

Track C: 'In-Vitro Only' Equivalence

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Issues Presented for Discussion

- Device design
- Pooling of particle size distribution data
 - Criteria for impactor stage groupings
 - Alternate sizing techniques
- IVIVC
 - Allowable limits of in vitro measurements to support bioequivalence
 - Variability in in vitro metrics for brand product
 - Physicochemical considerations
- Acceptability for pooling or harmonization of data from EU, Canada, US



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Themes that came up during discussion

- Distinguishing testing for 'similarity' versus 'therapeutic equivalence'
- 'Clinical relevance and ability to model what happens *in-vivo*' versus 'characterization of product performance'
- '*In-vitro* only' is an option, but not a common one; limits are conservative



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1 - Device Design

- The EMA and Health Canada guidance appear to be written with the assumption that any generic/second entry product will use a device that is the same as or very close to the original.
 - Why should design change be unacceptable if ED and PSD same as Reference Product
 - There are concerns regarding patient interface issues.
 - It is hard to be the same for a DPI .
- Should the guidance distinguish between the cases of a "same" device and different devices (but same formulation) and clarify the *in-vitro* & clinical requirements in both situations?
 - EMA guidance makes this distinction already.



Track C '*in-vitro* only' equivalence 2 - Stage Groupings

- Purpose of grouping of data
 - For QC or for estimating lung deposition
 - How to characterize *in vitro* those elements of the aerosol that contribute to clinical efficacy
- How to determine which impactor stages to combine
- Limits on differences for each stage: $\pm 15\%$
 - Dependent on amount of API sampled and API per stage
- Are we missing information about the aerosol by grouping PSD data



Track C '*in-vitro* only' equivalence 2 - Stage Groupings

- Concerns regarding losing information by grouping
- Need scientific justification of selection of groupings rather than those of convenience
- Other options discussed included using modified Human Respiratory Tract (HRT) impactor approach or MMAD
- Concerns on how to treat very low levels on stages
 - Variability between impactors; within reference product
- Differential mass weighting may be helpful in evaluating distributions



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3 - Alternate Sizing Techniques

- Likelihood of acceptability of alternative *in vitro* methods (e.g., alternative particle sizing techniques) incorporating
 - Simulation using patient-relevant flow patterns
 - Useful to incorporate but not sure about methodology
 - What flow rate(s) to use for DPIs and is flow rate or acceleration in flow rate the important parameter?
 - Induction port design
 - A lot of passion in the discussion on ports.....
 - Electronic lung
 - Does permit use of patient profiles but expensive compared to a standard impactor
 - Acceleration profiles
 - Acceleration in flow rate may be important for some DPIs



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4 - IVIVC

- IVIVC
 - Are the *in vitro* tests clinically relevant
 - Are there sufficient data correlating *in vitro* (stage groupings) with clinical outcomes
 - What do *in vivo* clinical tests tell us about regional deposition and response
 - We are not there yet but it would be helpful for justification of selection of tests and groupings.



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5 - Physicochemical Considerations

- Need methodologies for *in-vitro* testing if small differences exist (e.g., crystal structure) for drug product and excipients
- Microscopy
- Morphology, surface energy, specific surface area, shape, amorphous content
- Dissolution testing for some molecules
 - Useful during development



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- Are there practical situations when “*In Vitro Only*” tests would be sufficient for the approval of
 - Generic/second-entry product
 - Generally no! But maybe (solution based) MDIs.
 - Change in an approved product (e.g., manufacturing equipment change)
 - This depends on the kind of change.



Track C '*in-vitro* only' equivalence Finally....

You can always do PK!

Questions?