Bioassays for Establishing Equivalence
Linking API and Formulation to their Biological Effect

Sid Bhoopothy, PhD
Chief Operating Officer
Limited Access; Limited Success

Attributed to lack of generic-

- Topicals
- Ophthalmics
- Locally Acting GI
  + additional CDPs

Slow down of unique generic drug product approvals


In Vitro Based BE

API | RLD | PD Specific

In Vitro
In Vitro Characterization Based Equivalence

- **Input**
  - Active Ingredient & Excipient Attributes
  - Q1/Q2 Similarity

- **Process**
  - Characterization of CPPs
  - DOE for Process Variables
  - Controlled Reproducible Process

- **Output**
  - Formulation Function Characterization

**Target Product Profile**

**Critical Quality Attributes**

**Drug Substance**

**Formulation Variables Optimization**

**Drug Product**

**Q1/Q2 Similarity**

**Q3 Similarity**
Characterization Based Equivalence

Limitations

- Which attributes to measure?
  - Identifying key factors that impact BA

- How to perform?
  - Outcome can be methodology dependent

- Open-ended process optimization
  - Interpretation of differences observed; do they matter?

- No insights on site of action vs. formulation interaction
  - Complex, multifactorial and layered biology
  - API molecular diversity or multiphasic formulations

- Q1/Q2 not possible
  - Unable to use approach; Constraint
Opportunity for Innovation

Therapeutic Equivalence

Integrated Assays

Site of Action ↔ Formulation | Bio-relevant

PK Assays:
- Interaction
- Accumulation

Effect Assays:
- Enzyme upregulation
- Healing biomarkers

In Vitro CBE
API | Excipients | Physicochemical Characterization
Augmented Q3 - Bioassays

Target Product Profile

Critical Quality Attributes

Drug Substance

Formulation Variables Optimization

Drug Product

Active Ingredient & Excipient Attributes

Q1/Q2 Similarity

Characterization of CPPs

DOE for Process Variables

Controlled Reproducible Process

Augmented Q3

Assays to Support Postulated Mechanism of Action

Q3

Formulation Function Characterization

Bio-relevant Tools

Accurate | Sensitive | Reproducible

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Bioassay Development

**Strategy**
- Endpoint, methodology and mode of measurement

**Optimization**
- Various assay parameters
- Physiologically relevant conditions

**Qualification**
- Validation feasible
- Sensitive over a range of concentrations
- Reproducible
- Discriminatory

**Validation**
- Comply with relevant guidelines

**Pivotal Performance assessment**
- Multiple lots of RLD and Test formulations
- Quantitative Comparison
Bioassays - Integrated Effect

- Comparative Physicochemical Characterization
  - Local GI
    Dissolution, pH, viscosity, acid neutralizing capacity, re-dispersibility, specific gravity, PSD
  - Ophthalmic
    pH, rheology, crystalline habit, re-dispersibility, surface tension, osmolality, buffer capacity, PSD
  - Topical
    Crystal habit, rheology, PSD, pH specific gravity, water activity

- Inhibition Bioassay
  - Combined effect of changes to viscosity, dissolution, and specific gravity

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Bioassays - Orthogonal Measures

- Confirmation of the same endpoint using a different assay or methodology
- Closer to the targeted in vivo effect

- Assay outcomes are complementary
- Combined selectivity strengthens assurance of overall conclusions

**Bioassay 1 - Association**

![Graph showing Capacity Constant vs Formulations]

Error bars are the standard deviation of the mean (SD); dotted lines bracket the range of the RLDs.

**Bioassay 2 - Diffusion**

![Graph showing Rate of Transfer vs Formulations]

Error bars are the standard deviation of the mean (SD); dotted lines bracket the range of the RLDs.
Bioassays – Greater Relevance

- Quantify a single formulation property
- Evaluate multi-faceted formulation-related effect mechanisms
- Assess relevant interactions between doses
Bioassays – Mitigate Q2 Differences

- Bioassays represent product effect via multiple mechanisms between doses
- Selective to compositional differences
- May be used to construct a zone of “no bio-impact” with Q2 differences
<table>
<thead>
<tr>
<th>Pathways to Approval</th>
<th>In Vitro CBE</th>
<th>Bioassays- Integrated Approach that links API to Formulation</th>
<th>Clinical Studies</th>
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<tr>
<td><strong>Approach</strong></td>
<td>▪ Product Specific Guidance is required</td>
<td>▪ Independent of Product Specific Guidance availability</td>
<td>▪ Clinical Endpoint</td>
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<tr>
<td></td>
<td>▪ Q1/Q2/Q3</td>
<td>▪ Q1 Similarity</td>
<td>▪ Site of Action PK</td>
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<tr>
<td></td>
<td>▪ IVRT comparison for test and RLD formulations</td>
<td>▪ Q2/Q3 differences may be justifiable</td>
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<tr>
<td></td>
<td>▪ Orthogonal bioassays with in vivo relevance that complement physicochemical characterization</td>
<td>▪ Orthogonal bioassays with in vivo relevance that complement physicochemical characterization</td>
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<tr>
<td><strong>Risks &amp; Probability of Success</strong></td>
<td>▪ Knowledge, capability and experience under progress</td>
<td>▪ In vitro CBE risks mitigated with a “totality of evidence” approach</td>
<td>▪ Time consuming, expensive, potentially inconclusive</td>
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<td>▪ Frequent revisions to guidance based on new knowledge</td>
<td>▪ Knowledge, bioexemption capabilities and experiences are growing</td>
<td>▪ FDA Guidances acknowledge difficulty in approach and requests Sponsors to propose alternative reproducible methods</td>
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<td>▪ Product guidance is a recommendation/guide not a roadmap</td>
<td>▪ Wider product development applicability</td>
<td>▪ Opportunity to innovate to enhance patient access</td>
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<td>▪ Success based on Q1/Q2/Q3 being achieved limits utility</td>
<td>▪ Possible to overcome Q2 and Q3 differences</td>
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