Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

February 14, 2019

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

Re: Docket No. FDA-2019-D-5585 Bridging for Drug-Device and Biologic-Device Combination Products Guidance for Industry

Dear Sir or Madam:

The Combination Products Coalition ("CPC") welcomes the opportunity to provide comments on FDA's "Bridging for Drug-Device and Biologic-Device Combination Products Guidance for Industry" dated December 18, 2019 (the "Draft Guidance").

The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad, and unique perspective to these issues.

CPC greatly appreciates the FDA's efforts to provide needed guidance on the bridging of information approaches for drug-device and biologic-device single entity and co-packaged combination products and is pleased to see alignment across all three Centers and OCP. The development of a step-wise process approach and framework to conduct a gap analysis and for identifying (and closing) these information gaps is a valuable element of the Draft Guidance. The framework, with the addition of CPC's recommended revisions (Item 5 below), is consistent with and builds upon key ICH guidance documents (Q5e comparability, Q9 QRM) on comparability analysis and risk assessments. CPC further appreciates the ample references and broad allowances for leveraging prior experience throughout the Draft Guidance, demonstrating the willingness of FDA to consider prior knowledge of drug attributes and device platforms.

Unfortunately, CPC found the format FDA chose to use in the Draft Guidance to convey study recommendations to be confusing and limiting in the ability to provide useful guidance on the needed bridging information. By providing clear guidance that incorporates the Agency's current thinking, regulatory efficiency and consistency can be improved, which can lead to timely access to new and improved combination products for patients.

CPC has carefully evaluated FDA's Draft Guidance and we ask that the Agency consider these major overarching comments of concern, as well as our line-specific comments, which are provided in Appendix A.

Major Comments:

1. CPC requests FDA capture the scoping information scattered throughout the document in a concise Scope section of the document. CPC believes that single-entity combination products and co-packaged combination products would be in-scope of this guidance. Additionally, CPC requests FDA explicitly address cross-labeled combination products. This would include the possibility of excluding cross-labelled combination products from the Draft Guidance, although some concepts in the document may still apply to such products. We also request that FDA address all types of submissions and delineate which are within scope of this guidance.

2. The Draft Guidance should provide clear guidance on the risk-based approach for Bridging based on current FDA thinking and practice. Examples should be used to supplement the recommendations in the guidance to illustrate the application of the approach in practice. In this Draft Guidance, examples have been used in lieu of clarifying the expectations for bridging. Using this format, it is not clear what the Agency's recommendations are with regards to bridging. More explanatory text regarding circumstances and scenarios appropriate for using allowable approaches in addressing bridging information gaps will help facilitate more consistent and efficient meeting and interactions between sponsors and FDA. CPC welcomes FDA interactions and robust discussions and wishes to optimize those interactions by understanding FDA thinking as provided by clear guidance. Without an understanding of needed bridging information and allowable types of study designs, applicants are left with the onerous (and not always successful) task of scheduling a meeting and often asking elementary questions for every specific product issue and study design protocol in support of their individual application. CPC recognizes the challenge for a guidance document to outline the expectations for all bridging scenarios and appreciates the flexibility of the approach outlined in the current guidance. CPC suggests that FDA build on this guidance by adding examples of study design that could be used to satisfy the gaps identified in each case study. Giving sponsors additional guidance on the options to consider would better inform the proposals brought forward by applicants resulting in more efficient meetings and interactions. The sponsor's proposals would then be closer to FDA expectations, resulting in more meaningful conversations concerning the specifics of the proposals during the meetings. CPC recommends that the Draft Guidance include a section containing content similar to that contained Sections 1.4 and 2.1 in ICH Q5e, which outline the general principles and considerations for bridging. Some of this content may already be included within the Draft Guidance, but it is not clear whether the statements in the examples are intended to convey general FDA thinking and expectations, or if these statements are specific to the example. The overall understanding and readability would be improved if the general expectations and considerations were consolidated into a single section. CPC supports the inclusion of providing examples that are meant to be illustrative of the process in a manner which is supplemental to FDA recommendations on how to approach bridging, as this would advance industry's understanding of current FDA thinking.

CPC has identified additional relevant combination product bridging scenarios and recommends the inclusion of the case study examples as described in specific comment table for line 201 below. A framework incorporating a risk-based approach would be recommended as a core aspect to these case studies.

3. FDA Guidance should be written in a manner which clearly provides FDA recommendations, rather than conveying FDA recommendations through what an individual applicant intends to do. Framing study recommendations from the applicant perspective does not lend itself to being able to clearly express FDA's current thinking on the bridging of information topic. The format only conveys what an "an applicant intends to" and "information may still be needed", not what is needed to meet a consistent, scientifically sound risk-based study design approach. The Draft Guidance should clarify and provide clear guidance on FDA recommendations on how to approach and address bridging information gaps, not what an applicant "intends" to do. Lines 80-81 of the Introduction to the Draft Guidance indicates FDA's intent to provide explicit guidance by writing "The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required." However, industry is left wondering what it means relative to needed approaches and closing information gaps when the Agency states "applicant intends to"? By choosing to frame the information needed as what the applicant has determined will assure a successful approval, the FDA is elevating the regulatory importance of the studies the hypothetical applicant has chosen to conduct. Furthermore, the three examples do not include a conclusion of the outcome (e.g., FDA assessment of acceptability), leaving the reader of the guidance to wonder, "so what happened next?" and "was the applicant successful?" The hypothetical applicant case study format may not lend itself to providing FDA's true current thinking, and the end result is a Draft Guidance with limited utility for those applicants looking for guidance on bridging information for combination product presentations.

4. The Draft Guidance does not reflect current FDA allowable practice nor is consistent with recent combination product approvals. By choosing to provide guidance through an applicant's actions in a case study, sponsors may infer these are FDA's positions. Since not all examples previously accepted by the agency are represented in the case studies, the Draft Guidance could be seen as revoking allowable approaches for a given bridging scenario that have been documented in FDA's Summary Approvals. Further clarity is needed on the allowable bridging approaches applied to 1) leverage across population and indication for Human Factors (lines 306-309) and 2) submission of Design Verification/Validation documentation (lines 340-345). Further clarification is needed if differences are observed in PK profile between two presentations, as referenced in lines 356-359. As outlined in Item 6 below, in circumstances when differences in PK exposure between the two presentations do not meet the traditional BE criteria (i.e. 90% CI within 80-125%), alternative approaches (e.g. popPK, PK/PD and/or exposure response modeling) could be considered to justify that the differences in PK within a wider 90% CI would not affect efficacy and/or safety of the to be marketed combination product in the intended patient population. Examples of approved autoinjector devices with pharmacokinetic exposure (PK) parameters that marginally fell outside of traditional Bioequivalence Limits (0.80 to 1.25), as gleaned from summary approvals, include Rasuvo, Evzio, Plegridy, Cosentyx and Simponi.

5. While the framework in the Draft Guidance provides an overview of an analysis that a manufacturer would perform, CPC recommends that the framework consider current standards for a stepwise approach to identify the information gaps. CPC recommends that the Draft Guidance reference ISO 20069:2019 *Guidance for assessment and evaluation of changes to drug delivery systems,* as one potential framework for assessing changes to delivery systems and changes to medicinal products which have the potential to impact the combination product. This standard applies to drug delivery systems, but can be used to assess the larger population of combination products within scope of this Draft Guidance.

6. For the Draft Guidance to facilitate development of the type of analysis which CPC understands that the FDA is expecting applicants to perform, CPC recommends providing options and considerations for conducting the current Step 1, which is the key activity. For example, one option would be for sponsors to separate "identification of differences" and "analysis of the potential effect(s) of the differences" into two steps or sub-steps in the process, to increase the understanding of the depth of analysis that the FDA is expecting from applicants in order to provide compelling justifications for their bridging strategies. For the step relating to identifying differences, it would be helpful to industry to include options for methods to perform this step, such as performing a side-by-side comparative analysis or threshold analysis (e.g., as outlined in the *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications* draft guidance). Include considerations for applicants in assessing the product holistically, including formulation differences (e.g., volume, concentration, viscosity, pH), device differences (injection depth/angle, injection rate, function) and user interface differences (size, geometry, material surface properties, color, IFU). For the step relating to analyzing the potential effect(s) of the differences on the safety and effectiveness profile, it would be helpful to industry for the guidance to recommend applying a risk-based approach and to provide recommendations on product-specific factors which may increase or decrease the risk of the change, such as the therapeutic window of molecule and context of use (e.g., chronic vs. emergency). Include factors for the applicant to consider, such as recognizing that changes to the drug and changes to the device should be considered individually and in aggregate for potential effects taking into account the applicant's existing experience with delivery device and molecule. For example, the content in Lines 142-166 can be organized in an easier to understand tabular format (such as the one below), which shows the relationship between the potential effects on the safety and effectiveness profile of the combination and the changes which could be drivers for the potential effects.

Examples of Changes	**Potential Effect on Safety/Effectiveness Profile**
- Increase in drug concentration - Change in drug viscosity or formulation - Change in injection rate	- Change in local injection adverse reaction profile
- Change in drug formulation (even with an unchanged device constituent part)	- Change in performance (e.g., dose accuracy, aerosol particle size distribution)
- Change in manufacturing process	- Change in drug quality

- Change in device constituent part	
- Change in user interface of device constituent part	- Change in ability of intended users to safely and effectively use the product
- Changes in device (needle depth, rate of infusion) - Changes in formulation	Change in bioavailability and/or metabolic profile of drug, e.g., due to o different lung deposition profile - administration to a different tissue plane (even within the same route of administration)
- Changes in drug formulation	- Change in leachable and extractable profile of the combination product

It is also recommended to provide the suggestion to applicants to consider compiling the information from their framework analysis in a tabular format to facilitate review and analysis (see Appendix B for suggested table format completed for Example A).

7. Guidance is needed on FDA's position on 'real-life patient handling experience' in context of any perceived bridging information gap. This term, along with 'device robustness', were initially introduced in the May 2013 FDA draft guidance for *Rheumatoid Arthritis: Developing Drug Products for Treatment*. This information has been an expectation from FDA for combination products when bridging across presentations to further support assurance of proper patient handling. The information is often collected during the open label extension studies of the pivotal clinical trials. CPC is inferring, due to FDA omission of these type of studies, that FDA position has evolved and the current thinking is real-life patient handling experience is not an identified information gap when bridging cross combination product presentations. CPC requests FDA confirm the position that real-life patient handling experience studies are not required.

8. Revisions are needed related to PK and BA Statements in the Guidance. The reference to the February 2019 *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* draft guidance ('BA Guidance') at Lines 347-359 is inappropriate, as the BA Guidance does address combination products, delivery devices, injectable dosage forms or monoclonal antibodies, which represent a significant portion of combination products requiring bridging. The text indicates that additional clinical data may be necessary if PK differences are observed in the PK profile between the two presentations (e.g., in maximum concentration, in area under the curve, in shape of the concentration-time profile). The BA guidance states "When similarity in BA is not demonstrated, the sponsor should demonstrate that the differences in the rate and extent of absorption do not meaningfully affect the safety and efficacy of the drug product based on the available dose-response or concentration-response data." This BA Guidance seems to imply that clinical data would be needed to address PK differences where the BE range is wider than 80-125 limit (per Appendix A, section G). Please note in the guidance that sponsors continue to have the option to scientifically justify that differences in PK do not impact safety or efficacy, in discussion with FDA.

Overall, CPC believes that additional content is necessary within the Draft Guidance to provide the needed level of guidance for sponsors to adequately address bridging information gaps and the applicability of leveraging prior product experience. Acknowledging the limitations (and significant lag time) of making substantial revisions to a draft guidance, CPC is making the following requests:

1. CPC believes that additional bridging guidance is needed beyond what is currently provided in the Draft Guidance and are requesting a one-day public forum workshop to understand FDA's current thinking. Further understanding of the recommendations and examples on how to approach bridging to help clarify how to bridge to information gathered across development programs to leverage that information in support of an application. CPC welcomes partnering with additional industry trade groups and non-profit organizations in a collaboration with FDA to clarify and further define the bridging of information across combination product presentations.

2. CPC notes that combination product bridging often occurs concurrent to other changes to the product, including the change of a route of administration (for instance, adding a subcutaneous route of administration for a product that has previously been studied via intravenous administration). We appreciate the complex clinical and pharmacological issues raised in such situations that go beyond the scope of this guidance, however, we would appreciate further development of these considerations particularly for common types of biologic products (such as monoclonal antibodies for chronic administration with relatively longer half-life). We understand this would likely be a limited discussion within this guidance and may be better covered in a separate guidance.

We appreciate the opportunity to provide input on the proposed Draft Guidance.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

Appendix A: Line Specific Comments:

Line	Section	Comment	Proposed revision/Needed Clarity
N/A	Title Page	Title page should state Guidance for Industry and FDA Staff and OCP as signee. Line 19 states the guidance provides recommendations to industry and FDA Staff, but the title does not include FDA Staff. Sponsors would welcome FDA applying the principles and approaches in their review practices. Additionally, on the title page, the Office of Combination Products is listed as a contact for questions (e.g. Patricia Love), but OCP is not a signee of the draft Guidance. OCP should be added to the list of Centers on the title page.	Guidance for Industry and FDA Staff. Office of Combination Products (OCP)
20	Introduction	The Draft guidance would appear to cover those combination products submitted under IDEs or PMAs	This guidance provides recommendations to industry and FDA staff on how to approach bridging in new drug applications (NDAs), Premarket approvals (PMAs) or biologics license applications (BLAs) for drug-device and biologic-device single entity or co-packaged combination products
21-22	Introduction	Cross-labeled combination products are not included in the guidance. There are instances where bridging these types of combination products would be relevant.	…device and biologic-device single entity, or co-packaged, **or cross labeled** combination products including the following:
24-30	Introduction	It would be helpful to include in the scope of this Guidance Bridging of information related to a combination product that employs the same device and drug product with a different clinical indication for use.	Include in the scope of this Guidance Bridging of information related to a combination product that employs the same device and drug product with a different clinical indication for use, along with an example.
32-35	Introduction	Definition of bridging seems incomplete compared to the 'Steps' outlined in the Guidance. The current definition appears to only cover Step 1 of the 5 Steps	Expand the definition of bridging to be more comprehensive including leveraging existing data and justifying its use via scientific rationale.
35-39	Introduction	The Guidance only addresses retrospective leveraging of data for the purposes of bridging. The Guidance does not address strategic / pre-emptive use of a common device	Add information on how bridging and the contents of the Guidance may inform the development of platform devices for delivery of multiple different drug /

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		platform that is being developed for use with potentially multiple different drug / biologic products.	biologic products. Please consider including a case study.
41	Introduction	FDA states that ownership of relevant bridging/leveraging information may be necessary. FDA should also state that other options not requiring ownership may be available for this information or data.	or have a right of reference… **Information from publicly available information, including real world evidence, may also provide suitable bridging and leveraging information.**
47	Introduction	It is probably clearer to use the term "leverage" rather than "bridge to"	This guidance seeks to clarify how to **bridge ~~to~~ leverage** information gathered from another development program to **~~leverage that information in~~** support **~~of~~** an application that bridges one product to another.
54	Introduction	Include combination products submitted under IDEs or PMAs	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, investigational device exemption (IDE) under 21 CFR part 812, premarket approval under 21 CFR part 814 or a BLA under 21 CFR part 601
58, 125	Introduction, III	Include combination products submitted under IDEs or PMAs	Human nonprescription combination products that are the subject of an IND, NDA, IDE, PMA or BLA (as opposed to those covered in a final or tentative over-the-counter drug monograph)
62-65	Introduction	Persons responsible for development of a device constituent part (potentially a platform or co-packaged commercial device) are not usually the submission applicants. Suggest rewording by adding "Combination Product under review"	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~~ **development of the combination product under review are referred to as applicants.**
95-96	II	The guidance should align with the expectations for device convenience kits. Right of reference requirements should not be necessary for device constituents (particularly those provided physically separate in a co-packaged kit) that are	The guidance should allow for the reliance on the prior findings of safety and effectiveness or substantial equivalence for the approved device constituent part, without the requirement to obtain a right of reference.

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		used within their legally marketed intended use (listed or cleared for Class I/II, or approved for Class III devices).	
105	II Background	Specific examples would help clarify the scenario described in 101-105 where the applicant may be able to leverage relevant existing device-related data.	…a new combination product. **Specific examples may include a co-packaged, 510(k) cleared delivery device or approved device constituent part that would not need additional consideration of its material biocompatibility, sharps protection feature reliability, or device shelf life.**
112	II Background	The guidance should discuss and emphasize incremental risk here. Products can be different but add no additional risk for the same administration or even for a different route.	…early in drug development. **FDA's emphasis would be how or whether a difference adds significant or incremental risk to the therapy.**
115-117	III (p4)	Suggestion to take away the word ANALYTICAL from the heading,	DEVELOPING A~~N~~ ~~ANALYTICAL~~ FRAMEWORK FOR IDENTIFYING INFORMATION GAPS TO INFORM A BRIDGING AND LEVERAGING APPROACH
119-196	III	There is no mention of risk or a risk-based approach anywhere in this section. Device performance or manufacturer differences can be measurable but add no risk to the safety or effectiveness of product.	Add a discussion regarding how FDA will apply a risk-based approach and least burdensome principles in this step wise approach.
127-129	III	The Agency recommends that an applicant use the stepwise approach presented.	It would be easier to follow if these steps are illustrated in a flow chart format as well
131-196	III	It is unclear to CPC if it is FDA's expectation that applicants provide this step-wise format in the submission.	Please clarify the expectations regarding submission content.
131	III	Could the bridging assessment leverage data be from more than just one other product for 'Combination Product A'? This seems to be allowed considering line 177 of "consider whether other existing information, outside of that directly gathered…" reference to same device in combination with other drugs.	Clarify 'Combination product A' could refer here to multiple combination product**s** within a platform already marketed, that would be relevant to the bridging assessment.
132	III	Consider HF comparative analysis FDA guidance	Consider the FDA Guidance references below in the assessment of differences: • Comparative Analyses and Related Comparative Use Human Factors Studies for a

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			Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry, draft, January 2017 • Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, draft, February 2016. • Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications, draft, September 2018.
135-140	III	It would be helpful to include what is not changing and request to address all change types listed in this guidance. Following the same thinking, if the potential effect is required for each change, a note on the impact of what is not changing could help to highlight where the risk is and where is not, when bridging to 'Combination Product B'.	Clarify critical attributes that are not changing
142-143	III (p5)	When describing injections, the term should be injection time. When describing infusions, the term rate is appropriate. A change in injection rate, unless very significant, has not been shown to have a clinically significant effect. Industry is being asked to disprove a negative which may require a clinical data driven approach. Any manual administration encompasses a wide range of delivery rates which is already considered in the clinical evidence data set. Moving from a PFS to an autoinjector a minor change in delivery rate would not change the clinical history derived by manual injections.	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. 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 **significant** change in injection ~~rate~~ **time or infusion rate**
149-151	III (p5)	Suggest to add “and/or drug delivery” after drug quality	Changes in the manufacturing process and/or device constituent part that may affect drug quality **and/or drug delivery**

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152-153	III (p5) Step 1	This bullet point identifies an assessment of combination product B for the intended users, but it does not identify a step to review/ compare the user interface between the two combination products.	Add information around reviewing/ comparing the user interfaces between these two combination products. Clarification should also be provided to identify if/how these activities link to the "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications" Draft Guidance currently available.
155	III	Clarify what is meant by "metabolic profile" and distinguish from PK	Clarify metabolic profile
155-162	III	The listed section and bullets suggest bioavailability differences for needle depth, tissue plane or rate of infusion suggest the need for bioequivalence studies when a risk-based approach would conclude otherwise.	Delete this example or provide additional context to this consideration.
159	III(p5)	Similar to comment for line 142-143, this line uses infusion. Either use only one term or always use both.	Changes in the needle depth, tissue plane, **time of injection or** rate of infusion.
167-170	III (p5)	In the guidance, Step 2 for bridging requires knowledge of the safety and effectiveness submission requirements. However, since the approach for the guidance takes the perspective of the manufacturer to assess whether bridging is possible, it is not uncommon for manufacturer bridging assessments to be less conservative than the Agency's bridging assessment. Therefore, it would be helpful if there were more details in this guidance regarding safety and effectiveness requirements for combination products as the Agency's regulatory requirements for demonstrating safety and effectiveness for combination products are not always known by a manufacturer, or may have changed since the prior combination product approval being used for bridging, or may simply not align with the Agency's views.	Include details regarding how to assess clinical safety and effectiveness requirements for combination products. In particular, which specific risks and questions need to be addressed or considered by sponsors to meet clinical regulatory requirements for safety and effectiveness studies, real life patient handling studies, and device robustness studies. Furthermore, examples of allowable study design (e.g., number of patients, types of data needed to be collected, how the data should be collected, etc.) would be helpful.
167-170	III (p5)	The Guidance should make clear that non-clinical bridging tools are acceptable in bridging between presentations.	Include acknowledgement that other non-clinical bridging tools exist to bridge between presentations
188-189	III (p6)	We request that FDA provide additional clarity as to how the stepwise approach proposed in this Draft Guidance could interact with traditional design controls during combination product development.	One possibility is to differentiate the terminology used in the framework from that traditionally used during design verification/validation.

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201-533	IV (p6)	In the examples A-C it is difficult to discern what the outputs of Steps 1-4 are in the process and what gaps still exist and must be addressed via Step 5	Recommend including a table for each example summarizing the output of each Step in the process, including what gaps still need to be addressed in Step 5
201-533	IV (p6)	Examples A-C do not provide the result of the bridging exercise and whether the applicant's plans are acceptable to the FDA	Include the FDA position on the proposals for each example
201-202	IV (p6)	The guidance includes 3 bridging/leveraging examples. However, it would be helpful if additional bridging/leveraging example is included that identifies bridging/leveraging opportunities for post approval changes (e.g., smaller design changes or manufacturing changes). It would be helpful to better understand the Agency's views on leveraging existing verification and validation testing and whether it may be possible to justify conducting less testing to confirm the acceptability of the change (e.g., only conducting accelerated aging instead of both accelerated aging and real time aging, testing fewer process validation batches or testing reduced lot sizes, etc.). The Guidance would benefit from the addition of the proposed examples.	Add example related to primary container closure changes between presentations. In example, address in-vitro drug-device compatibility testing, stability testing and in vitro performance testing to help establish bridge between presentations. Add example or discussion of perceived bridging study considerations between a vial and syringe presentation to a pre-filled syringe presentation, including whether or not clinical data would likely be required to leverage previously collected safety and effectiveness data. Include an example that illustrates the maximum extent to which bridging could be utilized to bridge between two combination product presentations for applicants to fully understand what is feasible. For example, the Guidance should include an example in which, from a testing perspective, only a repeat of design verification testing is necessary to solidify the bridge between the safety and efficacy, etc. already established for a previous combination product presentation. Include examples of combination product changes that would necessitate PK comparability studies and well as the Agency views on why the PK studies would be necessary.

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			Guidance would benefit from a digital or software example, where post approval changes with software can occur frequently.
201	IV	We would appreciate the exploration of additional topic areas, including changes to container closure systems as a part of device constituent changes, changes to method of administration including injection depth/angle/time due to device constituent changes, changes to patient population and/or disease area (including expansion of subsets of a particular disease), etc.	Such considerations could be included in an appendix and do not need to be overly-detailed, but are useful as they go beyond the examples presented.
212-217	IV	This paragraph should be moved to an earlier section of the Guidance document	Move Lines 212-217 to Section II (Background) of the document as it contains general background information on recommendation to conduct clinical studies with commercial presentation of product.
212-217	IV	The intent of this paragraph is unclear whether FDA is recommending that applicants perform only pivotal clinical studies with commercial presentation, or if the FDA is acknowledging that if the applicant knows what the commercial presentation will be, then the applicant could perform an earlier clinical study with the commercial presentation to avoid the need to perform additional clinical studies after pivotal studies to bridge to the commercial presentation. Additionally, this section uses the term 'presentation' as well as 'device constituent parts' without drawing any distinction between the two terms. Finally, while it may be necessary to use the commercial presentation in the pivotal study for some combination products, it should not necessarily be required for all combination products. In some cases, such as drug delivery devices and autoinjectors, something as close as possible in functionality and usability to the final product may be appropriate.	Clarify whether an applicant could use the commercial presentation in earlier non-pivotal clinical studies to avoid needing to collect further clinical data on commercial presentation after pivotal clinical studies are completed with a presentation that is not the intended commercial presentation. If not FDA's intent, then revise to "…FDA encourages the applicant to conduct pivotal clinical studies using the presentation ~~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 would not be needed because the pivotal safety and efficacy data would have been developed with the final finished combination product. Indicate in this section of the Draft Guidance that for some combination products it may not be necessary for the Sponsors to use the final finished combination product in the drug clinical studies. It would also be

Line	Section	Comment	Proposed revision/Needed Clarity
			helpful got for the FDA to indicate in the Guidance a few examples to demonstrate this point.
219	IV	By using an example-based approach, the details become important when trying to decipher the applicability of the FDA expectations to the change which the applicant is considering, therefore, include additional details in the analyses, such as: • Volume and viscosity of the drug product, as the analysis for a 2 mL injection of a high viscosity product raises different considerations than an analysis for a 1 mL injection for a low viscosity product • Recommended to clarify the users and use scenarios. It is assumed to be patient, caregiver and HCP administered in home or clinical settings • Clinical characteristics of drug product should be clarified in the example as they are relevant in assessing the potential PK differences (e.g., long Tmax with extended period between doses or short Tmax with frequent dosing)	It is recommended to include additional details in the examples, as they are relevant to the analysis and the subsequent conclusions.
219 362 475	IV (p7)	Example A Example B Example C	Include a flow chart as well to illustrate each steps for ease of flow
222-230	IV (p7)	This should not matter if the company decides that ONLY the AI will be marketed. Companies may elect to either supply both a PFS and an autoinjector or only market the 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, **in addition to, or instead of the PFS 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

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			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.
230	IV	See comment for line 225. However, the guidance could clarify the case example.	**In this example, t**he applicant intends to market both the PFS and autoinjector presentations commercially.
237	IV(p7)	The term "method of injection" is too easily confused with the route of administration or tissue into which the drug is delivered. In this instance, the route of injection is still subcutaneous, and route of administration is a different issue. The intent of this example is to describe the differences in the attributes of the manual vs. the automated injection.	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~~ attributes related to injecting the drug constituent part, and 3) it has a different user interface.
258-260	IV	The guidance has included a theoretical example about injection times. As long as the autoinjector delivers in a time within the range of a manual injections, it should not be considered a "different" product that requires clinical data to support. Adverse reaction profiles are more likely determined by patient characteristics than device characteristics and, in any case, differences in injection site reactions do not rise to the level of significant clinical risks that would likely preclude approval or alter prescribing practices.	Revise accordingly or delete.
262-266	IV	The guidance has included a theoretical example about injection methods. Subcutaneous injections, as a route of administration, are inherently variable. There is no evidence that this variability or a more precise injection in comparison to manual delivery raises new significant patient risks.	Revise accordingly or delete.

Line	Section	Comment	Proposed revision/Needed Clarity
262	IV(p7)	It is not the fixed vs. variable delivery time, it is the potential significant decrease in delivery time and increase in velocity that may impact injection site reactions.	Added text: In this example, changes from a manual to automated delivery may result in a significant reduction in the time and increase in the velocity of the injection as compared to the manual delivery which can be slower and more variable. A significant decrease in the delivery time to the target tissue and a significant increase in velocity (which may result in delivery to a different injection depth in the same target tissue) may affect the local adverse reaction profile as compared to a slower and/or more adaptable manual delivery. Please note that if the automated delivery time and velocity are clearly within the range of those that would be experienced with manual deliveries, then this is not a change.
280-284	IV	This section describes how information from a PFS Phase 3 clinical study may be leveraged for an autoinjector presentation. It is unclear what is meant by 'testing' in the sentence, '…if the PK profile is shown to be the same through testing,…'	Clarify if the 'testing' referenced on line 282 would be limited to a clinical PK study with the autoinjector or if in-vitro test methods or modeling could be utilized to demonstrate that the PK profile is comparable between the PFS and autoinjector presentations
282	IV (p8)	The Guidance is not specific on what types of testing is meant when referring to 'nonclinical' testing throughout the document.	Add a footnote denoting what is meant by 'nonclinical' testing. Clarify if this is intended to mean device design verification testing and/or other types of in vitro testing.
298-309	IV (p9)	The text indicates that it will be challenging to bridge the human factors validation study for the autoinjector and indicates that the prior HF study was conducted with a different disease state, indication, and is used in a different patient population with differing injection sites. However, it is unclear why specifically these differences would necessitate a new human factors study. It would be more helpful if the guidance identified the specific patients risks that exist and gaps in the existing HF study/methodology that would need to be evaluated and why. Similarly, it	The guidance should address the specific patients risks that exist and gaps in the existing HF study/methodology that would need to be evaluated in a new HF study and why. *Proposed revision* The applicant recognizes, however, that since the product was developed for another population and indication, it will be challenging to bridge the applications. Specifically, the applicant has identified

Line	Section	Comment	Proposed revision/Needed Clarity
		would be helpful to understand the Agency's views on bridging prior real-life patient handling studies following the same types of changes. This sentence describes an example where the applicant decides it is challenging to leverage previous human factors validation data because of differences in patient user population and indication. Rather than broadly suggesting that a new HF Validation study should be run simply because there is a different patient user population/indication, the example should be more specific to have the Applicant consider if there are differences in the characteristics of the patient populations (e.g. cognitive and physical capabilities) that would affect use of the product, and if those differences impact ability to leverage data. Although the example is meant to be illustrative of the process rather than a specific development program, consideration of user characteristics is a key part of consideration of what distinguishes user populations. The guidance assumes that the leveraging across user groups and indication would be "challenging". However, FDA has accepted this type of bridging in recent drug approvals. It's unclear what circumstances would be truly challenging and why.	new patient risks (e.g. reduced dexterity and/or reduced cognitive ability) with the new patient population. As such, the applicant ~~and~~ intends to conduct a HF validation study and prepare a HF validation study report to be submitted as part of the marketing application. For similar changes, the guidance should also address the specific patients risks that exist and gaps in existing real-life patient handling study/methodology that would need to be evaluated in a new real-life patient handling study and why. Modify example so that the theoretical applicant considers whether the patient user population characteristics (cognitive, physical, etc.) differ between the two autoinjector products, and uses that determination to decide if a new HF Validation study is needed. If no key differences in cognitive and physical characteristics exist that would impact use of the product, then the previous HF data that is relevant should be leverageable. There can be acknowledgement that data specific to other differences in product use (e.g. the different injection sites) may need to be regenerated. If user characteristic differences do exist that can impact use of the product, then new HF validation data may need to be generated.
318-323	IV	Design verification tests can include only those parameters that are impacted by the different drug. Non-drug specific parameters should be accepted (e.g., extended needle length, activation force, cap removal force, etc.) Drug-specific bench verification testing should be sufficient for design validation, as they cannot be proven out by design validation/ simulated use activities. Acceptability of these	~~**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.**~~

Line	Section	Comment	Proposed revision/Needed Clarity
		specifications needs to be derived by other means and then verification is required. The requirements for dose accuracy and extended needle length are driven by the attributes of the drug and the need for delivery to the correct tissue space	
325-332	IV (p10)	The text indicates that additional clinical information to assess local AEs may be required as the new drug may impact injection time/rate which may impact pain of delivery. It would be helpful if the guidance explicitly includes examples for when/why the Agency would consider a difference in injection time to necessitate new local AE data as a justification could likely address whether the injection site pain risk necessitates clinical data.	The guidance should address specific examples for when/why the Agency would consider a difference in injection time to necessitate new local AE data as a justification could likely address whether the injection site pain risk necessitates clinical data. Additionally, the guidance should provide for mechanisms to obtain the local AE data (e.g., could this be gathered during the PK study referenced at line 347, or is a different type of clinical study expected?)
330	IV	There is no strong evidence that minor changes in injection time significantly impacts pain or that any slight differences in pain should be a significant prescribing consideration for an important therapy. Pain is typically associated with the formulation.	Delete the bullet
341-345	IV (p10)	The text indicates that the applicant intends to provide "a copy of design control documentation for the delivery system and combination product". It is unclear what is meant by "a copy".	*Proposed revision* The applicant also intends to provide ~~a copy of~~ design control documentation for the delivery system and combination product as a whole, . . .
347-359	IV	There are recent examples of approved autoinjector devices with pharmacokinetic exposure (PK) parameters that marginally fell outside of traditional Bioequivalence Limits (0.80 to 1.25). As gleaned from summary approvals, they include Rasuvo, Evzio, Plegridy, Cosentyx and Simponi.	The Agency should note in the guidance that sponsors still have the option to scientifically justify why any PK differences do not impact safety and effectiveness. It would also be helpful for the agency to provide options of PK comparability assessment tools for combination products for expected administration routes (e.g., SC, IM, IN, transdermal, inhalation, etc.) that are clinically relevant and risk-based. Revise the sentence starting on Line 356 from: **~~If differences are observed in the PK profile between~~**

Line	Section	Comment	Proposed revision/Needed Clarity
			~~**the two presentations (e.g., in maximum concentration, in area under the curve, in shape of the concentration-time profile), the applicant intends to gather additional information to evaluate clinical effect of these differences.**~~ To the proposed revision for clarity: **In circumstances when differences in PK exposure between the two presentations do not meet the traditional BE criteria (i.e. 90% CI within 80-125%), alternative approaches (e.g. popPK, PK/PD and/or exposure response modeling) could be considered to justify that the differences in PK within a wider 90% CI would not affect efficacy and/or safety of the to-be-marketed product in the intended patient population.**
353-354	IV (p10-11)	The phrase on "If no differences…" should be changed to "If…comparable".	If ~~no differences are observed in the~~ PK profile **is comparable**,
359		Reference to the Feb 2019 Bioavailability guidance is inappropriate, as the guidance does not mention combination products or delivery devices nor addresses injectable dosage forms or monoclonal antibodies, which represent a significant number of combination products requiring bridging.	Provide the context in this guidance for these products, or provide an alternate reference to cite
363	IV.B	Clarify that reference to Phase 3 infers generation/collection of pivotal clinical data to support marketing application. Under accelerated development programs this could equally be Phase 2 studies.	Add footnote denoting when referencing Phase 3 studies that under accelerated development programs the pivotal studies could be Phase 2 in some cases.
393-394	IV (p11)	The Guidance indicates in this example where the drug is the same, but design changes are made to an autoinjector, that "differences in functional performance of the device constituent part, if any, may affect the drug constituent	Proposed revision for clarity 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

Line	Section	Comment	Proposed revision/Needed Clarity
		part." The reference to the "drug constituent part" is unclear especially because quality of the drug constituent part is referenced in previous sentences in this bullet point.	contact with the drug and the formulation and the functional performance of the device constituent part remains the same and the ~~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.~~
396-400	IV	The guidance assumes that a PK study would be needed for a minor modification "without changing the interface". This appears to be an extreme, theoretical example where simple design verification testing and a risk analysis should be sufficient. Device improvements for usability would not likely be made if the assumption was a costly PK study to address the cited minor variability would likely be required. This would have a negative effect on introducing improvements related to usability that could be made in the lifecycle.	Delete the bullet.
404	Section IV.B.	Please clarify the intended meaning of "unchanged" in the context of device performance.	… to confirm that the device performance remains within the specifications of the clinically studied Prototype 1.
411-416	IV (p12)	The text notes that combination product characteristics such as dose accuracy, injection depth, injection time, and activation force are examples of factors that could affect the drug delivery and *should* be assessed over combination product shelf life. However, it is possible that these characteristics have alternate controls in place that ensure the CP meets its predefined specifications. As such, it should not be implied that these characteristics '*should* be assessed over the CP shelf life' as other controls may be in place to ensure product quality.	*Proposed revision* 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 (unless other controls are in place to ensure product quality that preclude an assessment over the product's shelf life).
428-432	IV	The use of the terms "unchanged" and "same" could be interpreted in a variety of ways, therefore it would be	Revise accordingly

Line	Section	Comment	Proposed revision/Needed Clarity
		important for the FDA to clarify the expectations. Comparability is the typical expectation of "sameness" for drug product changes and therefore should apply here. The tested parameters are likely different (e.g., remain within the previous acceptance criteria, but have different mean and standard deviation) and the guidance should be specific that these differences will not be considered to be a "difference in the products" that would require a PK study.	…injection angle and site of injection remain within the specifications ~~are the same~~ for Prototype 1
429, 435, 440	IV (p12)	The term used in Step 2 in line 404 is "…remains unchanged…" Draft Guidance should use same terminology throughout, so change "the same" and "remain the same" in bullets 429, 435 and 440 to "comparable"	Line 428: As noted above, testing confirmed that the dose accuracy, delivery time, injection depth, injection angle and site of injection are ~~the same~~ comparable for Prototype 1 … Line 434: Additionally, the activation force and injection time ~~remain the same~~ are comparable Line 440: The proposed indication, dosage, and administration are ~~the same~~ comparable and, as noted…
467		The sponsor should only need to submit verification data for any function that could be impacted (as identified by change control process). There should be no need to redo and submit "full design verification data."	The applicant intends to support the assessment through submission of data demonstrating comparability between the designs, including through submission of ~~full~~ applicable design verification data for…
475	IV.C	Example C should be changed to an injector, where the Sponsor has used the PFS based version in Phase 3 and wants to market an autoinjector (e.g., Example A) as this would provide a good opportunity for the example to show the scenario where a sponsor can leverage previous clinical data on device robustness and use in patients hands, thus limiting the clinical dataset that would be needed to PK. While considerations relating to inhalation products and products which are used to treat higher risk, emergency use scenarios are important to consider in the guidance, having these variables included in this example is a lost opportunity where FDA could have framed an example	Revise example C to be an injection-based example, to provide for a scenario whereby the device data can be leveraged for another combination product

Line	Section	Comment	Proposed revision/Needed Clarity
		which would allow for leveraging of clinical experience from use of the same platform autoinjector with multiple drug products.	
485	IV. C 481-484	The example describes the patient groups and implies but does not specifically indicate that both Combination Product A and B are for self-administration by the relevant patient groups.	Add that both Combination Product A and B are being developed for self-administration by the patient groups indicated.
508-521	Section IV.C.	Please provide additional clarity on the considerations for sponsors when bridging usability data between two combination products.	N/A
529-532	IV (p14)	For this example, the Guidance indicates "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." It is understood that because an NME is being incorporated with an existing device that phase 3 data may be required to determine safety and effectiveness of the drug or to fully characterize the drug constituent part. However, it is unclear why phase 3 clinical studies would be needed to address differences that could affect device design and performance. Phase 3 clinical studies should not always be required to use an existing device constituent part with a new NME, if other data can be generated demonstrating there is no negative impact on safety and effectiveness by using this NME with the device.	Provide clarification and examples around what device design and performance differences could not be addressed by design verification testing and would additionally require phase 3 clinical studies as cited in this example.

Appendix B: Proposed Sample Table Format - Identify Differences and Assess Potential Effects of the Identified Differences

Category	**Product bridging from:** PFS	**Product bridging to:** Autoinjector	**Identified differences**	**Potential effect to:**
Intended use				
User	Same	Same	None	N/A
Use environment	Same	Same	None	N/A
User interface	PFS	Autoinjector	Different user interface and performance attributes	Usability, functionality
Route of administration	Same	Same	None	N/A
Indication	Same	Same	None	N/A
Drug product				
Formulation	Same	Same	None	N/A
Dosage	Same	Same	None	N/A
Primary container	Same	Same	None	N/A
DP contact materials	Same	Same	None	N/A
Volume	Same	Same	None	N/A
Manufacturing conditions	PFS Process	PFS & AI Process	Addition of AI process may add shock, vibration, light exposure, time out of refrigeration stress the molecule	DP quality, container closure integrity
Transportation	PFS shipping routes	AI shipping routes	Addition of AI process may introduce additional supply chain shipments	DP quality, container closure integrity
Dosing related				
Rate of injection	User-controlled, variable	AI controlled, consistent	Differences in rate and consistency of rate may impact safe use, PK and local safety profile and may add shear/stress on the molecule due to the addition of the AI	DP quality/compatibility, PK, local AEs/tolerability, usability
Angle of injection	User-controlled, variable	AI controlled, consistent	Differences in angle and consistency of angle may impact safe use, local safety and PK	PK, local AEs/tolerability, usability
Depth of injection	User-controlled, variable	AI controlled, consistent	Differences in depth and consistency of depth may impact safe use, local safety and PK	PK, local AEs/tolerability
Completeness of injection	User-controlled, variable	AI controlled, consistent	Differences in the completeness of injection may impact safe use and PK	Usability, PK
Patient contact materials	PFS contact materials	AI materials	Additional AI materials may introduce biocompatibility risks	Safety (biocompatibility)
Performance	PFS functionality	AI functionality	New device constituent needs comprehensive functionality assessment	Functionality