Application of IVIVC in Formulation Development

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**In Vitro - In Vivo Correlation**

- It is a functional or qualitative relationship between *in vitro* dissolution and *in vivo* bioavailability parameters.

- An optimum correlation is one in which *in vitro* dissolution is predictive of *in vivo* behavior of various lots of products in target population.
**In Vitro - In Vivo Correlation**

**Parameters**

- *In Vitro:* Dissolution profile, amount dissolved in specified time, dissolution rate.
- *In Vivo:* Cmax, tmax, AUC, Ae % absorbed vs. time
- Technique: Deconvolution, Moment Theory

Knowledge of GI physiology, rate limiting step in absorption and site(s) of absorption may also help in in vitro - in vivo correlation determination.

Products differing in *in vivo* performance and in *in vitro* performance are essential to establish correlation.
**In-Vitro - In-Vivo Correlation**

- **Correlation:**
  - One or more of *in-vivo* parameters are correlated with *in-vitro* release parameter of the product. This involves products which differ in *in-vivo* as well as *in-vitro* performance.
  - Differences in *in-vitro* release profile are reflected in differences in *in-vivo* performance of the product.
  - Minimum three products needed to see the correlation
  - With two products, it is rank order relationship.

- **Association:**
  Acceptable *in-vivo* data are associated with acceptable *in-vitro* performance of the product.
In vitro - In vivo Correlation

**Level A**: Estimated by two stage procedure
- Deconvolution followed by comparison of the fraction absorbed to the fraction dissolved
- Represents a point to point relationship
- Generally linear and most useful

**Level B**: Estimated by utilizing the principles of statistical moment analysis
Mean *in vitro* dissolution time compared to mean residence time or mean *in vivo* dissolution time

**Level C**: Single point correlation
One dissolution time point to one pharmacokinetic parameter.
Genesis of the Workshop

• Origin of IVIVC – 1980s
  – IVIVC Workshops
    (1) 1985, Report- Pharm Res 4, 75-77, 1987;

• FDA Guidance in 1997
Application of IVIVC in Formulation Development

- Effective utilization of IVIVC concept. Workshop offers possible ways to overcome problems through effective utilization of IVIVC data.
- IVIVC is an important tool in development and evaluation of pharmaceutical dosage forms, especially Modified Release dosage forms.
- Contribute in development of quality of pharmaceutical products.
- FDA Guidance (1997) – Scientists indicate that it is not easy to establish IVIVC based on existing guidance.
- An interactive workshop – exchange between speakers and participants.
Potential Constraints in Establishing IVIVC

• Concerns –
• Difficult to develop and implement IVIVC
• Practical use of IVIVC
• Can the existing tools be used to establish product specifications?
For Discussion

• An empirical approach to a MR Formulation development is to retard the rate of release of the active ingredient, ideally, in a controlled and predictable fashion from a concept formulation.

• A minimum 3 formulations with different rate of release.

• Early BA studies to ascertain the potential IVIVC correlation.

• Adjusting rate of release from and fine-tuning the desired formulation.

• Repeat BA and or BE study to confirm result.
Bioavailability and Bioequivalence

• BA and BE parameters are meaningful if they can be used to determine product specifications and production criteria.
• In-vitro analytical specifications and product profile (attributes) will have to reflect in-vivo characteristics of the product.
• Statistical approaches will assist in a safe way of translating in-vivo data to in-vitro specifications
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Objectives

• Review the current status of IVIVC
• Discuss applications and potential benefits of IVIVC
• Review and evaluate different methodologies and their potential use in IVIVC Assessment
• Assess advantages and limitations for IVIVC in formulation development – when and how it may be established.
• Develop the basis for a summary paper on IVIVC and publication as a PQRI document.
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Program – Day 1
• Foundation and Advantages in IVIVC
• New methodologies Assessment
  – Simulation of IVIVC
• Breakout Sessions (4, A-D)

Program – Day 2
• Application of IVIVC
• Breakout Sessions (4, E-H)
• Where do we go from here?
• Conclusions and Next Steps