QUESTIONS DISCUSSED DURING THE ALTERNATIVE PROPELLANTS WORKSHOP ON OCTOBER 11, 2023

This workshop was organized by IPAC-RS and included speakers from industry, US FDA, and EMA/MPA. The workshop's program, speaker bios, and recording are freely available at IPAC-RS Workshop: Transition to LGWP Propellants for MDIs.

1. ***How can a generic be approved if it is submitted before the reference is switched to the new propellant? Could the comparison be to the existing product?***

EMA will want to see a reference product that has been approved and supported by file. Reference product should be an approved product. Once that reference product has gone through the transition, the generic will have no old comparator on the market, and then it would be appropriate for the generic to transition to a new propellant. If they are developed in parallel, EMA might consider data that was started before the transition with comparison to the old product.

This is an important question that FDA needs to decide, i.e., what constitutes the reference listed drug, is it the current propellant or the next generation propellant or is it both?

FDA have started discussions on this, but not worked out any specific position yet, so cannot comment on it now.

2. ***Would a change in propellant trigger the need for a new or updated Notified Body Opinion irrespective of device component changes?***

EMA haven't discussed this yet. The MDR is so new and there are no precedents yet. It may be the subject of a future discussion.

3. ***What are the CMC tests and requirements for spacers?***

In the US if the labeling points to the use of a spacer, then need to have data to support that.

If label says use a spacer in specific populations, then there is a need to do characterization studies with that spacer to compare to no-spacer. If the spacer is part of the actuator, that's a unique situation. If the label is silent on use of a spacer, CDRH clears individual spacers separately for general use and in that case there are no requirements for testing the MDI for the multitude of spacers that are out there.

EMA will require spacer data. Details are already in the guidelines, there is nothing new.

4. ***How does the robustness of statistical analysis data link to the amount of stability data?***

The IPAC-RS survey question on use of statistics was focused on what statistics should industry be doing i.e., PSG vs PBE. Then in the stability survey question, there were responses that said only 3 months of data may be required (assuming all the other data were showing BE). However, you have to have adequate stability to demonstrate these new propellants would be stable over the long term.

Overall, there is a need to follow ICH Q1A and Q1E, which recommends 12 months data to establish a shelf life. FDA wouldn't treat it differently from another MDI submission.

5. ***Regarding mechanisms to compensate for differences in densities of the propellants, increasing metering chamber size or other parameters of the product was mentioned. Does the panel have an opinion on the preferred option?***

Firstly, there would be a need to assess what isn't working. Either option may lead to other issues that have to be addressed. The panel generally agreed that starting with adjusting concentrations may be more feasible, but may require both changes to achieve the goal. Try to use the approach that is most straightforward but also consider whether two smaller changes may, or may not, be more beneficial than one large one.

6. ***Dr Bertha mentioned in his talk comparable DDU and APSD within 10%, stability data no new safety concerns or HF considerations. Is the Agency developing guidance for sponsors?***

FDA are currently not developing a guidance, but may eventually do this. From a CMC perspective, there will be no requirement to compare old pMDI to new pMDI. The new product will have to stand on its own data. However, if in vitro data are a good match, then it is expected in vitro lung deposition might be similar. So this might be something that will allow some relief in PK/PD data, but that is a question for those disciplines to address.

7. ***Can we rely on nonclinical data from the manufacturer of the propellant with no nonclinical studies required by pMDI manufacturer?***

EMA have addressed this, and want the data, but it doesn't matter who generates it. The same data set can be sent in by multiple companies, and it's up to them to work together. It is up to the companies as to how this is done.

8. ***Bridging toxicology, not in EMA Q&A document. Will additional guidance be issued?***

This is not a concept used in EU, and won't be in the future either.

9. ***On innovator products that are looking to demonstrate in vitro equivalence, what are the thoughts for particular in vitro BE expectations? PSG? PBE of key CQA? Or Definition of significant change?***

In the US the Product Specific Guidance (PSG) is meant for BE in generic realm where the product is a copy of the RLD, so not really applicable here. The new product needs to stand alone from a CMC perspective and doesn't need to show equivalence. There may be requirements from the other review disciplines, as this has not yet been worked out and as mentioned if in vitro equivalence can be demonstrated it would suggest in vivo BE. Best approach is to discuss with FDA, case-by-case.

For EMA quality characterization data packet is the same as changing the product. Therapeutic equivalence will have the same criteria as for generics.

10. ***What would be considered similar and what would be considered different for the delivery device itself?***

In the US, materials of construction and critical dimensions of the device such as the orifice diameter, cone angle, spray pattern, etc. would likely be significant and should be within the 10% criteria outlined in the 2018 Guidance. FDA use the criteria in the guidance to assess these types on changes by reviewing the data pre- and post-change. If the data are outside those accepted ranges, then the change could be supported by PK data.

Some companies may have a fear that showing no change in in-vitro data, may be questioned as potentially due to analysis sensitivity. The advice from FDA is to ensure all aspects of the change are considered, for example if an orifice size was changed, the company should not just consider APSD, but need to assess all aspects including clogging, cleaning for example.

11. ***It needs to be expedient to ensure access to patients. Is there flexibility related to CMC content, such as batch size for clinical/ stability, number of batches, risk assessments, etc.***

As part of the survey there were comments, that industry are looking seeking clarity on whether there might be any flexibility to ensure programs are initiated quickly, without having to wait for final equipment to be ready, for example.

FDA suggested that this might be a question for the Office of Pharm Manufacturing Assessment to address FDA Office of Pharmaceutical Manufacturing Assessment.

As an aside, be aware that changes in the colorants of the actuator may change electrostatic properties and may impact extractables.

12. Where can international harmonization of requirements be aligned?

EU and FDA have taken different views historically on registration requirements of generics, and it's unlikely that there will be alignment on this. It would require a large effort and currently there are no such initiatives in this area.

ICH and/or Pharmacopeias could look at something like this, but both would take a long time.

13. What can industry do to enhance the global expectations and streamline the data packages?

Continuing the conversations is crucial, and engaging in broader areas (such as PK and PD) and topics. There are intentions that IPAC-RS will continue these types of workshops to further the understanding on these LGWP propellant products.

14. As this transition is not as complex, so are there any data requirements 'out of scope' from a safety and efficacy perspective?

In-vitro still need to look at everything; EMA have covered requirements for EU.

15. How do we file excipient safety data if there is no DMF in EU?

In EU there is no system to register clinical/non-clinical data via a master file, but believe that companies could make agreements between themselves. The same information can be submitted by several companies. There is no reason why a propellant supplier, could not create a "master file" that can be used by their customers.

16. How does industry know the excipient has transitioned from 'Novel' to 'Established' in EU? Is there a communication that comes out that says when the excipient transitions from novel to established?

There is no specific system for this, but industry can just ask.

17. Should we expect review of current products with HFA be slowed down to prioritize review/approval of Low GWP products?

Both EMA and FDA confirmed that everything is the same and gets reviewed per regular timelines.

18. What is considered to be the preferred approach – removing existing excipient or adding a new excipient as part of the propellant change?

Removing things tends to be less onerous from a regulatory perspective; but if adding something improves the performance/achieves goals then that may be the best approach.