IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

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DRUG DELIVERY TO THE LUNGS

IPAC-RS Comments to the Draft Guidance for industry on Metered Dose Inhaler and Dry Powder Inhaler products - Quality Considerations

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Outline

- *Context of the guidance and commenting process*
- *Main overarching comment topics identified by IPAC-RS*
- *Examples of other significant comments submitted*
- *Summary*

Context of the guidance and commenting process

- *This Draft guidance is a revision of the original Draft Guidance that was first issued almost 20 years ago*
- *As the name indicates, it describes the expectations by FDA in relation to the CMC/Quality aspects of an inhalation product.*
- *Appreciate FDA's efforts to enhance this new draft and incorporate feedback from industry and other stakeholders*
- *Due to the extent of the topic, IPAC-RS requested FDA for an extension of the original deadline for comments (mid-June 2018) → Extension granted to end of September 2018*
- *IPAC-RS also proposed to FDA in September the realization a public workshop to discuss the main topics raised due to their complexity → FDA have provided some informal preliminary feedback that this may be possible*

Main overarching comment topics identified by IPAC-RS

- *Whilst supporting the introduction of QbD and other relevant aspects as part of the draft for review, IPAC-RS highlighted the need for FDA to clarify the expectations with respect to the following topics:*
  - *Incorporation of Quality by Design (QbD) and risk-based approaches*
  - *Regulatory alignment*
  - *Application of the Parametric Tolerance Interval Testing (PTIT) concept*
  - *Scope of Guidance application and implementation*
- *In addition, IPAC-RS provided a list of other specific comments as part of the overall set of comments.*

Incorporation of QbD and risk-based approaches

- *IPAC-RS appreciates FDA's inclusion of QbD and risk management principles into the Draft guidance.*
- *Further clarification is needed in terms of how to apply those ICH principles to the device part of the medicinal product*
- *Prescriptive requirements for development and testing included in the Draft guideline do not align with the ethos of using QbD approaches that could justify other control strategies for the product → Specific examples could be beneficial and IPAC-RS has offered help to FDA to provide these*
- *IPAC-RS encouraged FDA to extend risk management approaches to design changes during development of Metered Dose Inhalers (MDIs) or Dry Powder Inhalers (DPIs) occurring after the initiation of pivotal clinical trials in order to determine if in-vitro and/or in-vivo evaluation of the change is required*
- *IPAC-RS also proposed a number of new approaches that when adequately justified would support innovation → Abbreviated Impactor Measurement (AIM), Efficient Data Analysis (EDA) throughout the lifecycle, moving the spray pattern upstream, etc.*

Regulatory alignment

- *IPAC-RS welcomes the references to international guidelines, standards and industry best practices → IPAC-RS interprets this as a move to accept internationally agreed standards and approaches.*
- *IPAC-RS recommends that the FDA reference other recently published FDA Guidance on Human Factors in combination products in sections that discuss development or risk management.*
- *The technical and statistical terminology used should be aligned to appropriate consensus standards or should be explicitly defined to facilitate understanding by non-statisticians.*

Application of the PTIT concept

- *The inclusion of the PTIT as an alternative statistical approach to the counting test for assessing the delivered dose uniformity of MDIs and DPIs product batches is supported by IPAC-RS.*
- *But further detailed dialogue has been requested by IPAC-RS regarding the confidence, coverage proportion and limits proposed in the updated guidance*

Scope of Guidance application and implementation

- *The Draft guidance is clear about FDA's intent to apply it to both New Drug Applications (NDAs) and Abbreviated New Drug applications (ANDAs) also encouraging its applicability to both products in development and legacy products in post-marketing lifecycle management.*
- *However, IPAC-RS notes several examples that illustrate tensions in the application of the Draft guidance across the different stages of the product lifecycle, and differences in requirements for NDAs and ANDAs.*
- *As new requirements are recommended in the updated Draft guidance (eg: temperature cycling, in-use storage, etc), IPAC-RS requested a suitable transition or implementation period where both existing and new recommendations are acceptable.*

Other significant comments

- Recommend removing the listing of the potential CQAs/tests for drug substances and instead outline the need to identify and characterize attributes of the drug substance (as per any other formulation type)
- Terminology around container closure/device constituent parts needs to be clear and consistent and aligned with other FDA guidances
- More detailed discussion on the requirements outlined in 21 CFR Part 4 and how they apply to combination products such as MDIs and DPIs would be helpful
- Prescriptive identification of which components are “critical” in the absence of methodical approach is arbitrary and not consistent with the expectations of CDRH

Other significant comments (Cont)

- Text should focus on regulatory requirements or recommendations rather than extended discussion related to general information/observations on developing a formulation
- Rather than stating the device constituent part should be verified initially and on an annual basis by the applicant, applicants should be able to follow their own individual quality systems that provide supplier oversight
- The list of typical development and release/stability tests are misleading as they reads as ‘requirements’; it should be clarified that only applicable tests are needed and a justification for omitting a test is NOT required

Other significant comments (Cont)

- IPAC-RS continues to support the use of a suitably justified mass balance criteria as a system suitability requirement for APSD assessments, but does not support the application of mass balance limits as specification acceptance criteria
- The relationship between/requirements for USP <87> and <88> and ISO 10993 for the device constituent part should be clarified
- Stability conditions should be aligned with ICH (eg where protective secondary packaging is used, the routine stability test storage condition for the product in the presentation intended for distribution should include 30ºC/65 percent RH for one-half of the proposed expiration dating period; which is inconsistent with ICH Q1A (R2)

Summary

- *IPAC-RS generally very positive of the FDA efforts to provide an update to this guideline and to incorporate stakeholder feedback*
- *The comments raised are complex and significant in number. Therefore, IPAC-RS is hopeful that FDA will agree on organising a public workshop to discuss these comments in more depth*
- *Next steps → FDA review and consideration of all stakeholder comments, update of the draft guidance and issuing of a further draft or the final text for implementation in 2019; depending on the significance of the comments*

Backup Slides

All slides will be posted on the IPAC-RS website after the workshop.

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