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

Reference: Docket No. FDA-2024-D-2560 for "Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products; Draft Guidance for Industry"

Dear Madam or Sir,

PDA appreciates the opportunity to provide feedback to the FDA as the Agency provides recommendations related to the device design outputs that are essential for establishing and assessing drug delivery performance. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this important guidance.

PDA is a non-profit international professional association of more than 10,000 individual members who are industry professionals having an interest in fields of pharmaceuticals, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in the Public Docket on behalf of PDA's Biopharmaceutical Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,

Glenn E. Wright
President and CEO

CC: Josh Eaton, PDA; Carrie Horton, PDA; Jessie Lindner, PDA; Danielle Bretz, PDA

PDA (Parenteral Drug Association®) Comments to FDA Draft Guidance Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products

General Comments

Comment(s)
PDA recommends changing the draft guidance title from "Essential Drug Delivery Outputs for Devices Intended to Delivery Drugs and Biological Products" to "**Application of Essential Drug Delivery Outputs for Combination Products and Medical Devices: Guidance for Industry & Staff**". The current title, "Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products", does not clearly convey that the guidance applies to medical devices and device constituents for all current and future therapies (e.g., cell and gene therapy) for the various topics covered (verification & validation strategies, submission expectations and control strategy). Therefore, we recommend the Agency adopt the suggested title, or similar title, which does not limit it only to biological products. Additionally, we recommend inclusion of "Guidance for Industry & Staff" to ensure alignment of FDA review staff to these recommendations, ensuring consistency.
PDA recommends keeping Appendix C. Examples of Potential Essential Drug Delivery Outputs Based on Product type. In *Appendix C. Example of Potential Essential Drug Delivery Outputs Based on Product Type*, the draft guidance provides numerous examples of EDDOs identified and accompanying rationale. The examples provide clarity and early agreement on EDDOs for common drug delivery systems. PDA believes inclusion of these examples may reduce the number of meeting requests needed regarding identification of EDDOs once this guidance is finalized. Therefore, it is recommended to keep the Appendix when finalizing the guidance.
PDA suggests modifying the scope to only apply to standalone medical devices which are intended or indicated for delivery of a specific drug or biologic. This guidance would apply to many standalone medical devices that are indicated or used for "general delivery" and not for a specific drug or biologic and are not combination products. This would impact many medical devices such as syringes, needles, vial transfer sets, infusion sets, intravascular catheters, infusion ports, sterile fluid connectors, aerosol chambers, mouthpieces, and even standalone software that are not combination products, and which are not indicated or intended for use with a specified drug or biologic. Most, if not all, of these are already covered by FDA Guidance documents and/or international standards that have proven adequate to ensure the availability of safe and effective products. In the exceptional instance that one of these products is only marketable as part of the drug product under a NDA or BLA, then the drug is known and there may be some appropriate EDDOs for the combination product. In addition, the EDDOs identified in the appendices for inhalation and nasal delivery products are already well addressed in guidance and pharmacopeial monographs and would not necessarily be applicable if the product was marketed without a specified drug or biologic. While some of the ideas and approaches provided in the guidance may be helpful for some of these products, they should be excluded from this guidance and, if of value, integrated into the CRDH and CDER guidance documents and standards that already address these products.

SECTION I: INTRODUCTION *(lines 15-45)*

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
25, FN 8	FN 8: "Prior to this guidance, the term essential performance requirements (EPR) was generally used in communications between FDA and applicants for the EDDOs described herein. FDA is now using the term EDDO as we believe it is more descriptive."	PDA suggests the Agency provide a transition period of at least 1 year and a include a "grandfathering" approach. The transition period is suggested to occur after finalization to allow sponsors to update any design control procedures and internal processes. The proposed period of 1 year also coincides with CDRH's final rule to harmonize 21 CFR 820 with ISO 13485. The guidance should also allow Sponsors to continue to use EPRs and control strategies where FDA issued written agreement or acknowledgement for a given delivery system unless design changes were introduced.	In Footnote 8, the draft guidance acknowledges that it has been using the term "Essential Performance Requirement" in communications between FDA and industry. Given its use by FDA for years and the proposed definition being tied to design control requirements, some industry members may have included their own definition of EPRs in their quality systems and submission processes in advance of the draft guidance release. Additionally, FDA and sponsors may have come to an agreement via meeting request or marketing applications on EPRs and control strategies for a given delivery system.
28-29	"...demonstrate that the device drug-delivery function performs as intended."	PDA suggests adding the following text: "...demonstrate that the device drug-delivery function performs i**n a manner necessary to ensure delivery of the intended drug dose to the intended delivery site."**	Additional wording is consistent with the provided "definition" in this document.

SECTION II: SCOPE AND DEFINITION *(lines 48-61)*

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
50-52	"The focus of this guidance is the information and data developed and submitted to FDA regarding EDDOs for devices and device constituent parts of CDER-led and CBER-led combination products intended for delivery of a human drug, including a biological product."	PDA recommends that the language in the scope section is clarified to include drug delivery medical devices regulated by CDRH or CBER. PDA suggests modifying the text to: "The focus of this guidance is the information and data developed and submitted to FDA regarding EDDOs for **CBER or CDRH** devices and device constituent parts of CDER-led and CBER-led combination products intended for the delivery of a human drug, including biological product."	In the introduction of the guidance and subsequent sections, it appears that this guidance also applies to stand alone medical devices that undergo review at CDRH but have the intended use of delivering drug or biologics. However, the scope section does not clearly state that guidance applies to medical devices regulated by CDRH or CBER and can be misconstrued to only devices in CDER-led or CBER-led combination product reviews.
50-52	"The focus of this guidance is the information and data developed and submitted to FDA regarding EDDOs for devices and device constituent parts of CDER-led and CBER-led combination products intended for delivery of a human drug, including a biological product."	This should only apply to combination products where the drug is specified. Please reference the general comment to modify the scope of the draft guidance for details supporting this change and specific examples.	There are many standalone medical devices for which this guidance may not provide any additional value.
53-55	"Examples of products that are within the scope of this guidance include syringes, injectors…and vaginal systems."	PDA suggests modifying the text to: "Examples of products that are within the scope of this guidance include**, but are not limited to, prefilled** syringes, injectors…and vaginal systems."	There are products that are drug delivery implants used that are not listed in the scope. There may be future drug delivery products that are beyond syringes, thus having such flexibility will be helpful for the industry.

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
58-59	"Drug delivery includes successful product preparation and the initiation, progression, and completion of dose delivery."	Modification of the defined operations included under "drug delivery" would help separate EDDOs from other design parameters that are verified during development. PDA suggests modifying the text to: "Drug delivery includes successful **dose preparation** and the initiation, progression, and completion of dose delivery **to the delivery site**."	It is recommended that the Agency reconsider what is included under "drug delivery" for the purposes of this guidance. For example, "product preparation" could also include opening a carton, removing a blister lid, swabbing a luer connection with alcohol, or other user operations required to use the product, but do not necessarily qualify as activities that must be successful to deliver the intended dose of drug. It would be burdensome to include these parameters as EDDOs, as this may trigger more comprehensive design verification strategy/sampling, depending on the product and its intended use.
59-61	"EDDOs are system level outputs for which device drug-delivery function is dependent on the device design (see section V for more information)."	PDA recommends amending the definition to specifically state "not influenced by instructed technique" to distinguish between general user influence and ensure applicability to more complex combination products where instructed technique is necessary and/or critical to placement and function (e.g., implantable combination products). PDA suggests changing the text to: "EDDOs are system level outputs for which device drug-delivery function is dependent on the device design **and not influenced by instructed technique** (see section V for more information)."	In the draft guidance the Agency provides a definition for EDDO with various filters including "dependent on the device design". The Agency further elaborates in section V and Appendix A that it is intended to filter out device features that would otherwise meet the definition of EDDO but where the performance is informed by a user's injection technique. However, the definition as worded may cause confusion since certain EDDO examples mentioned in the guidance (e.g., Pre-filled syringe "cap removal" and "glide force") are informed by the user's strength, dexterity, vision or handling technique/postures.

SECTION III: BACKGROUND *(lines 64-127)*

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
70-71	"EDDOs are part of the information that is "essential for the *proper functioning* of the device" to deliver the drug..."	PDA recommends modifying the text to: "EDDOs **as a subset of the EDOs** are part of the information that is "essential for the proper functioning of the device" to deliver the drug..."	Clarification needed; are EDDOs the only expected EDOs, or one subset of EDOs?
72-73	"In accordance with this provision, manufacturers shall ensure that EDDOs are identified and approved before release..."	PDA suggests changing the text to: "In accordance with this provision, manufacturers shall ensure that EDDOs are identified and approved before **design** release..."	Adding "design" clarifies release. This is supported in the reference CFR 820.30(d).
77-78	"EDDO-related information, including verification and validation data, is provided in investigational and marketing applications for drug delivery devices and combination products..."	PDA recommends modifying the text to: "EDDO-related information, including **stage appropriate** verification and validation data, is provided in investigational and marketing applications for drug delivery devices and combination products..."	Make consistent with Section VIII.A.
84-87	"Drug-device combination products may be more complex than their individual constituent parts because, in addition to the individual constituent parts, the interactions of the constituent parts also need to be assessed, characterized, and	PDA suggests changing the text to: "Drug-device combination products may be more complex than their individual constituent parts because, **in addition to the performance of individual constituent parts**, the interactions of the constituent parts need to be assessed, characterized,	Clarify that interactions of constituent parts that directly impact product functions related to the delivery of the intended drug to the intended delivery site are covered by this guidance. Other interactions (like impact on the drug product) are not in scope of this guidance.

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
	controlled during product design, development, and production."	and controlled during product design, development, and production **if they directly impact required design outputs.**"	
101-116	"For combination products, FDA acknowledges that the terms design output…may address these design control requirements."	PDA recommends FDA identify and highlight examples of EDDOs that are also CQAs, and further describe how CQA testing may be leveraged in verification testing or control strategies. PDA suggests adding an example, or amend the examples, in Appendices A, B and/or D to include EDDOs that are also considered CQAs.	In *Section III. Background*, FDA acknowledges overlap between Critical Quality Attributes (CQAs) and the newly defined term "EDDO". PDA appreciates that the guidance allows sponsors to leverage data produced to assess CQAs to also verify EDDOs. However, the guidance does not provide an example of an EDDO/CQA nor do any of the appendices demonstrate how CQAs are part of the identification or control strategy processes. Leveraging CQA activities may significantly streamline combination product development and reduce redundant testing.
126-127	"Providing a basis for comparing the drug delivery performance and facilitating the assessment of EDDOs for bridging or leveraging data across products."	PDA recommends the guidance include a new section on how EDDO performance data, along with prior knowledge, can be used for comparing drug delivery performance to justify leveraging data across products. This would facilitate efficiencies in the FDA review process and accelerate the development of drug/biologic-led combination products.	The draft guidance does not explain how prior knowledge from an approved NDA, BLA or master files may be leveraged in INDs or premarket applications. Like the approach described for post-market changes, the ability to leverage "prior knowledge" can be supported by a comparative review of design and/or manufacturing changes and assessment of the impact on EDDO performance. If the impact is not significant, prior knowledge may be leveraged in lieu of repeated testing. Unlike definitions in

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
			FDA recognized standards (e.g., Primary function, Essential Performance), the proposed EDDO framework is well positioned to support this assessment because the definition is independent of drug/biologic to be delivered, risk profile, indications for use (patient, environment, etc.,) and can be applied to any drug delivery system. The efficiencies produced from leveraging prior knowledge may also expedite the review of therapies that rely on existing, well characterized delivery technologies (e.g., PFS, pen injectors, autoinjectors) currently on the market.
151-152	"EDDOs can be identified from existing design controls by using a filtering process illustrated in Figure 1 to identify specific design outputs."	PDA suggests changing the text to: "EDDOs can be identified from existing design **outputs** by using a filtering process illustrated in Figure 1 to identify specific design outputs."	These can only be identified from existing outputs. This is consistent with the flowchart.

SECTION V: IDENTIFYING ESSENTIAL DRUG DELIVERY OUPUTS *(lines 149-208)*

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
162-163	Figure 1 – Illustration of the EDDO Identification Process	PDA suggests replacing Figure 1 with a modified version to reflect the identification process within the	The draft guidance provides Figure 1 to illustrate how industry may use the EDDO definition to identify EDDOs for a given product. While the draft guidance discusses how the design outputs are

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
		context of the larger design control process. **(Proposed figure modification included at the end of this document.)**	derived via design controls (lines 167-168), it would be more effective to illustrate this sub-process within the broader design control process diagram provided in FDA's final guidance, *Design Control Guidance for Medical Device Manufacturers (1997)*. It may also help development teams understand its relationship to design inputs.
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)."	PDA suggests altering the text to: "**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; **dose preparation** and the initiation, progression, and completion of dose delivery)."	Dose preparation activities are considered specific to preparation of the combination product that would have a direct impact on drug quality or adequacy of drug delivery.
177-179	"**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."	PDA recommends clarifying system level for multi-constituent products by adding the following text: "**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). **If a system includes multiple constituents (e.g., CDER-led Pen injector combination product intended for use with a compatible 510(k) cleared needle), the system is defined as all the constituents required to achieve the intended use.** For more	The draft guidance does not clarify how sponsors approach systems that contain more than one regulated constituent part. For example, a single entity pen injector combination product can be used with a compatible 510(k) cleared pen needle, or a 510(k) cleared infusion pump may be used with a compatible 510(k) cleared infusion set that is not packaged with the infusion pump. Without this clarification, it may be difficult to apply the EDDO identification to complex multi-constituent combination products or medical devices.

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
		information see the discussion below following step 4 and in Figure 2."	
193	Figure 2 – Example of System Level and Component Level Outputs (Step 3)	PDA appreciates the example provided for System Level Outputs and Component Level Outputs using prefilled syringes. PDA suggests including an additional example focusing on more complex devices, such as an electromechanical on-body injection device.	Adding more examples would offer a broader perspective on how the System Level concept applies to more sophisticated devices, enhancing the relevance and comprehensiveness of the documentation.

SECTION VI: VERIFYING AND VALIDATING ESSENTIAL DRUG DELIVERY OUTPUTS *(lines 211-436)*

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
246 – 259	"During the product lifecycle, the product is exposed to multiple stressors that may influence performance of the device drug-delivery function. Preconditioning is a method to simulate exposing the product to stressors to which the product will likely be exposed during shipping, storage, and use (e.g., cleaning, reprocessing, storage (see section VI.A.1.a), or repeat use, as applicable). Applicants should identify preconditions applicable to the specific product, and verification testing should assess the ability of the product to withstand those	PDA suggests changing the text to: "During the **product's** lifecycle, the product **can be** exposed to multiple stressors **prior to use** that may influence performance of the device drug-delivery function. Preconditioning is a method to simulate exposing the product to stressors **prior to testing** to which the product will likely be exposed during shipping, storage, and **before each** use (e.g., cleaning, reprocessing, storage (see section VI.A.1.a), or repeat use, as applicable). Applicants should identify preconditions	For clarity, PDA suggests adding detail of when pre-testing exposure to stressed conditions should be applied during design verification testing. It is suggested to provide clarification of recommendations pertaining to emergency and non-emergency use products. PDA recommends the section from "Other Conditions" is relocated to the preconditioning section, as it describes preconditioning of a device before testing.

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
	stressors. Applicants should identify preconditions based on the risk of the product design, research and development characterization testing, intended use, how the product will move from the finished product manufacturer to the end user, and/or the conditions associated with use (see sectionVI.A.1.c). 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. In developing…"	applicable to the specific product, and verification testing should assess the ability of the product to withstand those stressors **before testing**. Applicants should identify preconditions…user and the conditions associated with use (see VI.A.1.c). **For reusable devices, the preconditioning methods should simulate the worst-case number of repeat use and reprocessing cycles. For example, preconditioning of reusable drug delivery devices after reprocessing should include cleaning and sterilization or disinfection methods identified in the proposed labeling. As a second example, the labeling for some metered dose inhalers calls for periodic cleaning of the actuator to prevent orifice blockage. Additionally, labeling for metered dose inhaler and reusable nebulizer components often calls for periodic cleaning to prevent contamination and/or changes in electrostatic properties to minimize capture of small particles/droplets and any change in respirable drug**.	

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
		~~Because of the risk to the patient should the device fail~~ **For emergency use drug delivery systems, sequential preconditioning is generally expected due to the risk of catastrophic patient harm that may occur if the delivery system fails,** and applicants should identify the sequence in which the preconditions should be applied. **Sequential preconditioning is not expected for non-emergency use products.** In developing…"	
268-269	"…these should all be considered before EDDO design verification."	PDA suggests changing the text to: "…these should all be considered **using a risk-based approach**"	Risk-based approach is prominent in ISO11608-1:2022 and is the common approach. This also aligns with line 327 as it is mentioned there.
280-305	"c. Other conditions In addition to the preconditions associated with storage and shipping, preconditioning may be warranted to assess stressors related to conditions associated with use. For drug delivery devices that do not have a recognized standard that includes preconditions or for which there may be preconditions in addition to those in a recognized standard, preconditioning should be conducted in the sequence of steps as specified in the instructions for use in the proposed	PDA suggests modifying the title of this section and changing the text to: "c. **In-Use** Conditions In addition to the preconditions associated with storage and shipping, **exposure to conditions to which the product is expected to be exposed to during use** may be warranted. For drug delivery devices that do not have a recognized standard **that includes expected in-use conditions** or for which there may be **expected in-use conditions** in addition to those in a recognized standard, **exposure to**	These are "in-use" conditions, not preconditions, and should be applied consistently with the sequence of steps in the IFU. Additionally, PDA suggests relocating the last paragraph to "preconditioning" section (this has been added in preconditioning comment above) as these are preconditions before testing, not "in-use" conditions to which the device is exposed during use (during delivery).

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
	labeling (e.g., storage and warm up time). Additionally, depending on the device design and instructions for use, more than one preconditioning method may be needed to account for potential failure modes. For example, for infusion pumps, verifying the EDDO of flow rate accuracy should account for any before-use instructions to precondition the pump…respirable drug."	**expected in-use conditions** should be conducted in the sequence of steps as specified in the instructions for use in the proposed labeling (e.g., storage and warm up time) **using any accessories or ancillary devices required for as described in the proposed or approved/cleared labeling.** Additionally, depending on the device design and instructions for use, more than one **expected in-use condition** may be needed to account for potential failure modes. For example, for infusion pumps, verifying the EDDO of flow rate accuracy should account for any before-use instructions to precondition the pump… ~~For reusable devices, the preconditioning methods should simulate the worst-case number of repeat use and reprocessing cycles. … particles/droplets and any change in respirable drug.~~"	
309-310	"Overall, the design verification assessment of EDDOs should occur after appropriate preconditioning."	"Overall, the design verification assessment of EDDOs should occur after **exposure to** appropriate **preconditioning and expected in-use conditions."**	Consistent with above recommendations regarding the preconditioning and **in use** condition sections.
329-330	"For example, a product with a higher risk profile would warrant a more	PDA suggests changing the text to: "For example, a product with a higher **patient** risk profile would warrant a	Specifying patient risk as the proper risk to adequately assess the sampling plan provides clarification to the reader.

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
	robust sampling plan than a product with a lower risk profile."	more robust sampling plan than a product with a lower **patient** risk profile."	
330-332	"Sampling recommendations in recognized standards may be used in developing sampling plans, as appropriate, based on product-specific risk considerations."	PDA recommends providing additional examples. One could follow the PFS example here to support clarity.	The addition of examples, such as on-body injectors or infusion pumps, could offer clearer guidance and enhance understanding for stakeholders.
332-335	"A design verification testing protocol should include a statistical sampling plan with the number of lots to be tested and acceptance criteria. The tested lots should be manufactured using principles that are representative of the commercial process (e.g., materials and methods of manufacture)."	PDA suggests modifying the text to: "A design verification testing protocol should include a statistical sampling plan ~~with the number of lots to be tested~~ and acceptance criteria. The tested **products** should be manufactured using principles that are representative of the commercial products (e.g., materials **used** and methods of manufacture)."	The statistical sampling plan and justification would include the number of lots to be tested as part of the documented plan. The expectation on number of tested lots would vary based on product type (for example, disposable prefilled syringes versus an electromechanical infusion pump), and should be negotiated between the sponsor and the Agency.
343-344	"EDDOs that would not change over time (e.g., physical dimensions such as needle length) would not warrant evaluation."	PDA recommends the language is revised to allow EDDOs where the sponsor has demonstrated that there is no *significant* change over time to be exempt from additional shelf-life or stability testing. PDA suggests modifying the text to: "EDDOs that would not **significantly** change over time (e.g., physical dimensions such as needle length, **or plastic parts with demonstrated resistant to degradation**) would not warrant evaluation."	In Section *b. Shelf-life and stability testing considerations*, the draft guidance states that sponsors do not have to provide aging data for EDDOs that do not change over time. For mature, well-characterized device constituent designs there is prior knowledge that can be leveraged to establish that certain EDDOs do not measurably change over time. The proposed text imposes a high bar that would discourage sponsors from leveraging prior knowledge, which the draft guidance explicitly states is an intent (lines 126-127) of an EDDO framework.

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
350-353	"This justification may include other testing information and an explanation as to how such testing information addresses or supports the omission of any identified precondition during shelf-life or stability testing."	PDA recommends adding additional types of acceptable verification methods such as literature, simulation testing, and anthropometric data to address or support omission of precondition or stability/shelf-life strategy for EDDOs.	In *Section B. Design Validation* for EDDOs, the guidance recommends the use of alternative methods to validate an EDDO such as literature, simulated testing and anthropometric data. We agree the same methods can be used to support a design verification shelf-life strategy.
360-361	"Such design verification shelf-life testing should be conducted using the final finished product under real-time aging conditions."	PDA suggests modifying the text to: "Such design verification shelf-life testing should be conducted using the final finished product **or production equivalent units,** under real-time aging conditions."	Recommendation of "production equivalent units" is in alignment with standard industry practice. For example, design verification units are commonly manufactured in the "intend to market" packaging configuration, but the final artwork may not be present on the label. The units themselves are considered representative of the final design and process but are not identical to the final finished product.
372-374	"The most appropriate method may depend on the application type, stage of development, and EDDO. For these studies, it is important that the protocol be designed with endpoints that have the capability of validating device performance."	PDA suggests not using terminology like "endpoints" to apply to all design validation activities. (See previous comment for associated suggested terminology.) PDA recommends changing the text to: "The most appropriate method may depend on the application type, stage of development, and EDDO. For these studies, it is important that the **design validation strategy** ~~protocol be designed with endpoints that~~ have the	PDA appreciates the summary of different validation approaches mentioned in the draft guidance. However, terminology such as "endpoints" preceded by a discussion on clinical studies suggests that conducting clinical studies is the primary or preferred methods for EDDO validation. As noted in later examples, other data (literature, simulated testing, etc.) may be adequate to validate an EDDO. For certain EDDOs like cap removal or glide force, it would be ineffective to have a clinical study

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
		capability of validating device performance."	protocol have endpoints linked to these EDDOs.
374 – 402	"For certain application types, examples of methods available to validate the EDDO specifications may include the studies identified below. • Clinical studies (and/or reliance on FDA's finding of safety/effectiveness for a reference listed drug (RLD) or reference product) •Pharmacokinetic/pharmacodynamic (PK/PD) or bioequivalence/ bioavailability studies … As appropriate, for certain applications, some EDDOs may be validated using alternative methods, such as: • Literature: e.g., injection site and patient population information to support the proposed injection depth specification • Simulated bench testing: studies designed to evaluate whether users are capable of using the prototype devices (e.g., exerting forces, hearing	"For ~~certain~~ **most** application types, examples of methods available to validate the EDDO specifications may include the studies identified below. **• Literature: e.g., injection site and patient population information to support the proposed injection depth specification** **• Simulated bench testing: studies designed to evaluate whether users are capable of using the prototype devices (e.g., exerting forces, hearing sounds) over the range of the EDDO specification** **• Anthropometric data: e.g., simulated strength testing of specific patient populations and postures, capability of specific populations' ability to hear specific tones** **…** For certain application types, other methods available to **support** the validation of the product may include the studies identified below.	The original listed studies do not validate the EDDOs. They validate the performance of the product. If anything, they are *supportive* of the verification of the EDDOs, but do not contain enough variables, and in many case samples, to validate the EDDO. For clarity, the way they are presented should be switched as *most* products are validated through simulated studies or literature. It is the exception that would require clinical data to validate the product performance.

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
	sounds) over the range of the EDDO specification • Anthropometric data: e.g., simulated strength testing of specific patient populations and postures, capability of specific populations' ability to hear specific tones"	**• Clinical studies (and/or reliance on FDA's finding of safety/effectiveness for a reference listed drug (RLD) or reference product)** **•Pharmacokinetic/pharmacodynamic (PK/PD) or bioequivalence/bioavailability studies**"	
392-394 and FN 39	"Simulated bench testing:[39] studies designed to evaluate whether users are capable of using the prototype devices (e.g., exerting forces, hearing sounds) over the range of EDDO specification" FN 39: "Applicants would have to manufacture devices that function at the limits of the specification to effectively validate the EDDO."	PDA recommends the Agency clarify expectations regarding effective validation of EDDO specification limits at the introduction of *Section B. Design Validation*.	In *Section B. Design Validation*, the draft guidance states that "Simulated Bench Testing" would be an appropriate method for validating an EDDO if performed "over the range of the EDDO specification". Footnote 39 also suggests validation of the EDDO limits. However, the draft guidance does not say that the same approach applies to other recommended forms of validation (e.g., clinical studies, literature, etc.). Understanding the Agency's expectation regarding design validation is necessary to ensure sponsors appropriately design their validation studies.

SECTION VII: CONTROL STRATEGIES FOR ESSENTIAL DRUG DELIVERY OUTPUTS *(lines 439-484)*

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
439-443	"VII. CONTROL STRATEGIES FOR ESSENTIAL DRUG DELIVERY OUTPUTS After completion of the design verification and validation processes described in section VI, a control strategy is used to ensure that each lot of the final finished product is manufactured to conform to the design outputs."	PDA recommends modifying the text to: "VII. **POST VERIFICATION & VALIDATION** CONTROL STRATEGIES FOR ESSENTIAL DRUG DELIVERY OUTPUTS After completion of the design verification and validation processes described in section VI, a **risk-based** control strategy **beyond verification and validation testing may need to be implemented** to ensure that each lot of the final finished product is manufactured to conform to the design outputs."	A control strategy for a particular product may consist of both upstream and/or downstream controls. EDDOs do not necessarily require downstream controls (i.e., testing at batch release), if appropriate upstream controls are implemented to ensure the final finished product is manufactured to conform to the design outputs. For higher risk products, such as emergency use devices, it may be necessary to implement additional downstream controls to ensure the required product reliability.
452-454	"For a lower risk product with less complex manufacturing processes, certain EDDOs may be adequately controlled with downstream controls."	PDA recommends the phrase is adjusted to state that there may be control strategies that are comprised entirely of upstream controls depending on the product risk, complexity of design and/or manufacturing process, and/or prior knowledge of historical performance. PDA suggests changing the text to: "For **some products**, certain EDDOs may be adequately controlled with downstream controls **or all upstream controls.**"	The control strategy section VII suggests that a lower-risk product may be adequately controlled with downstream controls only, whereas a high-risk product may be controlled through a combination of upstream and downstream controls. However, Appendix D provides an example of an autoinjector where an EDDO is effectively controlled using only upstream controls. Additionally, there are other attributes besides risks profile of a product that can inform the number and type of control applied (design/manufacturing complexity, volume and history of manufacturing) and performance of well understood manufacturing processes or device constituent designs should be

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
			considered as part of a control strategy evaluation.

SECTION VIII: INFORMATION TO PROVIDE IN APPLICATIONS *(lines 487-740)*

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
Entire Section VIII, 487-740	"VIII. INFORMATION TO PROVIDE IN APPLICATIONS…the new strategy is as effective as the original control strategy."	Shortly after finalization, PDA recommends making updates to eCTD Technical Conformance Guide (Nov 2022) and relevant eSTAR templates to reflect the submission expectations described in the draft guidance.	In *Section VIII. Information to Provide in Applications*, the guidance summarizes submission expectations for INDs, IDEs, Marketing Application and Post-market changes. However, it does not adequately describe where sponsors should provide this information in the submission. This clarification is important to ensure reviewers can easily locate the information requested in the draft guidance.
495-496	"The data provided in IND and IDE applications for drug delivery devices should reflect the development stage of the product."	PDA recommends the draft guidance is revised to adopt the approach recommended in CDRH final guidance *Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human Studies* for phase I clinical studies for consistency as well as provide clarity on the rigor of design verification and validation needed for phase I, II and III clinical studies.	In *Section A. IND and IDE Applications*, FDA states that data provided in IND and IDE applications for drug delivery devices "should reflect the development stage of the product". However, the draft guidance does not provide recommendations on what constitutes a phase appropriate approach. Specifically, there is ambiguity regarding what phase (I,II, or III) should design controls apply for a combination product, and if applied, the rigor of data expected in an IND application. Clarification is needed because while the

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
			final guidance *Current Good Manufacturing Practice Requirements for Combination Products* states that the production of a drug is generally *exempt* from compliance with regulations in parts 210 and 211 for a phase I clinical study, it does not specify any limits to the application of design controls per 21 CFR 820.30. Instead, the guidance refers to the preamble of the device quality system regulation in footnote 18 stating that "design control requirements are not intended to apply to the development of concepts and feasibility studies". Of note, CDRH's final guidance *Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human Studies,* recommends sponsors establish and maintain a design and development plan which includes essential design output identification, design verification, and design validation information. However, the plan "does not need to be submitted in the IDE application" for early feasibility studies.
534-559	"(1) Device description documentation…*Premarket Submissions* (December 2019)."	PDA recommends the guidance clarify how sponsors may appropriately use currently marketed medical devices (e.g., 510(k), DeNovo, PMA) or data from a master file, any limitations, and instances where sponsors would need to generate supplemental data to support investigational use.	In *Section A. IND and IDE Applications*, the draft guidance summarizes the information sponsors should provide in their application such as device description, device safety and performance data. However, the draft guidance does not discuss how a sponsor can leverage data from an approved medical device application

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			(e.g., 510(k), DeNovo, PMA) or master files to support an IND application. Many early phase development projects use currently marketed medical devices (e.g., syringes, catheters, infusion pumps) and device constituents (e.g., autoinjectors) to investigate the safety and/or efficacy of the drug or biologic before the final finished combination product presentation is determined. Without further clarification, a sponsor may unexpectantly receive a clinical hold for the device/device constituent, which would delay development efforts.
541-542	"(b) Describe the principles of operation of the device and how it functions throughout use."	PDA suggests adding a flowchart or acceptable examples: "(b) Describe the principles of operation of the device and how it functions throughout use. • **Acceptable flowchart** • **Acceptable examples**"	It would be helpful for readers if the Agency could clarify how the principles of device operation should be presented. Providing practical examples of what constitutes a proper explanation could greatly enhance understanding and ensure consistency in submissions.
548	"(e.g., by delivering a larger dose than intended)."	PDA proposes amending the example so it is clear that it is the harm resulting from a potential overdose that would qualify an EDDO as a "safety related" by adding the following text: "(e.g., by delivering a larger dose than intended **which leads to serious harm**)."	PDA agrees that the focus of review for IND applications should be on safety related EDDOs. However, the example provided regarding overdose does not adequately demonstrate why a large dose is a safety issue. Instead, the example appears to suggest that any overdose, regardless of drug or biologic, is considered a safety related EDDO.
566	"(e.g., infusion rate, dose range, injection time)."	PDA suggests the term is changed to "delivery" time" to better demonstrate EDDOs from novel or	PDA agrees that there are instances when a clinical study is necessary to validate an EDDO. However, in the proposed

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
		complex delivery systems may require clinical validation: "(e.g., infusion rate, dose range, **delivery** ~~injection~~ time)."	example, EDDO "injection time" is noted as a relevant clinical endpoint. PDA believes the term "delivery time" is a more appropriate example because "injection time" implies that clinical validation would be necessary for single bolus injectors (e.g., Autoinjectors).
569-570	"Also, such clinical studies should be conducted with the final finished drug delivery device."	PDA recommends the draft guidance is amended to allow for "appropriate surrogates" when using clinical studies to validate an EDDO if there is no significant impact to the clinical safety and performance. PDA suggests adding the following text: "Also, such clinical studies should be conducted with the final finished drug delivery device, **or appropriate surrogate. Any changes to the investigational device in pivotal clinical studies to the to-be-marketed commercial presentation may be acceptable if there is no significant impact to clinical safety and performance of the EDDO.**"	The draft guidance clarifies that the "final finished drug delivery device" should be used when clinical studies are used to validate an EDDO. However, there are instances when an EDDO may be effectively validated by a surrogate or representative test article, and the results can be leveraged by the final finished drug delivery device EDDOs. For example, a currently marketed infusion pump can be used in an investigation to validate the flow rate and dose range EDDOs. Later in development, the final finished drug delivery device can adopt the same EDDOs and refer to the clinical investigation that used the standalone infusion pump as validation for the EDDO specification as it has no impact to the clinical safety or performance.
623-625	"Performance data – Include acceptance criteria and performance data verifying and validating the final finished product. Applicants should use recognized standards and FDA guidance to inform design and testing, as applicable."	For consistency, PDA recommends that the submission expectations regarding performance data reference the same FDA guidance *Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions*.	When discussing performance data to be submitted for IND and IDE applications, the draft guidance states that sponsors may submit summary test results for tests using recognized standards and refers to FDA guidance *Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions*. However, in

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			Section B. Marketing Applications, the draft guidance does not state if summary performance data may be submitted nor in what format. Additionally, this change would further encourage the use of testing per FDA recognized standards developed in collaboration with industry.
670-671	"Applicants can consult with the appropriate product office for questions regarding control documentation to include in a submission."	PDA suggests changing the text to: "Applicants can consult with the appropriate product office for questions regarding **supporting evidence** ~~control documentation~~ to include in a submission."	Changing the term "control documentation" to "supporting evidence" provides clarity to the reader.
677-679	"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."	PDA suggests the Agency clarify that the approach described in Section C. *Submissions for Post-Market Change that May Impact Essential Drug Delivery Outputs* also applies to design and/or manufacturing changes between the same device type (Pre-filled Syringe to Pre-filled Syringe) and across different device types (Prefilled Syringe to Autoinjector).	In *Section C. Submissions for Post-Market Change that May Impact Essential Drug Delivery Outputs*, the draft guidance proposes an EDDO comparative approach when assessing a new design and/or new manufacturing changes. However, it is unclear if the proposed EDDO comparative approach is limited to a single drug delivery device type (e.g.,Pre-filled Syringe to Pre-filled Syringe) or if it applies to design and manufacturing changes between different drug delivery device presentations (e.g.,Pre-filled Syringe to Autoinjector). Manufacturers often use NDA/BLA supplements to introduce new device constituent designs to deliver the same drug. The proposed comparative approach could support those submission types and adequately

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
			capture the information necessary to introduce a new device type. Additionally, this approach is consistent with earlier statements in the draft guidance explaining that EDDOs provide "a basis for comparing the drug delivery performance and facilitating assessment of EDDOs for bridging or leveraging data across products".
655-656	"Provide documentation that demonstrates that the device EDDOs are met after preconditioning testing."	PDA suggests modifying the text to: "Provide documentation that demonstrates that the device EDDOs are met after preconditioning testing, **including justification and rationale for any changes or exclusions."**	The added text exemplifies general good practices for the reader to follow.
679-680	"Applicants should also perform an analysis of the impact of the change on the verification and validation of the previously identified EDDOs."	PDA recommends changing the text to: "Applicants should also **take a risk-based approach when** performi**ng** an analysis of the impact of the change on the verification and validation of the previously identified EDDOs."	Promotes consistent use of risk-based concepts as noted elsewhere in the draft guidance.

APPENDIX B: ESSENTIAL DRUG DELIVERY OUTPUT IDENTIFICATION EXAMPLE – AUTOINJECTOR *(lines 830-847)*

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
846	"Dose Accuracy"	PDA suggests changing the text to: **"Deliverable Volume"**	Wording consistency.

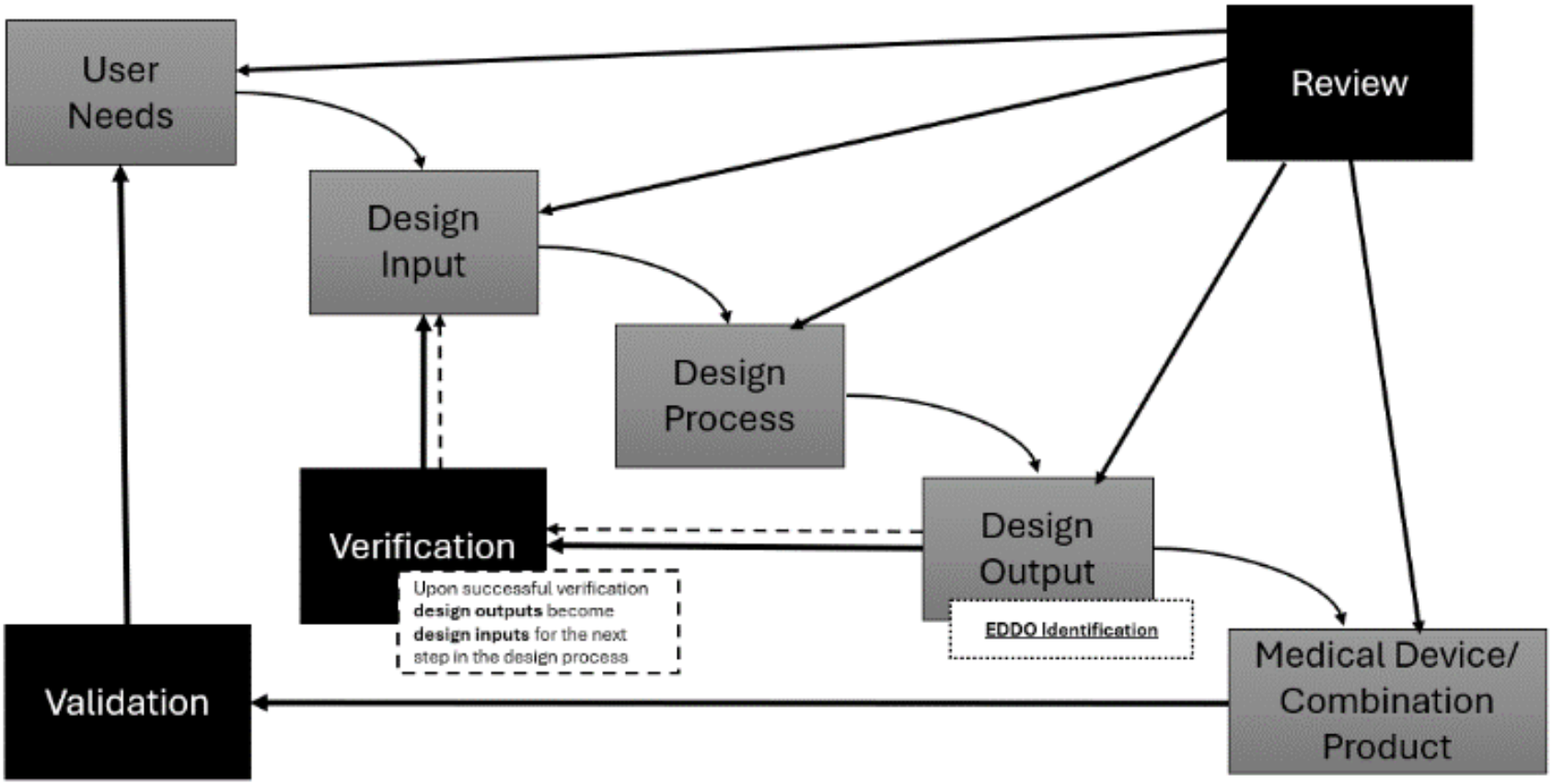
847	*(Context of whether a feature should be considered an EDDO)* "Audible feedback/clicks - Yes. It signals that the injection is complete and is dependent on the device. Visual feedback – Yes. It signals that the injection is complete and is dependent on the device. "	Audible feedback/clicks and visual feedback when used to signal when the injection is complete are not considered EDDOs, as they are dependent on user action (i.e., hearing or visually observing the feedback mechanism). PDA believes that end of dose feedback should not be considered an EDDO by this definition and should be removed.	The provided definition of EDDO is "the design outputs necessary to ensure delivery of the intended drug dose to the intended delivery site. Drug delivery includes successful product preparation and the initiation, progression, and completion of dose delivery". Audible or visual feedback is not required to complete the intended drug dose and is based on user action.
859	Table 2: Injectors "Dose accuracy"	PDA recommends changing each occurrence of "Dose accuracy" in the document to **"Deliverable volume".**	Wording consistency.

APPENDIX C: EXAMPLES OF POTENTIAL ESSENTIAL DRUG DELIVERY OUTPUTS BASED ON PRODUCT TYPE *(lines 848-895)*

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
873-874	"Delivery of intended dose • Pump delivery (spray weight) • Spray content uniformity • Spray pattern • Droplet size distribution • Particle size distribution (suspensions) Delivery to the target site • N/A"	PDA suggests moving "spray pattern" and "droplet size distribution" to the "delivery to the target site" column: "Delivery of intended dose • Pump delivery (spray weight) • Spray content uniformity • ~~Spray pattern~~ • ~~Droplet size distribution~~ • Particle size distribution (suspensions) Delivery to the target site • **Spray pattern** • **Droplet size distribution"**	Spray pattern and droplet size distribution impact the deposition of drug to the appropriate locations in the nasal cavity, and thus should be considered EDDOs impacting delivery to the target site.

Line Number(s) of referenced text	Referenced Text	Comment/Suggestion Proposed Change	Rationale
893-895	Table 6: Infusion Products Infusion Pumps Example: "Connection stability to IV or to separate administration set for SQ, etc." Subdermal Implants Example: "Implant compatibility with applicator (e.g., dimensional compatibility)"	PDA proposes removing the following compatibility EDDOs from the listed examples: Infusion Pumps Example: "~~Connection stability to IV or to separate administration set for SQ, etc.~~" Subdermal Implants Example: "~~Implant compatibility with applicator (e.g., dimensional compatibility)~~"	In *Appendix C*, the draft guidance provides several EDDO examples for common drug delivery systems to demonstrate the application of the proposed EDDO definition. Specifically, the infusion pump and subdermal implant examples include EDDOs specific to compatibility with other constituents or accessories. Compatibility as a standalone EDDO appears to be inconsistent with the EDDO definition of *system level* design outputs which the draft guidance states are "design outputs that are the *functions* necessary for the performance of the final finished product". Compatibility is not broadly considered a "function" of the final finished product but could be considered a form of preconditioning that impacts the EDDO performance (e.g., Poor compatibility leads to dose accuracy failure). Additionally, the draft guidance includes other examples that are also multi-constituent but do not list compatibility as an EDDO (e.g., Pen injector compatibility with cartridges or pen needles).

Modified Figure 1:



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