Breakout Session A

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Q1. Can IVIVC play a role in QbD of MR formulation?

- Input from both in vitro dissolution and in vivo PK studies can aid with developing a robust formulation.
- IVIVC is fundamental to QbD because it allows a link to the patient.
- Both generic and innovator firms have historically been concerned about QbD because the objective in drug development is optimal design of the product.
Q1. Can IVIVC play a role in QbD of MR formulation? (cont’d)

- FDA encourages industry to submit QbD information in order that regulators can understand the process and thinking underlying the development of the final formulation for marketing.
Q1. Can IVIVC play a role in QbD of MR formulation? (con’t)

• Development of QbD represents evolution of thinking of regulators and drug developers; QbD-like principles (“the process is the product”) were traditionally used by engineers and by developers of biotech products

• The QbD approach is particularly helpful in the development of formulations of poorly-soluble drug substances
Q1. Can IVIVC play a role in QbD of MR formulation? (con’t)

• Incorporating IVIVC into QbD allows developers to rely on the dissolution method to move within the Design Space while maintaining relevance in vivo.

• Incorporation of IVIVC into QbD can help to answer the question of whether a dissolution method is able to predict what happens in vivo – in other words, is the dissolution method biorelevant?
Q2. Should priority be given to review of submissions containing IVIVC data?

- Both discussion groups concluded that the answer to this question should be “NO”
- However, the incorporation of a robust and scientifically-sound IVIVC in a QbD submission could benefit the applicant if it facilitates the process of making the regulatory decision in a timely manner
Q3. Should IVIVC be part of QTPP?

- It is very difficult to establish a solid Level A IVIVC
- Some firms have begun conducting IVIVR as a way of developing an in vivo-in vitro association during development
- IVIVC and IVIVR can be useful when used toward the end of the development process to justify changes in formulation or manufacturing site
Q3. Should IVIVC be part of QTPP? (cont’)

• An IVIVC means additional work at the outset but in the long run it can be highly useful in reducing regulatory burden if submitted to support manufacturing, process, and site changes

• A large advantage to having an IVIVC established is that if changes take place during the life cycle of a product, there is no need to conduct additional in vivo BE studies
Q4. Should IVIVC be performed in patients or healthy subjects?

• Both groups agreed that healthy subjects should be used for IVIVC, except in the cases where safety precludes administration to healthy subjects.

• The objective of an in vivo BE study is to compare the product performance; the rate and extent of release from the formulation.

• Thus, under the above definition, two BE products will have the same effect in patients.
Q4. Should IVIVC be performed in patients or healthy subjects (con’t)?

• A discussion of whether IVIVC should be based on fed BE studies concluded, that, in most cases, food makes drug absorption more complicated, therefore, a fasting BE study is more discriminating about product performance.
Q4. Should IVIVC be performed in patients or healthy subjects (con’t)?

• A discussion of whether pharmacodynamic endpoints should be used rather than PK endpoints focused on the following points
  – The PD endpoint may lag substantially behind the PK endpoint, making a correlation challenging
  – Drug receptors associated with the therapeutic response may not be the same as those associated with toxicity
  – Drug plasma concentrations are most likely the best surrogate for safety and efficacy
Q4. Should IVIVC be performed in patients or healthy subjects (con’t)?

- A final discussion raised the issue of how an IVIVC should be related to drug release specifications in a USP monograph for a product