24 September 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
via online submission to https://www.regulations.gov/

RE: [Docket No. FDA-2024-D-2560] Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products

Dear Sir or Madam,

The International Society for Pharmaceutical Engineering (ISPE) appreciates the opportunity to comment on the draft guidance, *Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products.*

ISPE supports the FDA's efforts to develop guidance on this topic; however, the current title, "Essential Drug Delivery Outputs for Devices and Intended to Deliver Drugs and Biologics," does not clearly convey that guidance applies to medical devices and device constituents or all potential future therapies (e.g., cell and gene therapy) or the various topics covered in the guidance (verification & validation strategies, submission expectations, and control strategy). Therefore, we recommend the adoption of a title to reflect the various product types and therapies. Additionally, we recommend the inclusion of 'Guidance for Industry & Staff' to reflect that FDA review staff are also subject to these recommendations to ensure consistency.

While ISPE Members agree with the FDA's approach to linking EDDO to design outputs, it would be helpful to have more information on how the FDA distinguishes EDDO from design input requirements, which are also described in the draft guidance as being physical and performance requirements of a device (reference line 627). More explanation is given in the General and Specific comments below.

ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. ISPE's 21,000+ members lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world. ISPE does not take a political position or engage in lobbying activities or legislative agendas.

We appreciate the opportunity to submit these comments for your consideration. Please do not hesitate to contact me if you have any questions.

Respectfully,

Michael Rutherford
ISPE Interim President and CEO
MRutherford@ispe.org

cc: Scott Billman, ISPE Board Chair

Draft Guidance or Consultation Document title:

Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products

GENERAL COMMENTS ON THE DOCUMENT
1. ISPE appreciates that this guidance comprehensively addresses a critical gap: equivalent specifications for the device compared to drug CQAs and ~~this~~ represents a major advancement in regulatory science for drug delivery devices and combination products. We also appreciate the FDA's efforts to develop guidance specific to drug delivery devices that leverages existing regulations (e.g., design controls) to facilitate the development of combination products and reduce the need for post-approval change management submissions. We agree with the use of 'essential design outputs' to further the proposed fit-for-purpose verification and validation approaches. We hope the FDA will continue to build on this approach to refine guidance around control strategies further and provide further clarification with respect to the link between EDDO to CQAs and Established Conditions. For example, while the guidance does state that CQA are similar to design outputs, 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. Therefore, we recommend FDA provide an example of CQAs that are also EDDOs and how activities may be leveraged in verification testing or control strategies. Additionally, we believe the Essential Drug Delivery Outputs (EDDO) framework could be expanded to enable efficient use of so-called platform device constituents, or 'prior knowledge', to expedite the development of drug delivery systems. We also recommend that as the FDA is updating relevant guidance documents (e.g., Bridging for Drug-Device and Biologic-Device Combination Products) it will incorporate the EDDO guidance by reference to ensure a consistent review policy for drug delivery devices.
2. We recommend FDA update the eCTD Technical Conformance Guide (Nov 2022) and relevant electronic submission template and resource (eSTAR) to reflect the submission expectations described in the draft guidance specific to drug delivery devices and combination product applications. For example, in Section VIII. Information to Provide in Application, the guidance summarizes submission expectations for INDs, IDEs, Marketing Application and Post-market changes. However, it does not adequately describe where applicants should provide this information in the submission. This clarification is important to ensure reviewers can easily locate the information requested in

the draft guidance. Therefore, we recommend relevant CDER, CBER, and CDRH guides or templates are updated shortly after finalization.
3. We thank FDA for providing clear and transparent examples in Appendix C and, therefore, we recommend that Appendix C is included within the final guidance.
4. It is appreciated that FDA has accepted topics within the draft Guidance, which appear to be due to industry feedback, for example - applicants can justify upstream testing/evaluation as part of a device control strategy such that not all device functions are required to be tested on release.
5. In *Section B. Design Validation*, the draft guidance summarizes numerous methods that may be used to validate EDDOs. However, the list of proposed methods does not include Human Factors Formative or Summative evaluations. While we understand the intent of the human factors studies are to validate the device labeling and user interface, they may also effectively validate EDDOs such as audible/visual feedback. Additionally, early formative evaluations may use prototypes manufactured at the limits of the EDDO specification, which would satisfy the guidance recommendation regarding test articles for validation studies. While we agree the list is not intended to be exhaustive, human factors studies are commonly performed and may contain a wealth of information for applicants to leverage. Therefore, we recommend human factors formative and summative evaluations are added as potential validation approaches as well as any study design considerations.
6. ISPE 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 for the following reasons. 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 an appropriate phase 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 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 makes reference 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 applicants 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.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
N/A - Title	Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products	~~Essential Drug Delivery Outputs for Devices Intended to Delivery Drugs and Biological Products~~ **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 and Intended to Deliver Drugs and Biologics", does not clearly convey that guidance applies to medical devices and device constituents or all potential future therapies (e.g., cell and gene therapy) or the various topics covered in the guidance (verification & validation strategies, submission expectations, and control strategy). Therefore, we recommend the adoption of the suggested title or a similar title to reflect the various product types and therapies. Additionally, we recommend the inclusion of 'Guidance for Industry & Staff' to reflect that FDA review staff are also subject to these recommendations to ensure consistency.
Footnote 8 (FN8)	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.	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 **and clarifies the regulatory intent. This terminology change is also**	While we agree with FDA approach to linking EDDO to design outputs, it would be helpful to have more information on how FDA distinguishes EDDO from design input requirements, which are also described in the guidance @ FN 15 and line 627 as being physical and performance requirements of a device. Based on the definition of design output, cited in FN 16, it

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
		intended to clarify confusion regarding design inputs and design outputs with respect to EPR, now EDDO. This guidance clarifies that FDA considers EDDO to be part of the design outputs for a device. While this guidance does not describe the design input development process, the design inputs are used to develop the design outputs, including the essential drug delivery outputs, described in this guidance.	appears that EDDO would be derived from the design input requirements and considered as part of the design output. However, FDA thinking on this topic remains unclear. We believe that updating the information cited in FN8 could address this concern.
Line 51	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 the delivery of…	The focus of this guidance is the information and data developed and submitted to FDA regarding EDDOs for devices **regulated under CDRH** and device constituent parts of CDER-led and CBER led combination products intended for the delivery of…	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 and the phrasing *"…for devices and device constituent parts of CDER-led and CBER-led combination products…"* can be misconstrued to mean only devices in CDER-led or CBER-led combination product reviews. Therefore, we recommend that the language in the scope section is clarified to include medical devices regulated by CDRH.

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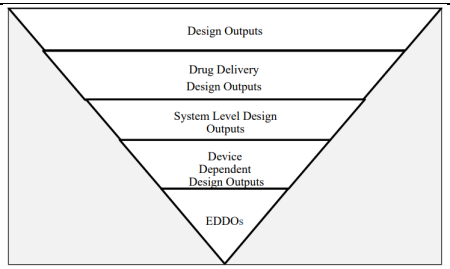
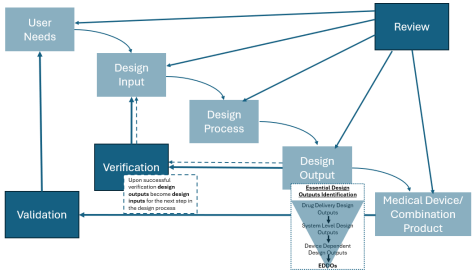
Line 80-82	In addition to being part of design control activities, the EDDO processes discussed in this guidance can also be used for defining a control strategy.	In addition to being part of design control activities, the EDDO processes discussed in this guidance can also be used for defining a control strategy **for the device**.	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 an entire combination product control strategy, including the drug product.
Figure 1		ISPE suggests consideration is given to revising the EDDO Identification Process Figure 1 to reflect the identification process within the context of the larger design control process. Example below: 	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 derived via design controls (lines 167-168) it could be helpful 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. Therefore, we recommend the guidance considers replacing it with a modified version of the design control waterfall diagram that is well understood by industry (Larger diagram shown on last page).
Lines 159-163	Figure 1	We propose the following footnote on Figure 1: **"This illustrative example provides guidance for applicants, who may make adaptions to this process, as needed."**	If the FDA does not replace Figure 1 as we have suggested, we request that FDA provide clarification. The proposed text is intended to clarify that the depicted process is an illustration for applicants when identifying EDDOs, that can be adapted as needed to applicants' internal procedures.
Line 167	"(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	(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	We agree with the interpretation of the design outputs definition. However, we have minor editorial changes to improve clarity.

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	requirements, design specifications, route of administration, drug characteristics, dosage form, and delivery volume). This information should be used to identify the design outputs).	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).	
Line 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."	"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 510k cleared needle), the system is defined as all the constituents necessary to achieve the intended use.** For more information see the discussion below following step 4 and in Figure 2."	In *Section V. Identifying Essential Drug Delivery Outputs*, the guidance describes the FDA's interpretation of 'System Level Design Outputs'. However, it does not clarify how applicants 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. Therefore, we recommend clarifying system level for multi-constituent products.
Lines 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 the 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).	(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 the design and manufacture of the product are adequately controlled. (This step is not intended to address usability because drug delivery performance that **may** depend **exclusively**	We agree with the FDA intent for Device Dependent Design Outputs. However, we recommend clarifying that drug delivery performance that is exclusively dependent on user performance as the criteria in order to help applicants understand the decision-making process more clearly. For example, some applicants may confuse glide force as being dependent on a user

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
		on the user is not an EDDO **such as injection time with a prefilled syringe system**).	performance because extrusion force with a PFS depends partially on the extrusion speed that the user is targeting. (Note that this is in multiple locations in the guidance, i.e., Figure 2). Therefore, making the point here that exclusively dependent on user performance is the factor for determining a specification is not EDDO.
Line 217-219	Examples of conditions that may impact performance include, but are not limited to, temperature, pressure, humidity, vibration and shock, and physical orientation.	Examples of conditions that may impact performance include, but are not limited to, temperature, pressure, humidity, vibration and shock, **drug-device interactions,** and physical orientation. **Use of additional devices described in labelling (e.g., pen needles) that influence drug delivery performance should be addressed as part of testing.**	Ensuring that interaction considerations are included in testing protocols is essential for maintaining the safety and efficacy of the combination product. Additionally, in *Section c. Other Conditions*, the draft guidance recommends preconditioning to account for potential failure modes in accordance with the instructions for use and refers to testing the to-be-marketed device with potential accessories. While we agree that preconditioning should be in accordance with the instructions for use, the guidance does not address testing with respect to compatibility with accessories or limitations. For example, if a pen injector is labelled for use with a specific pen needle brand, then verification testing should only have to be performed using the needle proposed in the labelling. It would be burdensome for applicants to perform verification testing with multiple pen needles brands that are not referenced in the approved/cleared labelling. While FDA-recognized ISO standards exist to evaluate the compatibility of a few device-to-device connections,

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			these standards are general and may not capture key dimensions, materials, lubricants, or manufacturing controls needed to ensure compatibility and overall performance of an EDDO. We recommend that the verification section includes a discussion on device-to-device compatibility and, just like preconditioning, limits the testing of accessories in accordance with the approved/cleared labelling.
Line 310	Overall, the design verification assessment of EDDOs should occur after appropriate preconditioning.	Overall, the design verification assessment of EDDOs should occur after appropriate preconditioning, **unless it is determined that certain design verification assessments of EDDOs are independent of preconditioning.**	An applicant should be able to provide a justification for not preconditioning the product before certain design verification testing if EDDOs are determined to be independent of preconditioning.
Line 318	… verification that the EDDO is maintained following preconditioning.	… verification that the EDDO is ~~maintained~~ **met** following preconditioning.	Clarify that design verification confirms design inputs are met (not maintained)
Line 327-335	Sampling plans for design verification testing for EDDOs should be risk-based, taking into consideration the indication for use, patient population, drug being delivered, context of use, and complexity of design and manufacturing. For example, a product with a higher risk profile would warrant a more robust sampling plan than a product with a lower risk profile. Sampling recommendations in recognized standards may be used in developing sampling plans, as appropriate, based on product-specific risk considerations. A	Sampling plans for design verification testing for EDDOs should be risk-based, taking into consideration the indication for use, patient population, drug being delivered, context of use, and complexity of design and manufacturing. For example, a product with a higher risk profile would warrant a more robust sampling plan than a product with a lower risk profile. **FDA recommends applicants consider conducting testing using the probability**	FDA states that sampling plans should be risk-based. However, there exist varying opinions on risk categorizations and the appropriate reliability/confidence intervals to apply to each risk level. The FDA's draft EDDO sampling plan section does not provide a clear set of guiding principles for industry to apply during development and testing of devices. Providing clarity to industry on the minimum set of expectations for EDDO test sampling plans will enhance clarity on expectations and increase quality

<table>
<tr><th>Section or Line Number</th><th>Current Text</th><th>Proposed Change</th><th>Rationale or Comment</th></tr>
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<td>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).</td>
<td><u>content in the following table as a starting point for sampling plans.</u>

<table>
<tr><td><u>Risk Category</u></td><td><u>Probability Content</u></td></tr>
<tr><td><u>Emergency Use</u></td><td><u>99.999% Pr / 95% CI</u></td></tr>
<tr><td><u>Non-emergency Use</u></td><td><u>95% Pr / 95% CI</u></td></tr>
</table>

Sampling recommendations in recognized standards may be used in developing sampling plans, as appropriate, based on product-specific risk considerations. <u>Where a device-specific standard has sampling recommendations that exceed the 95%/95% level for a non-emergency use product, FDA recommends applicants conform to the recommendations in the standard.</u> 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).</td>
<td>of premarket submission data received by FDA.

Additional risk categories could be defined. However, minimum level of risk categories is important for clarity and consistency.

The 95%/95% values are recommended as these align with many ISO standards and AAMI technical reports for drug delivery devices (e.g., ISO 11608, AAMI TIR 101).</td>
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Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Line 332	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 number of lots~~** and acceptance criteria.	Design Verification is the verification that design outputs meet the requirements of design inputs. Testing multiple lots using a representative (commercial) manufacturing process may induce a burdensome approach. Design verification testing could only commence when a representative manufacturing process is available. Other approaches could be used as discussed below. The FDA has already included recommendations for batch analysis testing at line 473 as part of control strategy development. We recommend FDA rely on this type of testing, combined with control strategy development, to assess suitability of manufacturing processes to consistently produce conforming devices.
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 343-344	EDDOs that would not change over time (e.g., physical dimensions such as needle length) would not warrant evaluation.	EDDOs that would not change over time (e.g., physical dimensions such as needle length, **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 applicants 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. Therefore, we recommend that an additional example is included to strengthen the point that EDDOs where the

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			applicant has demonstrated that there is no *significant* change over time to be exempt from additional shelf-life or stability testing.
Line 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.	This justification may include other testing information **(e.g., modelling)** and an explanation as to how such testing information addresses or supports the omission of any identified precondition during shelf-life or stability testing.	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. Therefore, we recommend *section b. Shelf-life and Stability testing considerations* also remarks on the use of literature, simulated bench testing, etc., to address or support omission of pre-conditioning or stability/shelf-life strategy for EDDOs.
Line 368	… and must include testing of production units …	...and must include testing of production units **or production equivalent units**..."	We recommend the language be revised to be fully consistent with the regulation.
Line 373-374	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. For certain application types, examples of method available to validate the EDDO specifications may include the studies identified below.	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 capability of validating device performance. For certain application types, examples of methods available to validate the EDDO specification may include studies identified below.	We appreciate 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 protocol have endpoints linked to these EDDOs. Therefore, we recommend not using

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
			terminology like 'endpoints' to apply to all design validation activities
Line 441	After completion of the design verification and validation processes described in section VI,…	After completion of the design verification and validation ~~processes~~ **activities** described in section VI,…	Clarify wording to focus on activities and not processes
Line 443 – 448	For a given EDDO, an appropriate control strategy may consist of one or more types of control steps at different stages of the manufacturing process. Some control steps are performed earlier in the manufacturing process (e.g., upstream controls such as in-process controls, control of process parameters, control of incoming materials, and purchasing controls). Other control steps are performed at the end of the manufacturing process (e.g., a downstream control such as lot release testing).	For a given EDDO, an appropriate control strategy may consist of one or more types of control steps at different stages of the manufacturing process. Some control steps are performed earlier in the manufacturing process (e.g., upstream controls such as in-process controls, control of process parameters, control of incoming materials, and purchasing controls). Other control steps are performed at the end of the manufacturing process (e.g., a downstream control such as lot release testing). **Certain control strategies may also control one or more EDDOs.**	In Section *VII. Control Strategies for Essential Drug Delivery Outputs*, the draft guidance recommends that the applicant identify upstream and/or downstream controls for each identified EDDO. However, certain EDDOs such as Audible feedback and Visual feedback (dose completion EDDOs) performance may be directly linked by design and upstream/downstream controls can be leveraged. Applicants can also support this linkage by providing R&D or design verification data. For example, the release testing of audible feedback (e.g., confirmation of click(s)) could serve as an effective control of visual feedback (e.g., clicks would not occur unless colored plunger fully completes travel and occupies window) as opposed to testing both EDDOs on release testing. Leveraging of EDDOs as controls themselves would be another opportunity for the EDDO concept to further efficiencies for combination products. Therefore, we recommend that EDDOs themselves could be appropriate controls.
Line 450-456	The control strategy developed should be risk-based. 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.	The control strategy developed should be risk-based. Therefore, the number and types of controls implemented, and the amount of information regarding the control	The FDA states that control strategy should be risk-based. However, the example for a lower risk EDDO strategy is limited to release testing. This implies the FDA is

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
	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.	strategy to include in an application should correspond to the product risks. For a lower risk product with less complex manufacturing processes, certain EDDOs may be adequately controlled with either **upstream or** downstream controls. A possible example is release testing a description of glide force and breakloose force on a PFS with a non-emergency use drug for administration by a health care provider. **Alternatively, for this lower risk example, an applicant could choose to provide an upstream controls-based strategy[FN] (e.g., COA for components, validation of siliconization process, etc.), in lieu of release testing.** In contrast, for a higher risk product, a combination of upstream and downstream controls may be needed to ensure consistent EDDO performance. **[FN]Refer to Appendix D for an example upstream control strategy.**	expecting release testing for lower risk products. We recommend modifying the guidance to explicitly provide the option for an upstream or downstream control-based strategy. For example, an applicant may have sufficient controls in place to assure quality of the EDDO without relying on release testing. We also recommend adding 'complexity of design and/or manufacturing process' and 'volume of manufacture' as factors that inform a control strategy approach and controls
Row 464	"*design assessment verification testing*"	Use "design ~~assessment~~ verification testing"	The terminology "design assessment verification" is confusing. We recommend use of the term design verification, which is consistent with the regulation.
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 labelled, descriptions of the	Provide a description of the device design, including any novel features and functionalities, including engineering drawings or diagrams of the device ~~with all~~	Clarify that this level of detail is not necessary for original submission content and is rather available upon request/inspection if necessary

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
	individual device components, or any other available information to explain the device design.	~~dimensions labelled~~, descriptions of the individual device components, or any other available information to explain the device design.	
Lines 546-550	(2) 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. In the overall device risk analysis section, include EDDO-related risks.	(2) 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. In the overall device risk analysis section, include EDDO-related risks.	Design validation should not be in scope of IND and should be removed from text.
Line 548	(e.g., by delivering a larger dose than intended)	(e.g., by delivering a larger dose than intended **which leads to serious harm**)	We agree 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. Therefore, we recommend 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' EDDO.
Lines 561-562 and	"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 EDDO validation **for high-risk drug delivery devices:"**	These scenarios should apply to high-risk drug delivery devices only.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
Lines 564-565	"If the clinical study is intended to obtain data to validate one or more EDDOs, [...]"	"If the clinical study is intended to obtain data to validate one or more EDDOs **for high-risk devices,** [...]."	
Line 566	(e.g., Infusion rate, dose range, injection time)	(e.g., infusion rate, dose range, **delivery** ~~injection~~ time)	We agree that there are instances where a clinical study is necessary to validate an EDDO. However, in the proposed example EDDO 'injection time' is noted as a relevant clinical endpoint. We believe 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). However, the clinical tolerability and pain with respect to injection time and volume has been well researched for single bolus injectors. Therefore, we recommend the term is changed to 'delivery time' to better demonstrate EDDOs from novel or complex delivery systems may require clinical validation.
Line 569-570	Also, such clinical studies should be conducted with the final finished drug delivery device.	Also, such clinical studies should be conducted with the final finished drug delivery device, **or appropriate surrogate[FN].** **FN – FDA draft guidance Bridging for Drug-Device and Biologic-Device Combination Products) . 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

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			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. Therefore, we recommend the draft guidance is amended to allow for 'appropriate surrogates' with a reference to the FDA draft guidance *Bridging for Drug-Device and Biologic-Device Combination Products (2019)* when using clinical studies to validate an EDDO if there is no significant impact to the clinical safety and performance.
Line 623-625	(2) 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. Provide the following data:	(2) 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. Provide the following data:, **as described in FDA guidance *Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions* (December 2019).**	When discussing performance data to be submitted for IND and IDE applications, the draft guidance states that applicants 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 Submission*. However, in *Section B. Marketing Applications*, the draft guidance does not state if summary performance data may be submitted nor in what format. For consistency, we recommend 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 Submission.* Additionally, this change would further encourage the use of testing per

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			FDA recognized standards developed in collaboration with industry.
Line 627	a. Design input requirements (i.e., the physical and performance requirements of a device that are used as a basis for device design) b. Design output specifications (e.g., device description, drawings, specifications, materials) c. Design verification plan/summary report, supporting data, and traceability d. Design validation plan/ summary report, supporting data, and traceability e. Risk analysis to evaluate the adequacy of the design verification and design validation plans	We recommend the following revisions: " c. design verification **<u>results</u>** ~~plan/summary report, supporting data, and traceability~~ d. Design validation results, **<u>including human factors</u>** ~~plan/summary report, supporting data, and traceability~~ e. risk analysis summary **<u>reports</u>**…. ~~adequacy of the design verification and design validation plans"~~	We recommend the following changes, including references to human factors, and updates to the text for clarity.
Line 670-671	Applicants can consult with the appropriate product office for questions regarding control documentation to include in a submission	Applicants can consult with the appropriate product office for questions regarding **<u>supporting evidence</u>** ~~control documentation~~ to include in a submission	Recommend changing the term 'control documentation' to 'supporting evidence' or 'documentation to support the control strategy' for clarity.
Line 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. Applicants should also perform an analysis of the impact of the change on the verification and validation of the previously identified EDDOs.	Please clarify that the comparative approach recommended for post-market changes to NDA/BLA supplements also applies to design and/or manufacturing changes across different presentations (e.g., 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

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			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). Applicants often use NDA/BLA supplements to introduce a new device constituent design to deliver the same drug. Therefore, the proposed comparative approach could support those submission types and adequately 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". Therefore, we recommend FDA clarifies that the approach described in Section C. *Submissions for Post-Market Change that May Impact Essential Drug Delivery Outputs* applies to changes between the same device type (Pre-filled Syringe to Pre-filled Syringe) and across different device types (Prefilled Syringe to Autoinjector).
742	N/A – content not present in draft guidance	ISPE recommends adding a section on Established Conditions, for example **(5) Established Conditions**	Footnote 67 makes reference to ICH Q12 and implies that FDA is considering how the EDDO and associated verification, validation and control strategy information would be incorporated into an applicant's proposed set of established conditions. However, the FDA's current thinking on the

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		For device constituent parts of drug-led combination products, applicants may submit established conditions for the device part of the combination product. When submitting ECs for the device, FDA recommends that applicants assess the "characteristics of the product that are essential for its safe and proper use (primary characteristics)" Applicants should consider the device EDDO and associated EDDO control strategies to be a part of a product's established conditions. [FN] See FDA draft guidance ICH Q12: Implementation Considerations for FDA-Regulated Products Guidance for Industry. This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic	relationship between EDDO and ECs are not clear based on the content of the respective guidance documents. There are opportunities to leverage these concepts together to clarify and streamline lifecycle management of the device constituents. We recommend the FDA include additional content and examples into the EDDO guidance to clarify this relationship. Additionally, to reduce confusion, we recommend harmonization of the language between the FDA's EDDO guidance and FDA's guidance ICHQ12 Implementation Considerations for FDA-Regulated Products. For example, Line 217 of the FDA ICHQ12 guidance includes language with a similar intent to the EDDO concept. We recommend FDA update its ICHQ12 guidance to explicitly refer to EDDO terminology to reduce any confusion between the two documents.
Line 747-748	We recommend applicants submit the proposed EDDOs and control strategy for Agency feedback.	We recommend applicants submit the proposed EDDOs, **an assessment explaining how they were determined,** and control strategy for Agency feedback.	In *Section IX. Interaction with FDA*, the guidance recommends applicants engaging early with the FDA to agree on EDDOs for their final finished combination product. While the section also contains recommendations on what to provide in a meeting background package (device description, illustrations, etc.,) it does not request for an EDDO identification assessment or justification. For novel,

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			complex or platform devices (i.e., devices that may be used for multiple programs) an EDDO assessment describing the identification process and rationale could facilitate discussions at meetings. The justification depth may also vary depending on the complexity of the delivery system or program (e.g., platform device). Therefore, we recommend *Section IX. Interaction with FDA* is amended to include an EDDO identification assessment.
Line 846 - 847	Audible feedback/clicks Yes. It signals that the injection is complete and is dependent on the device.	Audible feedback/clicks: Yes – **if they are the sole mechanism for dose confirmation** ~~It signals that the injection is complete and is dependent on the device~~."	Audible feedback should only be EDDO if it is the sole mechanism for dose confirmation.
Appendix C – Table 6 Infusion Products Lines 893-895	Infusion Pump Example EDDO: "Connection stability to IV or to separate administration set for SQ, etc." Subdermal Implants Example EDDO: "Implant compatibility with applicator (e.g., dimensional compatibility"	Remove the following EDDOs from the listed examples: Infusion Pump 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

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			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). Therefore, we recommend removing compatibility EDDOs from the examples in Appendix C and include device-to-device compatibility as a form of preconditioning in the design verification section of the guidance.
Line 923-924	The needle cover retraction distance is also a dimensional function that is not impacted by aging and subsequent assembly steps at the final manufacturing stage.	The needle cover retraction distance is also a dimensional function that is not impacted by ~~aging and~~ subsequent assembly steps at the final manufacturing stage.	If the device stability was low enough that this is realistically a potential impact between manufacturing and assembly steps, then it is highly probable that this would show up as a signal in design verification and accelerated aging studies. In other words, stability is not a suitable device design~~.~~ If FDA is trying to address the age of components between the time of component manufacture to assembly and release, then we recommend FDA directly comment on the need to assure that aspect as part of the accelerated aging design verification studies, and not try to address it here as part of the control strategy within section *VI.A.2.b Shelf-life and stability testing considerations*.

Add rows as needed

Larger diagram from comment on Figure 1.