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

Guidance for Industry

DRAFT GUIDANCE

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I. INTRODUCTION

This guidance addresses key aspects of drug delivery performance information for devices,[1] and combination products[2, 3] that include device constituent parts,[4] intended for delivery of a human drug, including a biological product[5] (herein referred to as *drug delivery devices*).[6] The guidance describes FDA's recommendations related to the device design outputs that are essential for establishing and assessing drug delivery performance. The guidance includes recommendations for the information and data to submit in investigational, marketing, and post-market change applications.[7] Generally, as discussed further in this guidance, essential drug delivery output (EDDO) refers to the device drug-delivery design outputs necessary to ensure the drug delivery function.[8] This guidance recommends an approach to identifying EDDOs, provides examples of EDDOs for specific types of devices, and describes the information and data related to EDDOs provided in an application.

[1] The term *device* refers to a device as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 321(h)(1)).
[2] See 21 CFR 3.2(e) for the definition of *combination product*.
[3] For the purpose of this guidance, the term *product* is used to refer to both stand-alone devices (i.e., not part of a combination product) and combination products.
[4] See 21 CFR 4.2 for the definition of *constituent part*. For the purpose of this guidance, the terms *device* and *device constituent part* are used interchangeably.
[5] The term *drug* refers to a drug as defined in section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)), and includes biological products as defined in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)).
[6] For the purpose of this guidance, the terms *drug* and *drug constituent part* are used interchangeably.
[7] For the purpose of this guidance, unless otherwise stated, the terms *applications* and *submissions* are used interchangeably and include, as applicable, initial, supplements to, and amendments to: investigational new drug applications (IND), new drug applications (NDA), abbreviated new drug applications (ANDA), investigational device exemption (IDE) applications, premarket approval applications (PMA), De Novo requests submitted under section 513(f)(2) of the FD&C Act, premarket notifications (510(k) submission), and biologics license applications (BLA), including BLAs submitted under section 351(k) of the PHS Act.
[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.

Device drug-delivery performance information is intended to demonstrate that the device drug-delivery function consistently performs as intended. FDA is providing recommendations for development and organization of this information and these data to improve the consistency of this information in applications. Ultimately, these recommendations are intended to facilitate and streamline development of drug delivery devices.

This guidance does not address all of the data and information to be submitted in support of drug delivery devices (e.g., it does not address drug-device compatibility, biocompatibility, sterility, human factors, electrical safety, electromagnetic compatibility, radio frequency wireless technology, or cybersecurity). Applicants should refer to applicable regulations and guidance for more information on what is required or recommended to be submitted to FDA in applications for such products.[9]

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

II. SCOPE AND DEFINITION

Scope: 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[10] intended for delivery of a human drug, including a biological product.[11] Examples of products that are within the scope of this guidance include syringes, injectors (e.g., autoinjector, on body injector), infusion products (e.g., infusion pumps), nasal sprays, inhalers, nebulizers, and vaginal systems.

Definition: EDDOs are the design outputs necessary to ensure delivery of the intended drug dose to the intended delivery site.[12] Drug delivery includes successful product preparation[13] and

[9] For additional guidance related to product development, see the *FDA Guidance* webpage to search for an FDA guidance document or to browse FDA guidance documents by topic. Information on these considerations may be found in applicable guidances. For example, for more information regarding injector delivery devices, see the guidance for industry and FDA staff *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* (June 2013). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[10] CDER-led and CBER-led combination products refer to combination products for which CDER or CBER has primary jurisdiction (i.e., is the lead Center). For information regarding Center assignment, see the guidance for industry and FDA staff *Principles of Premarket Pathways for Combination Products* (January 2022).

[11] If an applicant has a question about whether the concepts in the guidance apply to a specific product, contact the applicable review division in the lead Center.

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

[13] See Appendices A and C for examples related to product preparation.

the initiation, progression, and completion of dose delivery.[14] EDDOs are system level outputs for which device drug-delivery function is dependent on the device design (see section V for more information).

III. BACKGROUND

Design control requirements include establishing and maintaining procedures relating to design inputs[15] and design outputs[16] (21 CFR 820.30(c) and (d)).[17, 18] The design must be verified and validated throughout the lifecycle of the product as needed (see 21 CFR 820.30(f) and (g)).[19] The design outputs are driven by the design inputs that address the intended use of the device (21 CFR 820.30(c)). EDDOs are a subset of design outputs. EDDOs are part of the information that is "essential for the *proper functioning* of the device" to deliver the drug (i.e., the intended use of the drug delivery device) (21 CFR 820.30(d) (emphasis added)). In accordance with this provision, manufacturers shall ensure that EDDOs are identified and approved before release (21 CFR 820.30(d)). In addition, to ensure the quality of the drug delivery function throughout the product lifecycle, control and maintenance of the EDDOs are also necessary.[20]

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[14] Drug and drug constituent part attributes may impact appropriate drug delivery.

[15] Design input means the physical and performance requirements of a device that are used as a basis for device design (21 CFR 820.3(f)).

[16] Design output means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record (21 CFR 820.3(g)).

[17] 21 CFR 820.30(c) states that "[e]ach manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient." 21 CFR 820.30(d) states that "[e]ach manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements."

[18] On February 2, 2024, FDA issued a final rule amending the device quality system (QS) regulation, 21 CFR part 820, to align more closely with international consensus standards for devices and making conforming amendments to 21 CFR part 4 (89 FR 7496, available at https://www.federalregister.gov/d/2024-01709). This final rule will take effect on February 2, 2026. Once in effect, this rule will withdraw the majority of the current requirements in part 820 and incorporate by reference the 2016 edition of the International Organization for Standardization (ISO) 13485, Medical devices – Quality management systems – Requirements for regulatory purposes, in part 820. As stated in the final rule, the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the current part 820, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the FD&C Act. When the final rule takes effect, FDA will also update the references to provisions in 21 CFR part 820 in this guidance to be consistent with that rule.

[19] 21 CFR 820.30(f) states that "[e]ach manufacturer shall establish and maintain procedures for verifying the device design. Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF." 21 CFR 820.30(g) states that "[e]ach manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions."

[20] See 21 CFR parts 820 and 4.

EDDO-related information, including verification and validation data, is provided in investigational and marketing applications for drug delivery devices and combination products with drug delivery devices to demonstrate that the drug delivery device appropriately delivers the intended drug dose to the intended delivery site.[21, 22] 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.

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 controlled during product design, development, and production. The final rule *Current Good Manufacturing Practice Requirements for Combination Products*, codified at 21 CFR part 4 (CGMP requirements),[23] provided clarity regarding the applicability of CGMP requirements to combination products, along with a streamlined regulatory framework for demonstrating compliance with applicable requirements. Core requirements in the CGMP regulations provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. The guidance for industry and FDA staff: *Current Good Manufacturing Practice Requirements for Combination Products* (part 4 CGMP guidance)[24] further describes and explains the manufacturing requirements and regulatory framework for combination products. It includes a detailed discussion of design controls, including design inputs and design outputs for a combination product (section IV.A.2 of the part 4 CGMP guidance). As described in the CGMP requirements and part 4 CGMP guidance, the design control requirements at 21 CFR 820.30 apply as appropriate to combination products with device constituent parts (see 21 CFR 4.4(b)(1)(ii) and (2)).

For combination products, FDA acknowledges that the terms design output (see 21 CFR 820.3(g) and 820.30(d)) and EDDO could be interpreted as analogous to the ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009) drug product terminology for a critical quality attribute (CQA), "[a] physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."[25] Similar to the CQA concept, as noted above, EDDOs are essential for the appropriate functioning of the device, and in some instances, an applicant could expand CQAs to include device drug-delivery function features for a combination product. Likewise, a quality target product profile (QTPP),[26] which is similar to design inputs (see 21 CFR 820.3(f) and 820.30(c)), may assist an applicant in identifying CQAs, including those for drug delivery. As appropriate, studies conducted to verify that the CQAs are met may address EDDO

[21] These data are typically distinct from the manufacturing information documented and available for review as part of an establishment assessment or inspection to establish compliance with CGMP and QS requirements, as applicable.

[22] The data needed to support approval/clearance of a particular product depends on the application type.

[23] 78 FR 4307 (January 22, 2013).

[24] January 2017.

[25] See *ICH Q8(R2)* annex glossary at p. 18.

[26] A QTPP is "[a] prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." *ICH Q8(R2)* annex glossary at p. 18.

verification and validation (see 21 CFR 820.30(f) and (g)).[27] Applicants may be able to leverage CQA information to support EDDO identification, control, and maintenance processes. When the EDDO is amenable to verification and validation through analytical methods (see section VI), the chemistry, manufacturing, and controls (CMC) information may address these design control requirements.

EDDO identification, control, and maintenance processes also may facilitate development by:

- Informing the determination of which data to submit in an investigational or marketing application to demonstrate the drug delivery performance;
- Ensuring the appropriate device design attributes and manufacturing process steps are evaluated during lifecycle changes; and
- Providing a basis for comparing the drug delivery performance and facilitating assessment of EDDOs for bridging or leveraging data across products.[28]

IV. OVERVIEW OF ESSENTIAL DRUG DELIVERY OUTPUT PROCESSES

In developing EDDOs, there are three primary processes: identification, control, and maintenance.

- **Identification** of the EDDO defines the device drug-delivery function of the product and focuses design and development efforts to ensure appropriate drug delivery.
- **Control** of the EDDO ensures the product meets the device drug-delivery function quality standards. See section VII for information on control strategy.
- **Maintenance** of the EDDO ensures that any changes to the product made during clinical development or post-market that could adversely impact the EDDO are evaluated to help preserve the quality of the drug-delivery function.

The following sections provide information on identifying EDDOs (section V), EDDO verification and validation (section VI), and EDDO control strategies (section VII).

V. IDENTIFYING ESSENTIAL DRUG DELIVERY OUTPUTS

EDDOs can be identified from existing design controls by using a filtering process illustrated in Figure 1 to identify specific design outputs.

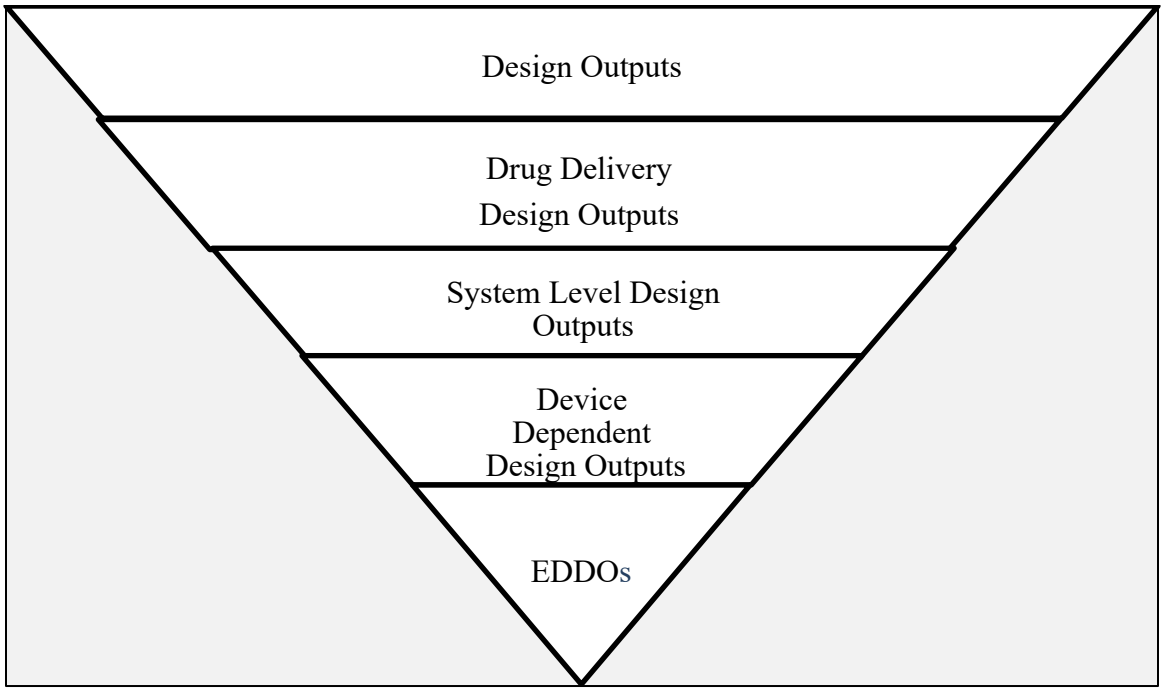
[27] For additional discussion of the relationship of drug development and device development terms related to design control, see the part 4 CGMP guidance at section IV.A.2.

[28] For additional information on bridging data across combination products, see the draft guidance for industry *Bridging for Drug-Device and Biologic-Device Combination Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

The EDDO identification process begins with all design outputs and then uses filtering steps to eliminate outputs that do not meet the EDDO definition, which results in remaining outputs that are the EDDOs. As noted in Section III, in some instances, the CQAs of a combination product may include EDDOs, and thus, the below EDDO identification process may be addressed by the determination of those CQAs.

Figure 1 – Illustration of the EDDO Identification Process

The figure illustrates, at a high level, the process for identification of EDDOs.



The following steps are useful in identifying EDDOs:

(1) **Design Outputs** – Begin by defining the proposed intended use, consider, e.g., the indications for use, population, and condition and frequency of use, and design inputs (e.g., user requirements, design specifications, route of administration, drug characteristics, dosage form, and delivery volume). This information should be used to identify the design outputs.

(2) **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).

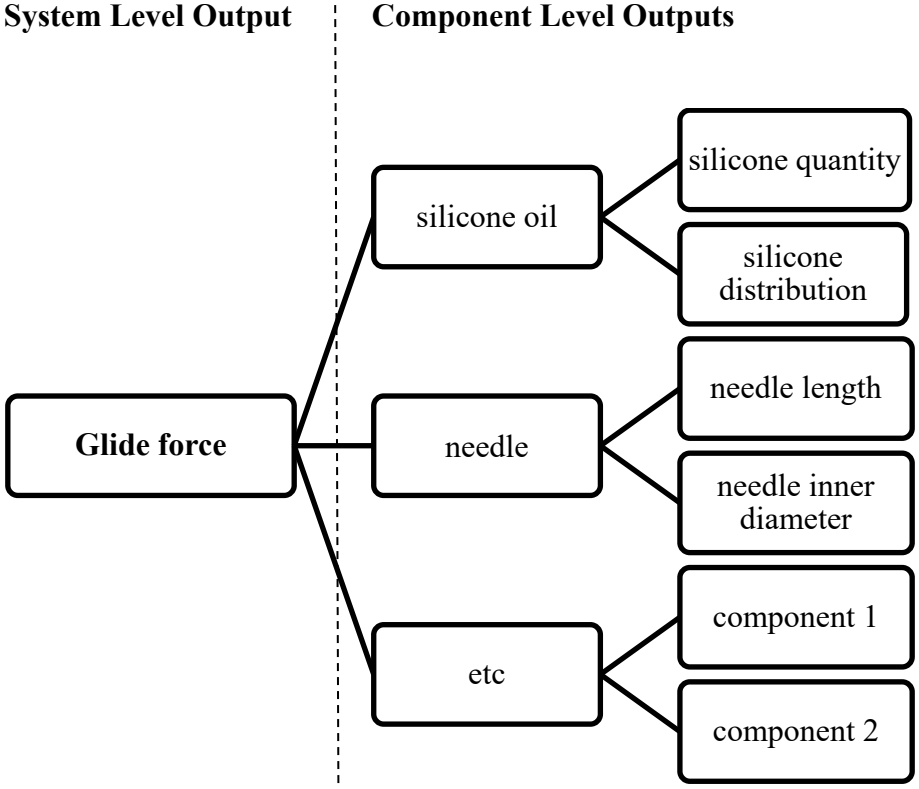
(3) **System Level Design Outputs** – Identify the drug delivery design outputs that are system level design outputs (i.e., design outputs that are the functions necessary for the performance of the final finished product). For more information, see the discussion below following step 4 and in Figure 2.

(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).

As described in step 3, an EDDO is a system level design output. We note that there are other design outputs known as component level outputs that are different from system level outputs. Component level outputs work together to achieve a system level output and are not EDDOs. Component level outputs support, but are subordinate to, system level outputs (see Figure 2).

Figure 2 – Example of System Level and Component Level Outputs (Step 3)

To help in identifying the EDDOs, Figure 2 illustrates the relationship between system level and component level outputs for a prefilled syringe (PFS) that includes a needle, silicone oil as a lubricant, and other components.



See Appendix A for a narrative illustration of the process concepts for identifying EDDOs for a PFS. Appendix B illustrates the distinction between EDDOs and other design outputs for an autoinjector. In addition, this document provides examples of design outputs for common combination products with drug delivery devices that are likely to be considered EDDOs (see Appendix C).

VI. VERIFYING AND VALIDATING ESSENTIAL DRUG DELIVERY OUTPUTS

While design verification[29, 30] and validation[31] activities are intended to address all design inputs and outputs, the following recommendations are specific to EDDOs. Appropriate verification and validation activities for EDDOs depend on the conditions (e.g., environmental conditions) to which the product will be exposed during production, shipping, storage, and preparation and the conditions associated with use. Examples of conditions that may impact performance include, but are not limited to, temperature, pressure, humidity, vibration and shock, and physical orientation. Also, during storage or shipping, a product may be exposed to more than one variation of a condition or sequences of conditions (e.g., ground by truck to air, ground by truck to boat, ground by rail to air to ground by truck). In addition to the storage and shipping stressors, there are stressors associated with the use environments (e.g., health care facility, school, home, first response environment). Verification and validation test reports provided in a submission should provide information on how the tests conducted, including the conditions and methods selected, are adequate to verify and validate the EDDOs.

Further, although the test methods used to verify and validate an EDDO are beyond the scope of this guidance, the test methods (e.g., mechanical or analytical) may differ for active (e.g., autoinjector, metered dose inhaler) and passive (e.g., some implants, vaginal systems) drug delivery devices.[32] See section VIII for details on verification and validation information included in applications.

A. Design Verification for EDDOs

It is important that prior to initiation of any clinical studies (or any *in vivo* bioequivalence studies, as applicable) or commercial distribution, applicants verify the performance of the product. How applicants conduct design verification testing is dependent on device design, intended use, and applicable regulations, standards, and guidances. Design verification generally includes preconditioning and subsequent verification testing to confirm that the device drug-delivery function is maintained in accordance with the instructions for use. The following sections provide considerations when developing a design verification approach. If an applicant intends to use an alternative design verification approach, we recommend providing an explanation of and rationale for the alternative approach and requesting Agency feedback in a formal meeting or communication with FDA (see section IX).

1. Preconditioning

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,

[29] Verification means "confirmation by examination and provision of objective evidence that specified requirements have been fulfilled" (21 CFR 820.3(aa)).

[30] Design verification shall confirm that the design output meets the design input requirements (21 CFR 820.30(f)).

[31] Design validation means "establishing by objective evidence that device specifications conform with user needs and intended use(s)" (21 CFR 820.3(z)(2)).

[32] Different analytical methods, including assays, and other mechanical methods can be used or leveraged, as applicable, for the specific product design.

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 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 section VI.A.1.c). Because of the risk to the patient should the device fail, sequential preconditioning is generally expected for emergency-use injectors,[33] and applicants should identify the sequence in which the preconditions should be applied. In developing the preconditioning methods, applicants may leverage test methods, acceptance criteria, and statistical analysis techniques from recognized standards.

a. Storage

Preconditions to simulate storage may include, for example, specific temperatures, temperature fluctuations, pressure changes, and humidity. A product may be subjected to different storage conditions throughout the product lifecycle (e.g., conditions at the manufacturing facility, warehouse, health care facility, pharmacy, or home setting), and these should all be considered before EDDO design verification.

b. Shipping

Preconditions to simulate shipping may include, for example, vibration, shock, and pressure changes, that may impact device drug-delivery performance. Some EDDOs (e.g., physical dimensions) would not be impacted by shipping and would not warrant preconditioning for shipping conditions. For the EDDOs that may be influenced by shipping conditions, shipping preconditioning representative of likely exposures (e.g., during shipping via air, ground by truck, ground by rail, boat) should occur before EDDO design verification.

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 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 and all aspects of the infusion pump system, including

[33] For additional information regarding preconditioning, see section V.4.a of the draft guidance for industry and FDA staff *Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA, or ANDA* (April 2020). When final, this guidance will represent the FDA's current thinking on this topic.

accessories (e.g., infusion sets). Preconditions for the infusion pump and infusion pump accessories may be different. Therefore, the various sequential preconditioning methods should be applied as appropriate for the components of the infusion pump system and in accordance with the proposed labeling.

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.[34] 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.

2. Design Verification Testing

Overall, the design verification assessment of EDDOs should occur after appropriate preconditioning. Depending on the product, the EDDO, and the specific types of preconditions, there may be different types of testing to verify that an EDDO is maintained throughout the range of conditions and use environments described in proposed labeling. This testing may include functional testing after preconditioning or it may be part of a design verification shelf-life testing program (see section VI.A.2.b). For example, an applicant may follow a protocol for assessing the impact of shipping preconditions on a specific EDDO. When used to evaluate a product that has been fully preconditioned, the protocol should enable assessment of the impact of actual preconditions associated with use (e.g., repeat use following the instructions for use including any reprocessing steps) and verification that the EDDO is maintained following preconditioning.

Regardless of the type of testing method, EDDO evaluation during design verification should address the applicable preconditions as described in section VI.A.1. If preconditioning is omitted, the associated protocol should provide a rationale for the omission.

a. Sampling considerations

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 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).

[34] Additional information regarding the reprocessing of medical devices can be found in the guidance for industry and FDA staff *Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling* (March 2015).

b. Shelf-life and stability testing considerations

Design verification testing should include an evaluation of EDDOs that may change over time or have age-related failure modes. Data provided to support a proposed expiration date should demonstrate that EDDO performance is maintained. For a combination product, such data can be derived from design verification shelf-life testing,[35] stability testing,[36] or both. For a combination product, the final determination of the expiration date is informed by the maintenance of EDDO performance and drug stability testing. EDDOs that would not change over time (e.g., physical dimensions such as needle length) would not warrant evaluation.

The testing to support a proposed expiration date should include consideration of the number of repeat uses of the product to deliver the drug and the potential impact of any associated cleaning and reprocessing cycles and interim storage between uses. This testing should consider and address the applicable preconditions as described in section VI.A.1 and include a justification for any applicable preconditions omitted during the shelf-life or stability testing. 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.

For combination products, to support the proposed expiration date, verifying the performance of certain EDDOs over time may be accomplished by relying on or leveraging drug stability testing results (e.g., for EDDOs subject to chemical degradation such as EDDOs for a vaginal system).[37] For EDDOs subject to physical or mechanical degradation, additional data to address design verification shelf-life testing of the device drug-delivery function may be appropriate to support expiration dating. Such design verification shelf-life testing should be conducted using the final finished product under real-time aging conditions. As appropriate, accelerated aging data may be used to establish the shelf life. When used, accelerated aging data should be confirmed by real-time aging data. Applicants who are considering this approach should discuss their proposals with the Agency (see section IX for more information).

B. Design Validation for EDDOs

To ensure appropriate validation, the applicant must ensure that devices conform to defined user needs and intended uses and must include testing of production units under actual or simulated use conditions.[38]

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

[35] Shelf life is "the term or period during which a commodity remains suitable for the intended use" (FDA guidance *Shelf Life of Medical Devices* (April 1991)).

[36] Stability testing refers to a requirement for drugs and combination products addressed in 21 CFR 211.166 and 21 CFR 4.4, respectively.

[37] For EDDOs that are evaluated as part of stability testing, information and data as described in ICH Q1A(R2) *Stability Testing of New Drug Substances and Products* (November 2003) and related FDA stability guidances are appropriate to support the proposed expiration date.

[38] Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents (21 CFR 820.30(g) and 4.4(a)).

the capability of validating device performance. 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 an example, when developing an infusion pump that is submitted in an NDA, the EDDO of flow rate would be evaluated through effectiveness data, PK/PD data, and safety data (e.g., adverse events, occlusion rates, infusion site reactions) in appropriately designed clinical 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:[39] 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[40]

- Anthropometric data: e.g., simulated strength testing of specific patient populations and postures, capability of specific populations' ability to hear specific tones

For example, for an NDA for a PFS, the EDDO validation testing might include clinical studies appropriately designed to validate deliverable volume and injection to the target site, analysis of anthropometric data[41] for cap removal force, and simulated bench testing using prototype PFS devices for breakloose and glide forces.

1. Additional Validation Considerations for ANDA Submissions and BLAs Submitted under Section 351(k) of the PHS Act for Combination Products

For an ANDA submission or a BLA submitted under section 351(k) of the PHS Act for a combination product, it may be possible to rely on an RLD or reference product, respectively, by providing a side-by-side comparison of EDDOs or EDDO performance[42] for the combination product against that for the RLD or reference product.

[39] Applicants would have to manufacture devices that function at the limits of the specification to effectively validate the EDDO.

[40] These simulated bench tests are different than human factors user validation studies.

[41] ANSI/AAMI HE 75:2009 (R2018) *Human factors engineering – Design of medical devices*, addresses how to perform this analysis.

[42] For example, if the specifications of the RLD or reference product are unknown to the applicant, then the application can use a side-by-side comparison of performance testing to verify that the ANDA or BLA submitted under 351(k) device performs similarly to the RLD or reference product, respectively.

If the comparison shows there are differences from the EDDO specifications in the RLD or reference product, then applicants may provide additional data to support that the specification is appropriate for an ANDA or BLA submitted under section 351(k) of the PHS Act, as applicable. For example, for the EDDO of activation force, if the specification or performance was different from the RLD or reference product, the applicant may provide data demonstrating the activation force is not too high such that the proposed combination product would not be therapeutically equivalent to, or biosimilar to or interchangeable with, as applicable, the RLD or reference product.[43]

FDA recognizes that in some instances applicants may not have certain information for comparison (e.g., if the RLD or reference product is discontinued or if the proposed combination product has different design features). In such instances, the applicant should contact the Agency through a controlled correspondence or pre-ANDA meeting request, or following procedures described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products,*[44] as appropriate, (see section IX) with a proposal for how to validate the EDDO.

2. Additional Validation Considerations for Premarket Notifications [510(k)]

For a 510(k), submitters compare the intended use (including indications for use) and the technological characteristics of their device, including EDDOs, to the predicate device. When there are differences in technological characteristics, which do not raise different questions of safety and effectiveness from the predicate device, FDA may request additional performance data, including clinical data as necessary, to assess whether the device is as safe and effective as the predicate device.[45]

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. 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).

[43] Information on differences in the user interface between an ANDA and its RLD is beyond the scope of this guidance. For additional information on identifying and analyzing differences between a proposed generic combination product and the RLD, see the draft guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017). When final, this guidance will represent FDA's current thinking on this topic.

[44] August 2023. When final, this guidance will represent the FDA's current thinking on this topic.

[45] Applicants submitting 510(k)s for their devices should address the submission recommendations included in the guidance for industry and FDA staff *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]* (July 2014).

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. 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.

When developing an upstream control strategy for an EDDO, it is important to consider the attributes and manufacturing process steps that can influence the EDDO, and describe why these attributes or process steps are the only ones that influence the EDDO. Appropriate controls should be identified for each attribute or process step, and the documentation used to verify these controls should be identified. For certain attributes, purchasing controls or an incoming test/examination, in combination with design assessment verification testing, may be sufficient (e.g., for the length of the syringe and needle that cannot change over the expiration dating period). For other attributes or process steps, a combination of controls may be appropriate. The description of the control strategy should include an assessment of how the effectiveness of an upstream control is impacted by the downstream manufacturing steps.

Information to support that in the context of the manufacturing process, the control strategy is adequate to ensure consistent EDDO performance is submitted as part of the marketing application, submitted upon request, or available during facility inspection, depending on application type (see section VIII.B). The supporting information may consist of batch analysis (i.e., testing the final finished product against the specification) or EDDO evaluation conducted as part of stability testing (see section VI.A.2.B). For more information, see regulations and guidance on specific application type submission requirements for manufacturing information. For products subject to premarket approval (e.g., under an ANDA, BLA, NDA, PMA), control strategy information is included in the application.[46] In contrast, 510(k) submissions generally do not include control strategy information as part of the 510(k) itself; however, information demonstrating control of the 510(k) device's manufacturing process must be available for FDA review during inspections.[47]

See Appendix D for an illustration of a control strategy for the final assembly of a syringe based autoinjector.

VIII. INFORMATION TO PROVIDE IN APPLICATIONS

This section describes the EDDO information and performance data included in investigational,

[46] Information on manufacturing controls must be included in such applications, see 21 CFR 314.50(d)(1)(ii), 314.94, 601.2(a), and 814.20(b)(4).

[47] See section 704(a) of the FD&C Act. Such records must be made available for FDA review during an inspection conducted under section 704(a)(1) of the FD&C Act or when requested by FDA in advance of or in lieu of an inspection as described in section 704(a)(4) of the FD&C Act.

marketing, and post-market change applications to demonstrate the device drug-delivery function.

A. IND and IDE Applications

The data provided in IND and IDE applications for drug delivery devices should reflect the development stage of the product. Bio-INDs under 21 CFR 320.31 for ANDAs are out of scope of this guidance.[48] It is understood that for combination products, the drug delivery device may be introduced after the investigational drug development begins. We understand that the device design may evolve based on study results. The device drug-delivery data submitted in an IND or IDE application[49] should reflect the development process, and applicants should consider the device design, the drug being delivered, the patient populations, study design, and risks to the study participants when determining the data to provide.

To support the first use of the device or device constituent part in a clincial study, it is important that applicants provide information demonstrating that the safety and performance of the device is adequate for the proposed investigation. Information from EDDO verification testing is provided to demonstrate that the device performs and the drug is delivered (dose and delivery site) as intended.

As development proceeds and the product design evolves, additional information may be needed to support the use of the final finished product in pivotal[50] clinical studies. As applicable, the submission should provide more comprehensive information that builds upon earlier safety information and study results, including information that applies to the device drug-delivery function. As product development continues, for any planned changes to the EDDOs of the device for commercialization, it may be possible to use the EDDO performance data from the clinical study design iteration to help bridge between prototypes.

For any required IDE and IND applications for drug delivery devices, requirements for submission content relevant to EDDOs include, but are not limited to the following, respectively:

- A complete report of prior investigations of the device and a summary of certain sections of the investigational plan, or, in lieu of such a summary, the complete investigational plan;[51] a description of the methods and controls used for the manufacture of the device; risk analysis; and description of the device.[52]

[48] A sponsor of a bio-IND under 21 CFR 320.31 with a drug delivery device may submit a controlled correspondence (see section IX) with any questions regarding the applicability of the information described in this section. For additional information on bio-INDs, see Manual of Policies and Procedures 5210.5, *Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs* (Rev. 3, April 14, 2022).

[49] For combination products, see footnote 10 for information on application types.

[50] For the purpose of this guidance, a pivotal study is a definitive study in which data are evaluated to establish the safety and effectiveness of the product; this study is submitted in a marketing application to support its intended use. Other terms for such studies include key, critical, and major studies.

[51] We note that the sponsor shall submit to FDA the complete investigational plan and a complete report of prior investigations of the device if no IRB has reviewed them, if FDA has found an IRB's review inadequate, or if FDA requests them. 21 CFR 812.20(b)(2).

[52] See 21 CFR 812.20(b)(2) and (3), 812.25(c) and (d), and 21 CFR 812.27(a).

- A brief summary of previous human experience with the product, an investigational plan; and information describing the composition, manufacture, and control of the product.[53]

As described above, depending on the application type, certain information on EDDOs is a required part of the application, while other information is recommended for submission. This section outlines considerations for this information that the applicant or submitter, depending on the context, is either required or recommended to "provide," "identify," "describe," or "compare," for example:

(1) Device description documentation –

(a) Provide a description of the device design, including any novel features and functionalities, including engineering drawings or diagrams of the device with all dimensions labeled, descriptions of the individual device components, or any other available information to explain the device design.

(b) Describe the principles of operation of the device and how it functions throughout use.

(c) Describe any accessories or other devices labeled for use with the device.

(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.

(3) Performance data[54] – Include summary test results using established test methods for the device (e.g., recognized standards, test methods discussed in FDA guidance) or complete verification test reports for unique or unrecognized test methods. Recommendations regarding the summaries and/or documentation can be found in the guidance for industry and FDA staff *Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions* (December 2019).

The following considerations apply when the clinical study results are part of the EDDO validation:

- If the clinical study is intended to obtain data to validate one or more EDDOs, it is appropriate for the clinical study protocol to include endpoints relevant to the performance of the device (e.g., infusion rate, dose range, injection time). Where

[53] See 21 CFR 312.23(a)(3)(ii), 312.23(a)(3)(iv), and 312.23(7)(i).

[54] As discussed in the part 4 CGMP guidance, investigational combination products that include device constituent parts may be subject to design controls under 21 CFR 820.30, which includes design verification of an investigational product.

possible, to support provision of evaluable EDDO data, applicants should submit such protocols for Agency feedback on the EDDO validation endpoints in a formal meeting or communication with FDA (see section IX). Also, such clinical studies should be conducted with the final finished drug delivery device.

- It is important that the clinical study protocol include safety endpoints that capture drug delivery device failures, malfunctions, and adverse events.[55]

B. Marketing Applications

For marketing applications for devices and combination products, requirements for submission content relevant to EDDOs include, but are not limited to the following:

- A PMA must include a complete description of the device, each of the functional components or ingredients (as described in FDA regulations), and the methods used in, and the facilities and controls used for, the manufacture of the device; and nonclinical laboratory studies.[56]

- A 510(k) submission must include a description of the device, a statement indicating the device is similar to and/or different from other comparable products including data and information to support that statement, and as applicable, appropriate supporting data to show that the manufacturer has considered what consequences and effects any changes or modifications or new uses might have on the safety and effectiveness of the device.[57]

- A De Novo request must include a complete description of the device and nonclinical laboratory studies.[58]

- NDA, ANDA, and BLA applications must include a description of the product, data to show that the final finished product meets specifications, a description of the manufacturing processes and controls, and stability data.[59]

Other data and information relevant to EDDOs, such as the establishment of design inputs and outputs and completion of design verification and validation testing, are needed to comply with design control requirements.[60]

For products subject to premarket approval (e.g., under an ANDA, BLA, NDA, or PMA), as described above, manufacturing control strategy information is required to be included in the application. In contrast, 510(k) submissions generally do not include control strategy information as part of the 510(k) itself; however, information demonstrating control of the

[55] Note that human factors considerations are outside the scope of this guidance; see section I.
[56] See 21 CFR 814.20(b)(4)(i), (ii), and (v); 21 CFR 814.20(b)(6)(i).
[57] See 21 CFR 807.92(a)(4); 21 CFR 807.87(f) and (g).
[58] See 21 CFR 860.220(a)(6) and 21 CFR 860.220(a)(15)(i).
[59] See 21 CFR 314.50(d)(1), 314.94(a)(9), and 601.2(a).
[60] See 21 CFR 820.30 for devices and 21 CFR 4.4 for combination products.

510(k) device's manufacturing process as part of complying with applicable GMP requirements[61] must be available for FDA review during inspection.[62]

As described above, depending on the application type, certain information on EDDOs is a required part of the application, while in other instances that same information is recommended for submission. This section outlines considerations for this information that the applicant or submitter, depending on the context, is either required or recommended to "provide," "include," "identify," "describe," or "compare," for example.[63]

(1) Device description documentation –

(a) Information in section VIII.A, item #1

(b) When applicable, include a side-by-side comparison of the to-be-marketed device with any earlier versions utilized in the provided verification and validation testing, identifying any design and manufacturing changes.

(2) Performance data[64, 65] – 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.[66] Provide the following data:

(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

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[61] See 21 CFR 820.70(a) and 820.180.

[62] See section 704(a) of the FD&C Act (21 U.S.C. 374(a)). Also see footnote 47.

[63] Master files may be useful tools to help preserve the trade secrets of a third party that are not known to the applicant. For more information on biologics, device, and drug master files, see CBER's Master Files for CBER-Regulated Products web page (available at https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/master-files-cber-regulated-products), CDRH's Master Files web page (available at https://www.fda.gov/medical-devices/premarket-approval-pma/master-files), and CDER's Drug Master Files (DMF) web page (available at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs), respectively.

[64] When submitting this information in an NDA, ANDA, or BLA, see section 5 in the FDA eCTD Technical Conformance Guide: Technical Specifications Document: Guidance for Industry *Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (July 2020).

[65] For additional information regarding information included in NDAs, ANDAs, and BLAs, see the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics* (July 1999).

[66] For questions about design control documentation, see the guidance for industry *Design Control Guidance for Medical Device Manufacturers* (March 1997).

(i) If changes are made after design validation, include a discussion, along with supportive data, of either why the validation data is still applicable or how the applicant validated the changes

(e) Risk analyses to evaluate the adequacy of the design verification and design validation plan

(3) EDDO – Identify EDDO(s) for the drug delivery device

To facilitate submission and review of the EDDO information, provide a summary of the EDDO information included in the application in the device description documentation, referencing the performance data section and supportive information. For NDAs, BLAs, and ANDAs, if the EDDO performance relies on or leverages CQA and related information in the CMC sections, the summary should reference the relevant sections.[67]

When verifying and validating the EDDO(s), include the EDDO(s) in the following evaluations, when applicable as discussed in sections VI and VII:

(a) Preconditioning – Provide documentation that demonstrates that the device EDDOs are met after preconditioning testing. See section VI.A.1 for additional considerations.

(b) Stability/Shelf-life testing – Include endpoints in the final finished product stability and shelf-life testing program to verify that EDDOs that could change with aging are maintained at expiry. See section VI.A.2.b for additional considerations.

(c) Control strategy – Provide a control strategy based on the product risk profile that ensures that the final finished product maintains its EDDO(s).[68] Include a summary of the controls implemented (upstream and/or at release), including a justification describing how the controls are sufficient to assure the quality of the EDDO is achieved. In the control strategy description, include supporting evidence such as engineering drawings, tolerance stack-up analysis, and manufacturing flow diagrams. FDA may request additional specific documentation referenced in the control strategy during the review.[69] Applicants can consult with the appropriate product office for questions regarding control documentation to include in a submission.

See section VII for additional information on developing a control strategy.

[67] If the application includes proposed established conditions (ECs) for the device constituent part, and the EDDOs constitute a subset of the proposed ECs, we recommend referencing the EC-related sections of the application for the EDDO information. See the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021) and the draft FDA guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021) (when final, this guidance will represent FDA's current thinking on this topic).

[68] See section VII for additional information.

[69] See Appendix D for an example of a control strategy for an EDDO where documentation to verify the control was either included (i.e., documentation from the applicant) or referenced (i.e., documentation from sources other than the applicant) in the submission.

C. Submissions for Post-Market Changes That May Impact Essential Drug Delivery Outputs

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.

For post-market change submissions for devices and combination products, requirements for submission content relevant to EDDOs include, but are not limited to the following:

- PMA, for changes requiring a submission/notice:[70] a supplement/notice must include identification of each change and the reason for each change (PMA supplements); must provide a full explanation of the basis for the changes (special PMA supplements); or must describe in detail the changes and summarize the data or information supporting the change (30-day notices).[71]

- 510(k) submission, for changes requiring a new 510(k):[72] a 510(k) must include a summary of how the technological characteristics of the device compare to a predicate device and what consequences and effects the difference(s) might have on the safety and effectiveness of the device.[73]

- NDA/BLA/ANDA, for changes requiring approval prior to distribution:[74] a supplement must include a detailed description of the proposed change; a description of the methods used and studies performed to assess the effects of the change, and the data derived from such studies.[75]

As described above, depending on the application type, certain information on EDDOs is a required part of the postapproval submission, while in other instances that same information is recommended for submission. This section outlines considerations for this information that the applicant or submitter, depending on the context, is either required or recommended to "provide," "include," "identify," or "describe," for example:

(1) Description of changes in comparison to the approved or cleared product

(2) Potential impact of the change to EDDOs

(3) Verification, validation, or both of potentially impacted EDDOs

[70] See 21 CFR 814.39(a), (c), or (f).
[71] See 21 CFR 814.39(c)(1), 814.39(d)(1)(ii), 814.39(f).
[72] Changes to a previously cleared device may require the submission of a new 510(k). See the guidance for industry and FDA staff *Deciding When to Submit a 510(k) for a Change to an Existing Device* (October 2017).
[73] See, e.g., 21 CFR 807.92(a)(6), 21 CFR 807.87(f) and (g).
[74] See 21 CFR 314.70(b), 314.97(a), and 601.12(b).
[75] See 21 CFR 314.70(b)(3), 314.97(a), and 601.12(b)(3).

If the specifications are unchanged, then provide verification data, including stability and preconditioning (e.g., storage, shipping, conditions associated with use) information when applicable. If an applicant does not believe that the change would be impacted by preconditioning, then provide a scientific justification and/or evidence that the performance is not expected to shift outside the validated specifications over time or after preconditioning.

To support the change, provide a side-by-side comparison between the new design or new manufacturing process/site EDDO and the original device design or manufacturing process/site EDDO to assess for potential shifts in performance that may lead to potential out-of-specification results. For an ANDA, in the case of shifts in performance, a comparison to the RLD may be appropriate.

If the specifications are changing, provide new EDDO validation data or a rationale for why the validation from the original application can be leveraged (e.g., tightening a specification).[76]

(4) Updated control strategy

To help ensure EDDO maintenance throughout the product lifecycle, include a re-evaluation of the control strategy to determine whether it is still applicable given the design changes, manufacturing changes, or both, including information to demonstrate that the control strategy is still effective.

Alternatively, if an applicant is making changes that necessitate a change to the control strategy, provide documentation for the changes made to the EDDO control strategy and information to demonstrate that the new strategy is as effective as the original control strategy.

IX. INTERACTION WITH FDA

During product development we strongly encourage applicants to begin developing and characterizing the EDDOs that will need to be controlled in the final finished product and to begin to develop a device control strategy for the product the applicant plans to market. We recommend applicants submit the proposed EDDOs and control strategy for Agency feedback. The EDDOs and control strategy could be discussed at multiple types of formal meetings or in other communications with FDA, depending on application type. These meetings should be used consistently with their intended purpose. Also, as appropriate for the type of submission and the

[76] See the draft guidance for industry *Bridging for Drug-Device and Biologic-Device Combination Products*, which includes information on how to determine the type of bridging data that may be appropriate. When final, this guidance will represent the FDA's current thinking on this topic.

753 combination product lead center, the meeting request information may vary.[77]
754
755 When seeking feedback on proposed EDDOs, the meeting background package should provide a
756 clear description of the product and its drug delivery function. This may include figures,
757 instructions for use, description of the intended user population, and context of use (e.g.,
758 immediate or emergency use versus chronic therapy, home versus clinical setting). The meeting
759 background package should provide specific EDDO questions and may request the participation
760 of an FDA office or staff with the appropriate expertise. If there are questions regarding the
761 control of EDDOs, the control strategy proposal should be provided. These meetings would
762 include discussion of the proposed control strategy and the proposed approach and timing of
763 EDDO validation (e.g., type of studies and completion before beginning the pivotal clinical
764 studies).

[77] For information on requesting FDA feedback, see the guidance for industry and FDA staff *Requesting FDA Feedback on Combination Products* (December 2020). For additional information on the process to request a meeting under user fee programs, see the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (August 2023) (when final, this guidance will represent the FDA's current thinking on this topic) and the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023) (when final, this guidance will represent the FDA's current thinking on this topic). ANDA applicants may submit a pre-ANDA meeting request or a controlled correspondence to obtain Agency feedback. See the guidances for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022) and *Controlled Correspondence Related to Generic Drug Development* (March 2024). See also the guidance for industry and FDA staff *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (June 2023).

APPENDIX A – ESSENTIAL DRUG DELIVERY OUTPUT IDENTIFICATION EXAMPLE – PREFILLED SYRINGE

In this hypothetical example, the applicant is developing a drug in a prefilled syringe (PFS) intended for subcutaneous injection that will be delivered by a health care provider (HCP) to a patient in a health care setting. The PFS is a glass barrel containing a 12mm prestaked needle. The labeling directs the HCP to administer drug using the PFS at a 30-45 degree angle while pinching the skin. The PFS is also manufactured with a needle safety device to mitigate the risk of accidental needle sticks. The device design requires the needle safety feature to be activated before completion of injection. During development, the applicant considers the design inputs in identifying the design outputs and identifies which design outputs are essential drug delivery outputs (EDDOs).

Step 1 – Identify Design Outputs

The applicant first identifies the device design outputs as part of design control activities. Design output requirements include all attributes of the device necessary to meet intended user needs and include, for example, specifications for deliverable volume, clarity of the barrel, biocompatibility, sterility, color of plunger rod, markings on the barrel, material performance characteristics, needle safety activation force, and needle guard characteristics.

Step 2 – Identify Drug Delivery Design Outputs

As design outputs are being developed, the applicant analyzes the tasks needed to deliver the intended drug dose with the PFS to the intended delivery site, including the successful product preparation and the initiation, progression, and completion of dose delivery, and identifies design outputs related to these tasks. These are the drug delivery design outputs.

Other design outputs unrelated to delivering the intended drug dose (e.g., biocompatibility and sterility) are further filtered to eliminate outputs that are not EDDOs (see Figure 1).

Step 3 – Identify System Level Design Outputs

The applicant analyzes the drug delivery outputs to identify system level drug delivery outputs. For example, the applicant determines that glide force is a system level drug delivery output because it is necessary for the progression and completion of the dose. (See Figure 2 for an illustrative example of the relationship between system level and component level design outputs.)

After assessing the device, the applicant identifies the following system level drug delivery outputs: cap removal force, deliverable volume, injection depth, and injection forces (breakloose force, glide force, needle safety activation force).

Step 4 – Identify Device Dependent Design Outputs

The applicant further analyzes the system level drug delivery outputs to determine which are dependent on the device design and which, if any, are dependent on the user. The applicant determines that the following system level drug delivery outputs are device dependent:

- Cap removal force – The force to remove the cap is dependent on the design and manufacture of the cap and its interface to the nozzle PFS barrel tip

- Deliverable volume – The volume of drug extracted during injection is dependent on the device design and fill volume (independent of the user)

- Injection forces – The injection forces, which include the force to initiate the injection (i.e., breakloose force), the force to sustain the injection (i.e., glide force), and needle safety activation force[78] are dependent on the device design (independent of the user)

The applicant determines that while the target injection site is subcutaneous tissue and the PFS is prestaked with a 12mm needle, the user controls the injection depth through the injection technique. The injection depth is dependent on the user and independent of the device; therefore, it is not an EDDO.

Based on these assessments, the applicant determines that the following are EDDOs for the PFS product. For this illustrative example, the EDDOs are categorized in the table by the different aspects of drug delivery (top row) to which they are related.

Delivery of intended dose	**Delivery to the target site**	**Product preparation**	**Initiation of dose delivery**	**Dose delivery progression**	**Dose delivery completion**
Deliverable volume	N/A	Cap removal force	Breakloose force	Glide force	• Glide force • Needle safety activation force

[78] If a device design does not require the user to overcome the needle safety feature to be activated before completion of injection, needle safety activation force would not be an EDDO.

APPENDIX B – ESSENTIAL DRUG DELIVERY OUTPUT IDENTIFICATION EXAMPLE – AUTOINJECTOR

As an illustrative example of the distinction between essential drug delivery outputs (EDDOs) and other design outputs, the table below lists design outputs that were identified following consideration of hypothetical design inputs. The resulting hypothetical product is an autoinjector with a prefilled syringe (PFS) subassembly device constituent part that is also the primary container closure for the drug constituent part. The table shows the outcome of applying the filtering steps to each design output. The design outputs that meet the criteria of each of the filtering steps are EDDOs. The design outputs with gray shading in one or more columns do not meet the criteria of a filtering step(s) and are not EDDOs (i.e., gray shading in the *System level* column means the design output does not meet the system level criteria and is therefore, not an EDDO). As an example, dose accuracy meets each of the criteria for an EDDO and therefore is an EDDO. In contrast, the design output of PFS-fill volume/container content, meets the criteria of a drug delivery design output but does not meet the criteria of system level or device dependent and therefore is not an EDDO.[79]

Design outputs	Drug delivery design outputs	System level	Device dependent	EDDO (yes or no) and rationale
Dose accuracy				Yes. The automated dose delivery is necessary to ensure appropriate drug delivery.
PFS-fill volume/container content				No. It is a component level output because the fill volume influences but is subordinate to dose accuracy.
Biocompat-ibility				No. It is not an output intended for drug delivery.
Container closure integrity				No. It is not an output intended for drug delivery.
Drop testing/ Shipping				No. It is not an output intended for drug delivery.
Packaging integrity				No. It is not an output intended for drug delivery.
Extended needle length				Yes. It ensures the needle is at the right depth and is dependent on the device.
PFS-needle length				No. It is a component level output because it influences but is subordinate to the extended needle length function.

[79] It should be noted that the EDDO identification is distinct from CQA identification; however, some design outputs in the table may also be considered critical from a drug quality and manufacturing perspective. Refer to section III for further explanation regarding the relationship between EDDOs and CQAs.

Design outputs	Drug delivery design outputs	System level	Device dependent	EDDO (yes or no) and rationale
Needle inner diameter				No. It is a component level output because it influences but is subordinate to the injection time function.
Activation force				Yes. It initiates drug delivery and is dependent on the device not the user.
Breakloose force				No. It is a component level output because it influences but is subordinate to the injection time function.
Glide force				No. It is a component level output because it influences but is subordinate to the injection time function.
Injection time				Yes. It ensures the drug is delivered to the intended space within the appropriate time and is dependent on the device not the user.
Override force				No. It is not an output intended for drug delivery because it is the force to overcome the needle safety mechanism, which is activated post drug delivery.
Drug visibility				No. It is not an output intended for drug delivery because the drug appearance assessment is a user action.
Stopper height				No. It is not an output intended for drug delivery because it is the depth that the stopper should be placed at in the syringe for compatibility with the autoinjector plunger rod, filling process, and to ensure the stopper does not come out.
Needle pullout force				No. It is not an output intended for drug delivery because this attribute is specific to the device durability ensuring the needle does not detach.
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.
Cap removal force				Yes. Cap removal needs to be completed before the injection can be administered and it is dependent on the device.
Rigid needle shield removal force				No. It is a component level output because it influences but is subordinate to the cap removal force function.

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APPENDIX C – EXAMPLES OF POTENTIAL ESSENTIAL DRUG DELIVERY OUTPUTS BASED ON PRODUCT TYPE

The following tables provide examples of potential essential drug delivery outputs (EDDOs) for different product types. Note that the EDDOs for specific products may vary due to product specific differences (e.g., indication, design inputs, product design and technology).

Table 1: Prefilled Syringes

Delivery of intended dose	Delivery to the target site	Product preparation	Initiation of dose delivery	Dose delivery progression	Dose delivery completion
Deliverable volume	Needle length[80]	• Cap removal force • Withdrawal force[81]	Breakloose force	Glide force	• Glide force • Needle safety activation force[82]

[80] If a device is designed such that needle length is validated to reach a specific delivery space or tissue independent of user technique (e.g., pinching, skin test bleb method), needle length is an EDDO.

[81] For some co-packaged combination products, an empty syringe or a diluent prefilled syringe is used to withdraw drug directly from a vial, or to reconstitute or mix a drug. The withdrawal force (a type of injection force) of this empty or prefilled syringe is an EDDO because it is necessary for the preparation of the drug for injection and the drug cannot be delivered to the patient unless preparation is successfully completed. If the empty or prefilled syringe used in preparation is also used to deliver the drug, breakloose force and glide force are EDDOs.

[82] If a device design requires the needle safety feature to be activated to complete drug delivery, needle safety activation force is an EDDO. Conversely, if a device design does not require the needle safety feature to be activated to complete drug delivery, then needle safety activation force is not an EDDO.

Table 2: Injectors

Device platform	Delivery of intended dose	Delivery to the target site	Product preparation	Initiation of dose delivery	Dose delivery progression	Dose delivery completion
Auto-injector	Dose accuracy	Extended needle length	• Cap removal force • Activation force (e.g., to start reconstitution process)[83] • Audible/visual/ tactile feedback of successful drug preparation/reconstitution[84]	• Activation force (shield) • Activation force (button)	N/A	• Injection time • Audible/ visual/ tactile feedback
On body injector	• Dose accuracy/ dose efficiency • Injection time[85] • Interval of delivery[86]	Cannula length	• Cap removal force • Activation force (e.g., to start reconstitution process)[87] • Audible/visual/ tactile feedback of successful drug preparation/reconstitution[88]	Activation force	Adhesion force	• Injection time • Audible/ visual/ tactile feedback • Adhesion force

[83] Depending on the design of the automated mixing/reconstitution feature, there may be alternate or additional EDDOs.

[84] If the injector design automates reconstitution of the drug prior to injection, features that ensure and/or indicate successful mixing of the drug are EDDOs because if the drug is not mixed then the efficacy is diminished. If the device does not allow for drug delivery when the drug is not well mixed, this may be considered adequate feedback depending on the drug/indication to address the EDDO of audible/visual/tactile feedback.

[85] On-body injectors are often intended to deliver a large volume (e.g., 1-3mL) of drug. Therefore, injection time is an EDDO for delivery of intended dose because if the speed is too high then there is a higher risk of tolerability issues impacting the delivered dose. In addition, injection time is an EDDO for dose delivery completion similar to an autoinjector.

[86] On-body injectors may be used to replace two separate autoinjectors and may be designed to deliver injections at intervals. Therefore, that interval of delivery would be an EDDO.

[87] See footnote 83.

[88] See footnote 84.

Continued – Table 2: Injectors

Device platform	Delivery of intended dose	Delivery to the target site	Product preparation	Initiation of dose delivery	Dose delivery progress-ion	Dose delivery completion
Pen injector	Dose accuracy	N/A	• Cap removal force • Activation force (e.g., to start reconstitution process)[89] • Audible/visual/tactile feedback of successful drug preparation/reconstitution[90]	Injection force[91]	N/A	• Injection time[92] • Audible/ visual/ tactile feedback
Jet injector	Dose accuracy	Penetra-tion depth	• Cap removal force • Activation force (e.g., to start reconstitution process)[93] • Audible/visual/tactile feedback of successful drug preparation/reconstitution[94]	• Activation force (shield) • Activation force (button)	N/A	• Injection time • Audible/ visual/ tactile feedback

[89] See footnote 83.
[90] See footnote 84.
[91] If the pen injector is automated (i.e., does not manually deliver the dose), the EDDO may be activation force rather than injection force.
[92] If the pen injector is automated, then injection time is an EDDO.
[93] See footnote 83.
[94] See footnote 84.

872 **Table 3: Nasal Sprays**[95]
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Delivery of intended dose	Delivery to the target site	Product preparation	Initiation of dose delivery	Dose delivery progression	Dose delivery completion
• Pump delivery (spray weight) • Spray content uniformity (SCU) • Spray pattern • Droplet size distribution • Particle size distribution (suspensions)	N/A	N/A	Activation force	N/A	N/A

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876 **Table 4: Inhalation Products**
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Device Platform	Delivery of intended dose	Delivery to the target site	Product preparation	Initiation of dose delivery	Dose delivery progression	Dose delivery completion
Metered dose inhaler (MDI) - non-breath actuated	Emitted drug	Aerodynamic particle size distribution (APSD)[96]	Priming or repriming[97]	Device actuation force	N/A	• Counter accuracy[98] • Counter actuation force

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[95] For additional information on nasal spray products, see the guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* (July 2002).

[96] Aerodynamic particle size distribution (APSD) characterizes the particle/droplet size distribution of delivered aerosolized drug. APSD is a critical parameter, and its control is crucial for maintaining the quality of inhalation drugs. This parameter is dependent on the formulation, container closure system, and device delivery mechanism. The optimum APSD for most oral inhalation products has generally been recognized in the range of 1 to 5 um. For more guidance conducting these tests, please refer to USP <601> for aerosols, sprays, and powders and USP <1601> for nebulizer products. For guidance on information to provide to FDA regarding test setups and data presentation in submissions, please refer to the draft guidance for industry, *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products—Quality Considerations* (April 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[97] This attribute is applicable to most MDIs where a priming and repriming function is present.

[98] If the counter is not accurately measuring the doses dispensed, the patient may dispense the drug and not receive a dose because the device is empty (under counting). For additional information to avoid undercounting, see design recommendations included in section III.B of the guidance for industry *Integration of Dose-Counting Mechanisms into MDI Drug Products* (March 2003).

881 **Continued – Table 4: Inhalation Products**
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Device platform	Delivery of intended dose	Delivery to the target site	Product preparation	Initiation of dose delivery	Dose delivery progression	Dose delivery completion
Dry powder inhaler (DPI) - both pre-metered and device metered	• Metered dose • Emitted drug	APSD[99]	Dose loading[100]	Trigger mechanism[101]	Trigger mechanism	Counter accuracy[102]
Nebulizers[103]	• Total dose • Rate of delivery	• Patient Interface[104] • APSD[105]	N/A	Breath synchronization[106]	Breath synchronization[107]	Audible/visual /tactile feedback

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[99] See footnote 96.
[100] Single-dose DPIs are designed to require loading of doses and multi-dose DPIs are designed with internal mechanisms to cycle to new dose blisters or load drug from an internal reservoir into a dosing chamber.
[101] Additionally, some device features dictate the appropriate airflow for activation (e.g., triggering flow rate) and may be considered an EDDO.
[102] See footnote 98.
[103] Applicable to inhalation solutions, inhalation suspensions, solutions for inhalation, and drugs for inhalation solutions dosage forms, as opposed to inhalation powder and aerosol.
[104] The amount of drug delivered to the lung will depend on the route of inhalation (e.g., full-face mask or mouthpiece) as well as seal and resistance to flow. Additionally, different materials which may have different electrostatic properties which can attract and capture smaller droplets, add sources of leak and dead space, and may decrease respirable dose.
[105] See footnote 96. For nebulizers, APSD is dependent on the patient interface, in addition to the formulation, container closure system, and device delivery mechanism. See also footnote 95.
[106] Some nebulizers are designed to attempt to nebulize only during patient inhalation. Design implementation of synchronization includes both simple one-way valve (selective flow during inhalation or exhalation) and more complex sensor-driven electromechanical actuation systems.
[107] See footnote 106.

888 **Table 5: Vaginal Systems (VS)**
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Delivery of intended dose	Delivery to the target site	Product preparation	Initiation of dose delivery	Dose delivery progression	Dose delivery completion
Drug release rate and consistency [108]	• VS physico-mechanical properties, such as:[109] - Dimensions - Durometer/ hardness - Tensile strength - % elongation/force at break - Compression strength (including fatigue resistance) - Twisting during compression - Seal integrity (if applicable) • Applicator/inserter physico-mechanical properties, such as: - Dimensions - Force needed for delivery - Assessment of correct deployment	N/A	N/A	• VS physico-mechanical properties, such as:[110] - Dimensions - Durometer/ hardness - Tensile strength - % elongation/ force at break - Compression strength (including fatigue resistance) - Twisting during compression - Seal integrity (if applicable)	N/A

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[108] This includes the initial burst effect, if applicable. Release rate is a reflection of dose accuracy over time.
[109] For vaginal systems, the VS physico-mechanical properties ensure that the vaginal system can be inserted, remains in place for the duration of the use period, and can be removed. If these fail after the vaginal system is inserted, the vaginal system may fall out, leading to an incomplete dose, or may cause physical harm to the user.
[110] See footnote 109.

893 **Table 6: Infusion Products**
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Device platform	Delivery of intended dose	Delivery to the target site	Product preparation	Initiation of dose delivery	Dose delivery progression	Dose delivery completion
Infusion pumps [111, 112]	• Flow rate accuracy/ consisten-cy[113] • Dose accuracy [114] (if applicable)	• Needle/ cannula depth • Connection stability to IV or to separate administration set for SQ, etc. • Needle/ cannula insertion force	Drug cartridge insertion force (if applicable)	• Button activation force (mechani-cal) • Dose status[115]	• Adhesion force (if applicable) • Dose status	Dose status
Subdermal implants (and applicators if applicable) [116]	Dose accuracy or Drug release rate and consisten-cy	Implantation depth indicators	Implant compatibility with applicator (e.g., dimensional compatibility)	Applicator ejection force	N/A	Dose status (if applicable)

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[111] When bolus feature is present the EDDOs for on-body injectors also apply.
[112] The form factor of infusion pumps can vary significantly. However, this table is meant to apply to a wide array of form factors such as body-worn, body-attached, and conventional infusion pumps. Additional EDDOs may exist depending on the functionality and intended use of the infusion pump.
[113] Accuracy and/or consistency depending on the drug characteristics, indication, and/or safety profile.
[114] For pumps that include a bolus dose function, in addition to continuous infusions.
[115] Dose status is applicable throughout the initiation, progress, and completion of the infusion; however, whether dose status communication is achieved through audio, visual, tactile or other means is dependent on the pump design. Furthermore, this guidance does not address the causes that might result in interruption of a dose such as occlusion, motor failure, etc., since each pump design is different. Therefore, depending on the design and technology of the pump, outputs other than dose status may be EDDOs for dose initiation, progression, and completion.
[116] The examples of potential EDDOs identified for subdermal implants and applicators are based on the two most common forms: passive delivery moderated by polymer degradation and active delivery using an osmotic engine.

APPENDIX D – EXAMPLE OF A CONTROL STRATEGY FOR THE ESSENTIAL DRUG DELIVERY OUTPUT OF NEEDLE EXTENSION LENGTH FOR AN AUTOINJECTOR

The following is an example control strategy for the needle extension length for an autoinjector assembled with the prefilled syringe (PFS) at the final finished combination product[117] manufacturing facility. The applicant is ultimately responsible for the control of the essential drug delivery output (EDDO). This example shows how the applicant can leverage information regarding the design and manufacturing from suppliers and purchasing agreements (e.g., certificate of analysis), which are part of the purchasing controls (21 CFR 820.50), to adequately control the EDDO upstream.

In this example, supplier A is the syringe and needle manufacturer, supplier B is the autoinjector subassembly manufacturer, and the applicant is the manufacturer of the final finished combination product. The applicant performs the following manufacturing steps, which include:

(1) Manufacturing the primary container (PFS) – filling and stoppering the syringes from supplier A with drug,

(2) Manufacturing the autoinjector – Inserting and securing the PFSs into autoinjector subassemblies from supplier B, and

(3) Final packaging and labeling of autoinjector.

As shown in the table below, the length of the syringe and needle are not subject to change after filling or assembly into the autoinjector, or over the autoinjector shelf life. Therefore, control of the length of the syringe and needle is effective at supplier A (the syringe and needle manufacturer). 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. Therefore, control of the needle cover retraction distance is effective at supplier B.

The applicant provides an engineering analysis demonstrating that the needle cover retraction distance specification is compatible with the syringe/needle and would yield an adequate needle extension length. Therefore, this control is effective at the component level at supplier B. Validation of the specification is through the engineering analysis performed by the applicant.

The applicant determines that the final needle extension length for the autoinjector is dependent on the process steps to assemble the syringe into the subassemblies. Therefore, the applicant provides a process risk assessment to support which steps impact this EDDO, the applicant's in-process work instructions relating to this process step, and validation data to show this process step is controlled and yields autoinjectors with adequate needle extension lengths.

See sections VIII.B and VIII.C for control strategy information to include in applications.

[117] For purposes of this guidance, the final finished combination product is the product intended for marketing and submitted in the marketing application.

939 **Table 1 – Example of a control strategy for needle extension length, an EDDO for an**
940 **autoinjector**
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Design attribute or manufacturing process step	**Control at supplier A**[118]	**Control at supplier B**[119]	**Control at final manufacturer**	**Documentation used to verify the control at final manufacturer/applicant and submitted**
Length of syringe and needle	100% dimensional check of overall syringe/needle	N/A	Incoming acceptance per COA	Engineering drawing (#XXXX)
	In-process control (IPC) check of syringe dimensions			None
	Certificate of analysis (COA) for each syringe batch released			COA
Needle cover retraction distance	N/A	IPC dimensional check for autoinjector components /subassem-blies	Tolerance analysis ensuring needle extension is compatible with design to 'X' CpK level	• Engineering report explaining tolerance analysis and justification of CpK values • Engineering drawing (Doc# XXXX) of component A • Engineering drawing (Doc# XXXX) of component B

[118] In a marketing application, a proposed control strategy does not need to include the referenced documentation (e.g., from sources other than the applicant) to verify the control. However, the Agency may request the referenced documentation. Additionally, the Agency may request protocols, test methods, or work instructions for controls at suppliers during review of the application depending on the criticality of the EDDO and the method of control upstream (e.g., if the applicant is relying on the supplier's control information). When requested, the supplier can provide this information directly to the applicant or through reference to a master file with an appropriate Letter of Authorization.

[119] Ibid.

Design attribute or manufacturing process step	**Control at supplier A**[118]	**Control at supplier B**[119]	**Control at final manufacturer**	**Documentation used to verify the control at final manufacturer/applicant and submitted**
Subassembly assembly step #x	N/A	100% check to ensure key components were assembled correctly and interact to assure needle extension	Adequate change control and purchasing control agreements are in place to ensure notification of any changes to components	Purchasing control agreement between final manufacturer and supplier B
Step #x - assembling subassemblies and syringe	N/A	N/A	Process risk assessment to determine assembly steps impacting needle extension	Process risk assessment
			Push/snap force of fixture	• Work instruction • Validation of snap force
			Fixture height	• Tolerance analysis of fixture height and impact on overall needle extension length • Work instruction for fixture set up and calibration
			Performed process validation and verified that device manufacturing from PQ engineering runs[120] met needle extension specifications	Process validation report (includes autoinjector extended needle length testing)

[120] An engineering run is representative of the intended manufacturing process for the to-be-marketed product.