Combination Products Coalition

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FDA-2018-D-1098

VIA ELECTRONIC SUBMISSION

June 18, 2018

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

Re: Docket No. FDA-2018-D-1098: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products—Quality Considerations

Dear Sir or Madam:

The Combination Products Coalition ("CPC")[1] welcomes the opportunity to offer comments on FDA's "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products—Quality Considerations: Guidance for Industry" ("Draft Guidance"). Our comments below focus on the combination product aspects of the Draft Guidance, and are intended to provide suggestions to help align the Draft Guidance with respect to development and registration expectations for these products as a whole (i.e., not just restricted to MDI and DPI products).

We appreciate the opportunity to provide input on the Draft Guidance and are happy to meet with the Agency to clarify or discuss any of our suggested revisions.

Yours truly,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

[1] 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.

Line #	Comment
All	The Draft Guidance is only signed by CDER and not CDRH, and instead on line 33 this document points to "applicable requirements and regulations outlined in appropriate regulations and guidances, respectively, from CDRH." Typically, CDRH provides a consultation on submissions that incorporate a drug delivery device (including MDI and DPI products), and it is vitally important for industry that a single cross-center approach is provided to streamline the development and review process. To accomplish that, CPC highly recommends that the contents of this guidance document (and any others that cover drug delivery device combination products) be coordinated with and co-signed by CDRH.
All	Throughout the document, but beginning in the Regulatory Status section at line 114, the Draft Guidance includes fundamental drug and device terminology (including design inputs, verification, validation, design outputs, and QTPP, CQAs, respectively) and how they relate to each other. The document continues to equate/conflate these to a large extent (i.e., discussion of CQAs starting at line 147), although these are fundamentally distinct concepts that are well defined in other sources (i.e., ICH guidance for drug terminology, regulation and guidance for device terminology). This document should be more careful in applying these terms (like CQAs) for device constituent parts where these may be considered "essential design outputs" but the process for identifying and controlling these attributes will likely be handled differently than for drug attributes. Optimally, this terminology alignment would be consistent across various types of delivery devices (not just MDI and DPI products) and given it does not exist in other guidances issued to date, it would be better placed in a more general guidance that applies more broadly to drug/device combination products rather than this specific MDI and DPI products.
524	Performance testing of the device constituent part is mentioned in the context of the control strategy and it is noted that this is "typically done by the vendors or fabricators of the device constituent part and verified initially *and on an annual basis* [emphasis added] by the applicant under their internal quality system." We recommend that this section be less prescriptive and instead mention that verification of such testing should be done using a risk-based approach dependent on the component or constituent that is supplied and its function or intended use within the overall product.
574	The statement that "if upstream controls can be used to confirm that a batch of product meets a CQA related to an attribute on the specification, that attribute does not need to be tested at release for every batch" is appreciated particularly as it relates to device components and/or constituents, which is aligned with a risk-based approach to an overall control strategy. Allowing such flexibility in an approach versus a regimented requirement of testing all critical attributes (either CQAs or essential design outputs) at release provides for a more efficient control strategy as well as better quality of the overall product by controlling attributes upstream when possible.

Line #	Comment
734	We recommend that QMS information in general as well as specific QMS information to demonstrate compliance with 21 CFR Part 4 should be allowed to be included in a regional section (3.2.R) as that would provide flexibility for applicants who are submitting a product in multiple markets, since most of this information would only be applicable to the US market. Additionally, this section of the CTD (3.2.P.3) is considered by FDA to be an established condition, which conceptually would not apply to QMS procedures, which are typically within the scope of pre-approval and surveillance audits in order to maintain compliance with applicable regulations; inclusion in a regional section would help clarify this status. Furthermore, per the FDA eCTD Technical Conformance Guide (section 4a), it is acceptable to locate QMS information in 3.2.R.
980	Table 7 includes a number of attributes, including device constituent part data (i.e., functional and performance characteristics) that would be required for inclusion in 3.2.P.7, which is considered by FDA to be a section that includes established conditions. Some of this data may be controlled through means other than release testing per the product control strategy, and such items may be more appropriately described in other sections such as 3.2.P.2.3 or a regional section (3.2.R).
Multiple	Section J (Labeling) includes guidance on Instructions for Use (IFU), see line 1152 for MDI and 1317 for DPI; we would like to ensure that this content is aligned with the upcoming draft guidance on IFUs as described in the PDUFA VI commitment letter (to be issued by end of FY 2019). We appreciate the reference to FDA guidance *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* in order to harmonize the approach to such information between medical devices submitted to CDRH and combination products that include a device constituent submitted to CDER (or CBER).