Session 2: High Risk Drug Products – IVIVC and IVIVR

Overview

- **High-risk drug products, with particular emphasis on extended-release (ER) formulations and immediate-release (IR) products utilizing complex solubilization technologies.**

- **Developing and applying In Vitro-In Vivo Correlations (IVIVC) and In Vitro-In Vivo Relationships (IVIVR) to ensure product quality and bioequivalence.**

1. Dr. Rajesh Savkur (FDA) - Defining BE Safe Space Through IVIVC/IVIVR

High-Risk Product Classification:

- ER Products: Release mechanism serves as the rate-limiting step for absorption. Minor formulation modifications can substantially alter pharmacokinetics (PK). Risk escalates progressively from matrix tablets to osmotic pump systems.
- IR Products: Complex solubilization technologies including amorphous solid dispersions, nanoparticles, and lipid-based formulations result in formulation-dependent bioavailability profiles.

Regulatory Strategy:

- Level A IVIVC is the preferred approach for BCS Class 1/3 ER products.
- Multiple Level C or PBBM-based approaches are recommended for BCS Class 2 ER and complex IR products.
- Very high-risk products, including narrow therapeutic index (NTI) drugs and those with complex mechanisms, require in vivo studies as the default approach.

Case Studies:

- IR product with amorphous solid dispersion: Multiple Level C IVIVC successfully established clinically-relevant dissolution criteria.
- ER product: Level A IVIVC provided support for biowaiver approval of a Level 3 manufacturing site change.

2. Dr. Yihong Qiu (QPD Solutions) - Linking Dissolution to Performance for ER Products

- IVIVC/R serves as a critical bridge between in vitro drug release and clinical performance, facilitating science-based lifecycle management decisions.
- Comprehensive understanding of API properties, formulation design, and release mechanisms is essential for developing predictive dissolution methodologies.

Methodology:

- In vitro test conditions should be adjusted to align with in vivo apparent absorption when discrepancies are identified.
- Emphasis on USP apparatus suitable for quality control (QC) testing rather than complex multi-compartment systems.

Case Studies:

- NTI ER product: Developed Level A IVIVC using a modified dissolution method. This approach successfully detected polymer quality drift that the initial method would have missed, preventing potential clinical impact.
- Weak acid sodium salt ER: Addressed challenges including salt disproportionation and absorption window limitations. Developed a biphasic dissolution method that mimics in vivo absorption conditions.

3. Dr. Sanjaykumar Patel (Merck) - High-Risk IR Products (ASDs)

Control Strategy for ASDs:

- Maintain drug in amorphous state throughout shelf-life through robust manufacturing processes and stringent moisture control.
- Sink conditions provide an effective starting point for dissolution method development.

Case Studies:

- **QC Method Development:** Selected dissolution media (1.5% Brij 35) based on clinical relevance studies that demonstrated sensitivity to hardness and moisture variables.
- **Crystallinity Impact:** Studies showed that up to 10% crystalline content impacted dissolution profiles but demonstrated no significant effect on Cmax or AUC in clinical studies.
- **Manufacturing Process:** Level C IVIVC established critical linkages between critical process parameters (CPPs), critical material attributes (CMAs), and in vivo performance to support moisture control strategy.
- **DoE Approach:** Dissolution modeling established direct relationships between spray-dry conditions, compaction force, tablet hardness/moisture, and in vivo performance outcomes.

4. Dr. David Sperry (Eli Lilly) - ASD Dissolution Control Strategy and Safe-Space

Product Characteristics:

- Drug with very low aqueous solubility and low permeability formulated as an IR amorphous solid dispersion.
- Multiple studies confirmed no crystallization risk in the formulation.

Dissolution Method Development:

- Selected conditions: pH 6.8 with 1x% SDS, 75 rpm paddle, chosen for robustness.
- Mechanistic studies identified tablet erosion as the rate-controlling mechanism.
- Method effectively discriminates for solid dispersion drug load, disintegrant level, and tablet solid fraction.

Safe-Space Establishment:

- Dose-proportional exposure (AUC and Cmax) observed across the strength range despite strength-dependent dissolution rates.
- Demonstrates that absorption is not limited by dissolution or solubility within this dose range.
- The range of dissolution rates across strengths represents a validated safe space for establishing specifications.

Common Themes

Mechanistic Understanding:

All presentations underscored the importance of understanding release mechanisms, API properties, and formulation design as the foundation for successful IVIVC/R development.

Clinical Relevance:

Dissolution methods and specifications must be anchored in clinical data that clearly demonstrates safe-space boundaries and ensures patient safety.

Lifecycle Management:

IVIVC/R enables science-based post-approval changes, supports biowaivers, and ensures quality assurance throughout the entire product lifecycle.

Risk-Based Approach:

Higher-risk products necessitate more extensive characterization and rigorous validation of in vitro-in vivo relationships to ensure product quality and therapeutic equivalence.

Break out sessions-B (High Risk Drug Products-IVIVC/IVIVR)

Group B-1 (Dr. Arthur Okumu, Dr. Philippe Berben and Dr. Tessa Carducci)

1. What unique dissolution method capabilities are needed for high-risk IR products (eg. ASDs)?
2. What are the necessary data requirements in establishing clinical relevance/IVIVR/safe space for high-risk IR and MR DPs?

Group B-2 (Dr. Hansong. Chen, Dr. Siddhi Santosh Hate, Dr. Susan Ewing)

1. What are minimum and preferred data requirements to justify a dissolution method of a high-risk drug product?
2. What are challenges in establishing clinical relevance for high-risk IR and MR DPs?

Group B-3 (Dr. Ethan Stier, Dr. Filippos Kesisoglou, Dr. Alexander Kubinski)

1. What are the Barriers for establishing IVIVC/IVIVR for high-risk IR and MR products?
2. What unique dissolution method capabilities are needed for a MR product?

Group B-4 (Dr. Haritha Mandula, Dr. Nikolay Zaborenko, Dr. Jing Li)

1. What are the Barriers for establishing IVIVC/IVIVR for high-risk MR products?
2. What are the necessary data requirements in establishing clinical relevance/IVIVR/safe space for high-risk MR DPs?