Bridging for Drug-Device and Biologic-Device Combination Products

Guidance for Industry

DRAFT GUIDANCE

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December 2019
Combination Products

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Bridging for Drug-Device and Biologic-Device Combination Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to industry and FDA staff on how to approach bridging in new drug applications (NDAs) or biologics license applications (BLAs) for drug-device and biologic-device single entity or copackaged combination products including the following:[2]

- Bridging of information related to a combination product that employs a different device constituent part or parts[3] with the same drug constituent part or parts[4] as the proposed combination product

[1] This guidance has been prepared by the Office of Surveillance and Epidemiology and the Office of New Drugs in the Center for Drug Evaluation and Research, in cooperation with the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, and the Office of Combination Products at the Food and Drug Administration. This guidance is one of several documents FDA is issuing to fulfill the performance goals under the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI).

[2] See section 503(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the definition of combination products in 21 CFR 3.2.

[3] See constituent part definition in 21 CFR 4.2.

[4] For purposes of this guidance, except where specifically indicated, references to *drug* or *drug constituent part or parts* include a drug or biological product constituent part submitted as part of a combination product for approval or approved under section 505(c) of the FD&C Act (21 U.S.C. 355(c)) or licensed under section 351(a) of the Public Health Service Act (PHS Act). Some of the principles applicable to products submitted for approval under section 505(b) of the FD&C Act or licensure under section 351(a) of the PHS Act may also be applicable to products submitted for approval under section 505(j) of the FD&C Act or licensure under section 351(k) of the PHS Act. In addition, the scientific principles discussed in this guidance may be applicable to combination product submissions under sections 515, 513(f)(2), or 510(k) of the FD&C Act.

- Bridging of information related to a combination product that employs a different drug constituent part or parts with the same device constituent part or parts as the proposed combination product

For the purposes of this guidance, the term *bridging* refers to the process of establishing the scientific relevance of information developed in an earlier phase of the development program or another development program to support the combination product for which an applicant is seeking approval. Once the applicant has established the relevance of such information to (i.e., bridged to) its product, the applicant can leverage that information to streamline its development program.[5] From a scientific perspective, an applicant must bridge its current application to information developed in an earlier phase of the development program or another development program if the applicant wishes to leverage that information in its current application. For certain types of applications, the use of information from another development program may require that the applicant own the information or have a right of reference.[6]

With respect to the recommendations and examples in this guidance, it is assumed that the applicant owns or has a right of reference or use that allows the applicant to use information from another development program.

This guidance seeks to clarify how to bridge to information gathered from another development program to leverage that information in support of an application. To facilitate that process, this guidance describes an approach for an applicant to identify and address information gaps for an application.

This guidance applies to the following:

- Human prescription combination products that are the subject of an investigational new drug application (IND) under 21 CFR part 312, an NDA under 21 CFR part 314, or a BLA under 21 CFR part 601

- Human nonprescription combination products that are the subject of an IND, NDA, or BLA (as opposed to those covered in a final or tentative over-the-counter drug monograph)

[5] There are certain regulatory considerations that apply to reliance on certain types of information in certain applications (e.g., reliance on a previous finding of safety and effectiveness for a drug the applicant does not own or to which it has no right of reference in a 505(b)(2) application) but discussion of those considerations is beyond the scope of this guidance. See the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999). When final, this guidance will represent the FDA's current thinking on this topic. 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.

[6] See, for example, 21 CFR 314.3, "Right of reference or use is the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an NDA [new drug application], including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary."

All such products in this guidance are referred to as combination products. Except where it is specifically indicated that this is not the case, the terms *drug* and *drug constituent part* are used interchangeably and also refer to biological products and biological product constituent parts; the terms *device* and *device constituent part* are used interchangeably, and persons responsible for product development are referred to as *applicants*.

Although this guidance is intended to help applicants consider the type and scope of information that may be leveraged for a combination product development program, this guidance does not address all of the issues applicable to any particular combination product. The Agency encourages applicants to contact FDA to discuss specific information needed to support their individual applications.[7]

This guidance does not discuss the appropriate regulatory pathway an applicant should use to bring a particular combination product to market.[8]

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. BACKGROUND

While drugs, devices, and biological products retain their discrete regulatory identities when they are constituent parts of a combination product, combination products comprise a distinct category of medical products that can be subject to specialized regulatory requirements.[9] Accordingly, the regulatory requirements for combination products arise from the statutory and regulatory requirements applicable to drugs, devices, and biological products.[10] Consistent with section 503(g) of the Federal Food, Drug, and Cosmetic Act, FDA is committed to applying a consistent, risk-based approach to address similar regulatory questions, including scientific questions, using relevant expertise from the lead and consulted centers within FDA.

[7] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent FDA's current thinking on this topic.

[8] See the draft guidance for industry and FDA staff *Principles of Premarket Pathways for Combination Products* (February 2019). When final, this guidance will represent FDA's current thinking on this topic.

[9] See the final rule, "Current Good Manufacturing Practice Requirements for Combination Products," published January 22, 2013 (21 CFR Part 4, Subpart A; 78 FR 4307-22) and the final rule, "Postmarketing Safety Reporting for Combination Products," published December 20, 2016 (21 CFR Part 4, Subpart B; 81 FR 92603-26).

[10] Ibid.

Depending on an applicant's development program, there may be circumstances in which an applicant has its own existing information (or rights of reference to information) about another combination product or a proposed constituent part that may be leveraged to support approval of the proposed combination product if an appropriate bridge can be established. In general, FDA would require additional data and information only if the information were needed to address additional questions of safety or effectiveness raised by the proposed use or function of a constituent part in the combination product.[11] For example, in general, if a stand-alone device proposed to be used as a device constituent part of a combination product has been previously approved or cleared, the applicant may be able to leverage relevant existing device-related data, provided that the data has been bridged (i.e., shown to be scientifically relevant), for the development of a new combination product.

In some cases, the amount of information that can be leveraged for such proposed combination products may be minimal, or leveraging may not be possible. For example, a change in route of administration for a complex biological product may raise additional safety and/or efficacy considerations, and such considerations may make it difficult to bridge to the proposed combination product. Discussions with the Agency about planned leveraging are appropriate to identify questions early in drug development.

III. DEVELOPING AN ANALYTICAL FRAMEWORK FOR IDENTIFYING INFORMATION GAPS TO INFORM A BRIDGING AND LEVERAGING APPROACH

Developing a framework that identifies where information gaps may exist in a combination product development program is an important task for applicants. The following information assumes that applicants are familiar with existing FDA regulations, guidance documents, and resources on drug and device development available from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, and the Office of Combination Products to assess the information that should be included in an IND, NDA, or BLA, as appropriate. Under this premise, the example of a framework below supposes that an applicant seeks to bridge from the FDA-approved, drug-device (delivery system) Combination Product A to proposed Combination Product B. The Agency recommends that an applicant use the stepwise approach presented below to conduct a gap analysis for the proposed Combination Product B:

Step 1. Identify all differences between Combination Products A and B, and consider the potential effect of the individual and aggregate differences on the safety and effectiveness profile for Combination Product B.

[11] See section 503(g)(3) of the FD&C Act: "The [FDA] may require that the sponsor of such combination product submit to the [FDA] only data or information that the [FDA] determines is necessary to meet the standard for clearance or approval, as applicable, under this Act or the Public Health Service Act, including any incremental risks and benefits posed by such combination product, using a risk-based approach and taking into account any prior finding of safety and effectiveness or substantial equivalence for the approved constituent part relied upon by the applicant."

Specifically, for Combination Product B in comparison with Combination Product A, the safety and effectiveness profile should include a clear, comprehensive listing of the differences in the device constituent part, the drug constituent part, and the combination product as a whole. Some examples of the potential effect of a change in drug or device constituent part for Combination Product B compared to the existing safety and/or effectiveness profile for Combination Product A include the following:

- Changes to the local injection adverse reaction profile including those related to an increase in drug concentration, a change in drug viscosity or formulation, or a change in injection rate

- Change in the dose accuracy of the same device constituent part when the drug formulation is changed

- Changes in the manufacturing process and/or device constituent part that may affect drug quality

- Change in whether the intended users can use Combination Product B safely and effectively when the user interface of the device constituent part changes

- Changes in the bioavailability of the drug and/or its metabolic profile that can occur because of changes in the device, formulation, or route of administration, such as the following:

  – Changes in the needle depth, tissue plane, or rate of infusion

  – Change in drug formulation that results in differential lung depositions even when the drug is administered with the same device

- Changes in drug formulation that can affect the leachable and extractable profiles of the combination product

Step 2. Identify existing information for Combination Product B (i.e., information that has been gathered or generated through studies and assessments of the proposed combination product itself) and compare it to the safety and effectiveness submission requirements necessary for approval.

Step 3. Identify and explain how and why existing information on Combination Product A can be bridged and leveraged to support approval of Combination Product B, taking into account the considerations in Step 1 and the information already gathered in Step 2.

Step 4. Focus on any information gaps remaining from Steps 2 and 3, and consider whether other existing information, outside of that directly gathered for Combination Product A or B,

can be reviewed and used to address these gaps under the proposed regulatory pathway as described in Step 5 below.[12]

Step 5. Compare findings from Step 2 through 4 and identify the remaining gaps in information that need to be addressed in the product application.

After completing a gap analysis, FDA recommends that applicants meet with FDA's lead center review division along with consulting reviewers to discuss what new information or studies may be needed to support the application for Combination Product B.

Special considerations: The stepwise framework and associated analyses described above represent general considerations regarding how the applicant should prepare an application. However, leveraging may be challenging or not possible with some combination products because they contain complex constituent parts and/or are likely to be affected by seemingly minor changes. For example, combination products that include certain biological products or complex delivery systems may not allow the same degree of leveraging as would be possible for a combination product that includes a well-characterized drug or a well-understood device. Nonetheless, the framework and associated analyses in this guidance are at least potentially applicable to such combination products.

IV. BRIDGING AND LEVERAGING EXAMPLES

In this section, we present three case examples to illustrate how an applicant might appropriately apply the above stepwise framework and associated analyses to determine the bridging strategy and informational needs in a development program, which it would then present to FDA. It is important to note that the cases represent hypothetical examples. The approach taken provides one acceptable way to break down the thought process around preparing applications from an applicant's viewpoint. We recognize that many applicants would likely be considering multiple steps from the framework simultaneously. Most importantly, these considerations and recommendations are not intended to apply to any particular development program. Product-specific considerations will lead to differing informational requirements by FDA. We encourage applicants to discuss their particular development program and bridging strategy with FDA.

If the applicant determines early in a drug development program that the intent will be to market multiple presentations or a presentation that is different from that studied in early development,[13] FDA encourages the applicant to conduct clinical studies using the device constituent parts with which it intends to market the combination product (i.e., the final finished combination product). By doing so, bridging to clinical data likely would not be needed because the data would have been developed with the final finished combination product.

[12] Note that use of certain sources of information may not be permitted under certain regulatory pathways, but that discussion is beyond the scope of this guidance.

[13] For the purposes of this guidance, the term *presentation* refers to the device constituent part of the combination product.

A. Bridging Within an IND from a Drug Developed in a Prefilled Syringe to a Drug Developed in an Autoinjector

In this hypothetical case example, the applicant is developing a combination product containing a new molecular entity (NME) drug constituent part with the initial plan to market it in a prefilled syringe (PFS) presentation, intended for home use by laypersons, including patients. During the course of development, the applicant decided that it would also like to market the NME in an autoinjector presentation. The final finished combination product for the newly proposed presentation will be an autoinjector assembled around the original PFS. The primary container closure in direct contact with the drug (i.e., barrel, plunger, and needle) remains the same and the drug formulation remains the same. The route of administration (subcutaneous) is the same. The applicant intends to market both the PFS and autoinjector presentations commercially.

Using the stepwise framework, the applicant's gap analysis identifies the following:

Step 1. The applicant identifies the differences between the first and second presentations. The principal difference is the change of the device constituent part made by adding an autoinjector to the PFS combination product. In this case, the autoinjector results in three key changes: 1) it adds a new secondary container closure, 2) it changes the method of injecting the drug constituent part, and 3) it has a different user interface.

In considering the potential effect of the individual and aggregate differences on the safety and effectiveness of the autoinjector combination product as a whole, the applicant identifies the following gap-analysis considerations:

- The difference in the user interface leaves an unanswered question regarding whether the user interface design supports safe and effective use, which may change its safety and effectiveness profile as compared to the PFS.

- Changes in assembly of the prefilled syringe into the autoinjector could change quality considerations for the drug constituent part if the manufacturing process for the autoinjector adversely affects the drug, including, but not limited to, degradation associated with assembly and the effect of the process on sterility. Likewise, chemistry, manufacturing, and controls (CMC) considerations in this context include impacts on syringe resistance to breakage, functionality throughout shelf life, and expiration dating.

- Changes in the method of injecting the drug constituent part may affect the local adverse reaction profile because of a change in the rate at which the drug is delivered to the target tissue. For example, it is expected that the PFS is associated with more variability in injection time with real world use, whereas the autoinjector is designed to meet a specific injection time specification.

- Changes in the method of injecting the drug constituent part may affect the pharmacokinetic (PK) profile of the drug. For example, changing the delivery method may lead to differences including consistency or variability of injection angle,

tissue depth (potentially associated with the rate of drug delivery as determined by the injection time), and completeness of the injection.

- Assembling the autoinjector around the PFS will require, among other things, assessment of design features of the additional autoinjector combination product.[14]

Step 2. The applicant has not yet developed information specifically for the drug combined with the autoinjector presentation and, therefore, will have to either leverage existing information or develop new supporting data.

Step 3. The applicant conducted phase 3 studies with the PFS presentation. These studies provided data on PK, nonclinical data, toxicity, safety and effectiveness, and leachable and extractable profiles. The applicant identifies the following information that could be applied to the new autoinjector combination product and the associated rationale:

- Because the proposed drug, indication, dosage, formulation, and route of administration are the same, the applicant believes that if the PK profile is shown to be the same through testing, then nonclinical, toxicity, and safety and effectiveness

[14] Combination products are subject to 21 CFR part 4, which sets forth current good manufacturing practice (CGMP) requirements for combination products. The constituent parts of a combination product retain their regulatory status (as a drug or device, for example) after they are combined. The CGMP requirements that apply to each of the constituent parts apply to the combination product they constitute.

For single-entity and co-packaged combination products that include both a drug and a device, such as those covered in this guidance, manufacturers may implement a streamlined approach for these combination products (21 CFR 4.4(b)). Under this approach, combination product manufacturers may meet the requirements of both the drug CGMPs and device quality system QS regulation by designing and implementing a CGMP operating system that demonstrates compliance with the drug CGMPs and the following provisions from the device QS regulation: 21 CFR 820.20 (management responsibility); 21 CFR 820.30 (design controls); 21 CFR 820.50 (purchasing controls); 21 CFR 820.100 (corrective and preventive action); 21 CFR 820.170 (installation); and 21 CFR 820.200 (servicing). See 21 CFR 4.4(b)(1). One of the specified QS regulation provisions codifies the obligation to comply with 21 CFR 820.30 design controls requirements for these drug-device combination products, including design verification and validation. See 21 CFR 4.4(b)(1)(ii). Design control activities confirm that there are no negative interactions between constituent parts and ensure that their combined use results in a combination product that is safe and effective and performs as expected. The focus of design control discussion in this guidance is the information required to demonstrate that the final combination product achieves its identified performance targets under the identified conditions of use, as opposed to the procedural requirements of 21 CFR 820.30 for developing and managing such information (e.g., requirements concerning design and development planning and design history file). Data needed to make such design verification and validation demonstrations vary depending on the combination product and its intended use but typically include, among other things, bench data, preclinical/clinical testing data, and human factors (HF) studies. For further information on design control requirements for combination products, see the guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017) (2017 CGMP Guidance for Combination Products).

Moreover, a biological product regulated under section 351 of the Public Health Service Act is also, by definition, a drug or a device. Accordingly, for combination products that include a biological product, in addition to complying with the drug CGMP and device QS regulation requirements as applicable in accordance with 21 CFR part 4, manufacturers of such products must comply with the CGMP requirements in 21 CFR parts 600 through 680 that would apply to the biological product if it were not part of a combination product (21 CFR 4.4(b)(3)).

data gathered in the existing clinical program for the PFS presentation could also apply for the autoinjector presentation.

- Because the primary container closure (the PFS) is the same for both presentations (drug will be in contact with the glass of the PFS, elastomeric plunger, and needle with use), and because the applicant expects that the secondary container closure autoinjector materials, during manufacture and storage of the combination product, will not come in direct contact with the drug or change its characteristics, the applicant believes that the leachable and extractable profile gathered for the PFS presentation should also apply for the autoinjector presentation.

Step 4. The applicant considers whether other existing information may be leveraged to support the items in Step 4. In the course of examining other available information, the applicant identifies the following:

An autoinjector with the same user interface was previously approved as part of a combination product with another drug in the applicant's portfolio. The approved combination product was developed for a different disease state and indication and for use in a different patient population with differing injection sites. The approved combination product has been marketed for two years and there are currently no adverse compliance actions or postmarketing safety issues under investigation by the applicant. The applicant considers whether it is appropriate to establish a bridge between the previously approved combination product and the proposed autoinjector in order to leverage human factors validation data. The applicant recognizes, however, that since the product was developed for another population and indication, it will be challenging to bridge the applications and intends to conduct a HF validation study and prepare a HF validation study report to be submitted as part of the marketing application.[15]

The applicant also believes that it should be able to bridge the autoinjectors with regard to device performance that is unrelated to the drug since this would be unchanged between the products. In particular, because the previously approved autoinjector design used the same syringe with the same prestaked needle for its prefilled drug, the applicant believes it can leverage design verification data unrelated to the drug being injected (e.g., extended needle length, autoinjector activation force, and cap removal force). The applicant, however, intends to generate additional verification data on factors affected by the drug (e.g., dose accuracy, injection time, etc.). Additionally, the applicant considers the possibility that the change in indication, injection site or user population could impact the acceptability, from a validation perspective, of dose accuracy, extended needle length, injection time, autoinjector activation force, cap removal force and other autoinjector performance specifications. Therefore, the applicant plans to provide design validation confirming that the autoinjector performance specifications are adequate for the new drug.

[15] Regardless of whether HF studies are submitted for the marketing application, such studies and/or analysis of whether the studies are needed may still need to be included as part of design control documentation for the combination product. See, for example, 21 CFR 820.30(g) & (j).

Step 5. The applicant determines that the following information may still be needed:

- Human factors (HF) validation data for the autoinjector presentation to support the new user interface.

- Local adverse event data to assess how the new interface may affect pain on delivery. This may include any potential change to injection time, which may change the rate at which the drug is delivered to the target tissue.

- CMC and engineering data: syringe resistance to breakage, functionality, maintenance of sterility over shelf life, degradation of the drug from the assembly process, and expiration dating. Note that the company's testing related to sterility and degradation would primarily be intended to verify that the new process did not create issues.

- Design verification and validation data for the autoinjector presentation,[16] including dose accuracy and injection time.[17] The applicant also intends to provide a copy of design control documentation for the delivery system and combination product as a whole, including documentation of design requirements and specifications, design verification, design validation, and risk analysis for use of the applicant's previously approved autoinjector with a new drug.

- The applicant intends to assess how any changes in drug delivery affect the PK profile of the combination product. Changes in delivery include changes in the tissue plane in which the drug is delivered, changes to the rate of delivery (because of change in injection time between the PFS and autoinjector), and changes in the consistency of the injection angle. The extent to which existing safety data or effectiveness data can be bridged and leveraged will depend on PK comparisons that will allow assessment of any differences in bioavailability between the products. If no differences are observed in the PK profile the applicant will leverage nonclinical, toxicity, and safety and effectiveness data gathered in the existing clinical program for the PFS presentation. If differences are observed in the PK profile between the two presentations (e.g., in maximum concentration, in area under the curve, in shape

[16] See, for example, 21 CFR 820.30(f)-(g). Design verification confirms that the combination product meets the applicant's design requirements/specifications (21 CFR 820.30(f)); see also 2017 CGMP Guidance for Combination Products, at 23. Design verification activities may include, for example, performance tests, safety tests, or visual inspections (2017 CGMP Guidance for Combination Products, at 23). Design validation ensures that the combination product is designed correctly to achieve its intended purpose(s) (21 CFR 820.30(g)). Design validation may include simulated use testing or clinical/nonclinical evaluation, including HF and software validation (2017 CGMP Guidance for Combination Products, at 24).

[17] 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).

of the concentration-time profile), the applicant intends to gather additional information to evaluate clinical effect of these differences.[18]

B. Bridging From One Autoinjector (Prototype 1) to Another Autoinjector (Prototype 2) for the Same Drug; After Phase 3 Studies Have Been Completed but Before NDA Submission

In this hypothetical case example, the applicant developed an autoinjector for Drug Product X, which was used through completion of its phase 3 clinical studies. During the course of development for submission, the applicant decided to make modifications to the TBM autoinjector (Prototype 2) to improve its functionality; however, the applicant does not intend to modify the device performance specifications (e.g., dose accuracy, injection time). In this case, the primary container closure in direct contact with the drug (i.e., barrel, plunger, and needle) remains the same. The assembly process used during manufacture to form the autoinjector remains the same. The drug formulation remains the same. The route of administration is the same (subcutaneous). The user interface is the same.

Using the stepwise framework, the applicant's gap analysis identifies the following:

Step 1. The applicant identifies the differences between the clinically studied autoinjector (Prototype 1) presentation and the TBM autoinjector (Prototype 2) presentation. The dimensions and materials of the internal components of the rear and front shell subassemblies of the combination product were modified to improve the functionality for the combination product without changing the user interface.

In considering the potential effect of the individual and aggregate differences on safety and effectiveness introduced by the device modifications, the applicant identifies the following considerations:

- The revision of the autoinjector would not be expected to change the quality considerations for the drug constituent part if the container closure in direct contact with the drug and the formulation remains the same. The manufacturing process for Prototype 2 is comparable to that for Prototype 1, so the manufacturing process for the revision of the autoinjector would not be expected to affect the quality of the drug constituent part. However, differences in functional performance of the device constituent part, if any, may affect the drug constituent part.

- Device changes may affect the PK profile of the drug. For example, changing the dimensions and materials of the rear and front shell subassemblies' internal components may lead to differences including consistency or variability of injection angle, tissue depth (potentially associated with the rate of drug delivery as determined by the injection time), and completeness of the injection.

[18] For further information, see the draft guidance for industry *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* (February 2019). When final, this guidance will represent the FDA's current thinking on this topic.

Step 2. The applicant did not gather new clinical data for the TBM product, but as reflected in Step 3 conducted verification testing on the TBM autoinjector (Prototype 2) to confirm that device performance remains unchanged between the clinically studied (Prototype 1) and TBM (Prototype 2) versions of the device. This included testing in accordance with relevant standards as well as an assessment of certain performance requirements that the applicant has identified as potentially affected by the modifications to the components and that, if affected, could adversely affect the device's operations. In this case, the following performance requirements were included in the verification testing of the TBM device (Prototype 2):

- Dose accuracy
- Injection depth (needle extension)
- Injection time
- Activation force

The applicant is aware that the above are examples of factors that could affect the drug delivery and should be assessed over combination product shelf life. The applicant has compared the identified performance requirements for both autoinjector prototypes (1 and 2) and determined that the performance requirements remain unchanged between the clinically studied (Prototype 1) and TBM (Prototype 2) versions of the device.

Step 3. The applicant previously conducted phase 3 studies with Prototype 1 of the autoinjector presentation. The applicant has also performed design verification testing and completed HF validation testing on the clinically studied autoinjector (Prototype 1). The applicant identifies the following information that can be applied to the modified TBM autoinjector (Prototype 2) presentation:

- As noted above, testing confirmed that the dose accuracy, delivery time, injection depth, injection angle and site of injection are the same for Prototype 1 and TBM Prototype 2 bridging that information for these presentations; therefore, the applicant has determined that the PK studies conducted using Prototype 1 of the autoinjector can be leveraged.

- The user interface is not changing. Additionally, the activation force and injection time remain the same; therefore, the applicant has determined that the HF data between Prototype 1 and 2 can be bridged. Accordingly, the HF data collected for the combination product using the Prototype 1 autoinjector can be leveraged for the combination product using the Prototype 2 autoinjector presentation.

- The proposed indication, dosage, and administration are the same and, as noted previously, there is no change to the delivery of the drug (e.g., dose accuracy, injection time, injection depth). Therefore, the applicant has determined that the nonclinical, toxicity, and safety and effectiveness data gathered in the existing clinical program using the Prototype 1 autoinjector presentation can be bridged to the Prototype 2 autoinjector presentation and leveraged.

- The primary container closure is the same for both Prototype 1 and Prototype 2 autoinjectors, and the applicant can demonstrate that the autoinjector components and materials used during manufacture and storage of the combination product do not come in direct contact with the drug. Therefore, the applicant has determined that the CMC information for the drug constituent part and leachable profile gathered using the Prototype 1 autoinjector presentation can be bridged to the Prototype 2 autoinjector presentation and leveraged.

- The primary container closure remains the same and the injection time remains unchanged from the clinically studied Prototype 1 autoinjector to the TBM Prototype 2 autoinjector. Therefore, the applicant has determined that it is possible to bridge information regarding the products and leverage the drug-device compatibility study from Prototype 1.

Step 4. The applicant determines that there is no other existing information that may be leveraged.

Step 5. The applicant believes no new information needs to be generated beyond that described above. The applicant intends to support the assessment through submission of data demonstrating comparability between the designs, including through submission of full design verification data for the TBM Prototype 2 to demonstrate that device performance is comparable to Prototype 1. In addition, the applicant intends to include a side-by-side comparison of the user interface for the combination product using Prototype 1, which was evaluated in the HF validation study, and the combination product using Prototype 2 as part of the NDA submission to facilitate review to demonstrate that there are no differences in the user interface.

C. Bridging of Data From Combination Product That Employs the Same Device Combined With a Different Drug

In this hypothetical case example, the applicant previously developed Combination Product A, which was approved by FDA in an NDA and includes a prefilled drug cartridge attached to a metered-dose inhaler. Combination Product A is indicated for the prevention and relief of bronchospasm in patients 18 years of age and older with reversible obstructive airway disease. The applicant is now early in the development of Combination Product B, which combines an NME drug constituent part with the same metered-dose inhaler as in Combination Product A. For Combination Product B, the applicant is seeking an indication of prevention and relief of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

The same route of administration applies to Combination Products A and B. Both combination products require the same actuation force to administer an inhalation. Both combination products are intended for use in an emergency-use scenario to rapidly reverse bronchospasm.

Using the stepwise framework, the applicant's gap analysis identifies the following:

Step 1. The applicant identifies the differences between Combination Products A and B. The key differences are the change in the drug constituent part and the inclusion of a pediatric age group.

In considering the potential effect of the individual and aggregate differences in the safety and effectiveness profile of the two different drugs and the combination product as a whole, the applicant determines that full characterization of the NME will be required to establish safety and effectiveness of the drug constituent part. Additionally, the inclusion of the pediatric age group leaves an unanswered question of whether this user population can use the product safely and effectively.

Step 2. The applicant has not yet developed any information for Combination Product B and, therefore, will have to either leverage existing information on the device constituent part or develop new data.

Step 3. The applicant determines that the user interface is the same between Combination Products A and B, and the uses, and environments of use of the products is unchanged.[19] For the adult population the results of their use-related risk analysis did not identify any new or differing use-related risks between Combination Products A and B, thereby creating a bridge for adult user interface information between the products. The applicant believes, however, that an assessment will be needed in the pediatric population to assess HF since that group was not studied for Combination Product A. In addition, the applicant determines that the design control system developed for Combination Product A may be usable, subject to the assessment discussed in Step 5, for design verification and validation of Combination Product B.

The applicant also determines that it could rely on previously conducted biocompatibility studies with Combination Product A (assessing contact of the mouth and lips with the plastic of the inhaler) because the materials remain the same.

Step 4. The applicant determines that there is no other existing information that may be leveraged.

Step 5. The applicant determines that it will need to conduct studies to fully characterize the NME in Combination Product B and reassess the applicability of the design inputs and outputs (design specs) for Combination Product A because of the change in drug and intended patient population. Also, because of these differences between Combination Products A and B that could affect device design and performance, the applicant determined that phase 3 clinical studies of Combination Product B, including the TBM device, are needed as well as other design verification testing for Combination Product B. In addition, the applicant intends to produce a HF validation study report for the pediatric population.

[19] See the guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016) for more information.