lists design outputs that were identified following consideration of hypothetical design inputs. The resulting hypothetical product is an autoinjector with a prefilled syringe (PFS) subassembly device constituent part that is also the primary container closure for the drug constituent part. The table shows the outcome of applying the filtering steps to each design output. The design outputs that meet the criteria of each of the filtering steps are EDDOs. The design outputs with gray shading in one or more columns do not meet the criteria of a filtering step(s) and are not EDDOs (i.e., gray shading in the *System level* column means the design output does not meet the system level criteria and is therefore, not an EDDO). As an example, dose accuracy meets each of the criteria for an EDDO and therefore is an EDDO. In contrast, the design output of PFS-fill volume/container content, meets the criteria of a drug delivery design output but does not meet the criteria of system level or device dependent and therefore is not an EDDO.	As an illustrative example of the distinction between essential design inputs (EDIs) and other design inputs, the table below lists design inputs that were identified following consideration of hypothetical user needs. The resulting hypothetical product is an autoinjector with a prefilled syringe (PFS) subassembly device constituent part that is also the primary container closure for the drug constituent part. The table shows the outcome of applying the filtering steps to each design input. The design inputs that meet the criteria of each of the filtering steps are EDIs. The design inputs with gray shading in one or more columns do not meet the criteria of a filtering step(s) and are not EDIs (i.e., gray shading in the EDI column means the design input does not meet the EDI criteria and is therefore, not an EDI). As an example, dose accuracy meets each of the criteria for an EDI and therefore is an EDI. In contrast, the design input of biocompatibility, meets the criteria of an essential design input but does not meet the criteria of EDI and therefore is not an EDI. Once the design outputs are finalized, the design output associated with the EDI becomes the EDDO e.g., glide force is the EDI, a glide force specification of X N +/- Y N is the EDDO.	See General Comments

Location	Original Text	Proposed Changes	Rationale/Comment(s)
Line 872 Table 3	Nasal Spray Delivery of intended dose = Droplet Size Distribution Particle Size Distribution Spray Pattern	Update terminology 'Particle Size Distribution' to 'Aggregated Drug Particle Size Distribution' to align with the existing FDA Guidance "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products--Chemistry, Manufacturing, and Controls Documentation". Move Droplet Size Distribution and Aggregated Drug Particle Size Distribution from 'Delivery of intended dose' to 'Delivery to the target site'	Align with terminology in existing FDA Guidances. Droplet size distribution and aggregated drug particle size distribution are aligned with the delivery to the target site (rather than the delivery of intended dose).
Line 876 Table 4	For MDI and DPI Delivery of intended dose = Emitted Drug	correct 'emitted drug' to 'delivered dose' where noted for MDI and DPI to align with the "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products- Quality Consideration" (2018 draft guidance) and USP <601>	Align with terminology in existing guidance and documentation.
Line 883		Add a table non-pressurized metered dose inhalers (also known as soft mist inhalers)	Soft mist inhalers are an important category of drug-device combination products and should be included in the consideration.
Line 846		Table 2 (or Table B-1)	Give a number to the table in Appendix B, e.g., as Table 2 or Table B-1.
Line 935	…in-process work instructions relating to this process step, and validation data…	… in- process work instructions relating to this process step, and process validation data…	Important to make distinction between process validation and design validation