IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

1500 K Street NW • Washington DC • 20005
Telephone +1 202 230 5607 • Fax +1 202 842 8465
Email info@ipacrs.org • Web www.ipacrs.org

May 7, 2019

IPAC-RS Comments on FDA 'Principles of Premarket Pathways for Combination Products Guidance for Industry and FDA Staff'

(Docket Number FDA-2010-D-0078) (https://www.fda.gov/media/119958/download)

These comments have been prepared by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), which is an association of pharmaceutical companies that develop, manufacture and market orally inhaled and nasal drug products (OINDPs). IPAC-RS seeks to advance the science of OINDPs by collecting and analyzing data, conducting joint research and development projects, and engaging with the wider regulatory and scientific community on areas of importance to the stakeholders interested in the high quality, safety, efficacy and availability of OINDPs. IPAC-RS would be willing to meet with the Agency to discuss these issues further in an appropriate setting, including a public workshop.

General Comments

1. The 510(k) route, which was used by some drug/device combination products, is now discouraged (lines 303-304). It is assumed this is only for integral combination products, not co-packed? This route was used with devices, which used a similar platform to 510(k) cleared devices. This had an impact on how device changes were addressed and the route was better harmonised with drug device combination including CE-marked devices in the EU. It is unclear why this 510(k) route is no longer acceptable; and if this is the case could the FDA recommend an acceptable alternate pathway that the second constituent could follow.
2. The examples provided do not list changes impacting the device only, including those not impacting intended use or performance. Adding an example of a drug delivery device change being part of a drug / device combination product would be beneficial.
3. In section B.1 'New Drug Application', the guidance outlines how the applicant may establish a scientific bridge between inhaled/oral dosage forms but also using data generated on asthma to support COPD indications. We would appreciate clarification on what the 'scientific bridge' consists of (especially across indications), if possible.

Specific Comments:

Page, Line or Section of the Document	Original Language	Proposed Changed Language	Justification of Proposed Change	Importance of the comment (critical regular or minor)
Line 340 – 341	…. such as an inhaler copackaged with a novel corticosteroid for treatment of asthma.	…such as a novel corticosteroid for asthma delivered via inhalation. The drug-device combination product may, for example, be an inhalation aerosol (also known as metered dose inhaler) or inhalation powder (also known as dry powder inhaler). These products consist of a drug formulation and a device constituent part (also known as the drug delivery system).	Term 'inhaler' is not defined. Utilized definitions within FDA Draft Guidance MDI and DPI – Quality Considerations (April 2018), sentences have been refined. Sentence starting with "The drug-device combination…" sourced from MDI/DPI guidance lines 16-18. Sentence starting with "These products consist of…" sourced from IPAC-RS comments for the lines of 59-66, 87-89 & 226-230 of the MDI/DPI guidance. Determination of single entity or co-packaged in these product types is not critical to the theme of the paragraph. Co-packaged may yield additional requirements not feasible without a device registration which has not been a topic in the Agency's previous communications on inhalation dosage forms.[1]	Regular
Line 344	"…combination product composed of the corticosteroid formulated for inhalation and an inhaler."	"drug-device combination product (inhalation aerosol or inhalation powder) consisting of the drug formulation containing the corticosteroid and the device constituent part."	Adopted language and definitions from lines 16-18 and 59-71 of the MDI/DPI guidance referenced above.	Regular

Line 351	"…upon FDA's NDA approval of an inhaler/corticosteroid combination product…"	"…upon FDA's NDA approval of a drug-device combination product containing the corticosteroid…"	Aligned terminology with recommendations for lines 340-341 and 344.	Regular
Lines 352-353	"…approval of a combination product consisting of the same corticosteroid combined with an inhaler for treatment of chronic obstructive pulmonary disease."	"…approval of a drug-device combination product containing the same corticosteroid for treatment of chronic obstructive pulmonary disease."	Aligned terminology with recommendations for lines 340-341, 344 and 351. Removed redundant and undefined term "combined with an inhaler" due to specifying drug-device combination product early in sentence.	Regular
Lines 377-379	"ANDAs for drug-led combination product should also include sufficient information to demonstrate that the non-lead constituent part is compatible for use with the final formulation of the drug constituent part."	Please change the footnote to incorporate reference to line numbers of the cited draft guidance or clarify this statement is applicable to the CMC recommendations specified within the stated guidance. Alternatively, change the sentence at lines 377-379 to the following "ANDAs for drug-led combination product should also include sufficient information to support the analysis of the proposed user interface for the generic combination product when compared to the user interface for the RLD."	The referenced guidance (37) within the footnote discusses primarily Comparative Analysis and Related Comparative Use Human Factors Studies. There is a brief section in the cited human factors guidance regarding CMC requirements. Lines 109-111 of the cited human factors guidance state the delivery device constituent part should be shown to be compatible for use with the final formulation of the drug constituent part through appropriate studies (referring to CMC studies). The use of the words 'compatible for use with the final formulation' in association with the human factors guidance is in conflict with the statement at line 102 of the HF guidance. "the recommendations in this guidance generally focus on the analysis of the proposed user interface for the generic combination product when compared to the user interface for the RLD and are not intended to address all of the information necessary to support approval of a	

	generic combination product, including the delivery device constituent part."

[1] FDA Jurisdictional Update: Metered Dose Inhalers, Spacers and Other Accessories. https://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm103179.htm accessed 01 April 2019.