Bioassays for Establishing Equivalence

Linking API and Formulation to their Biological Effect

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ABSORPTION SYSTEMS®

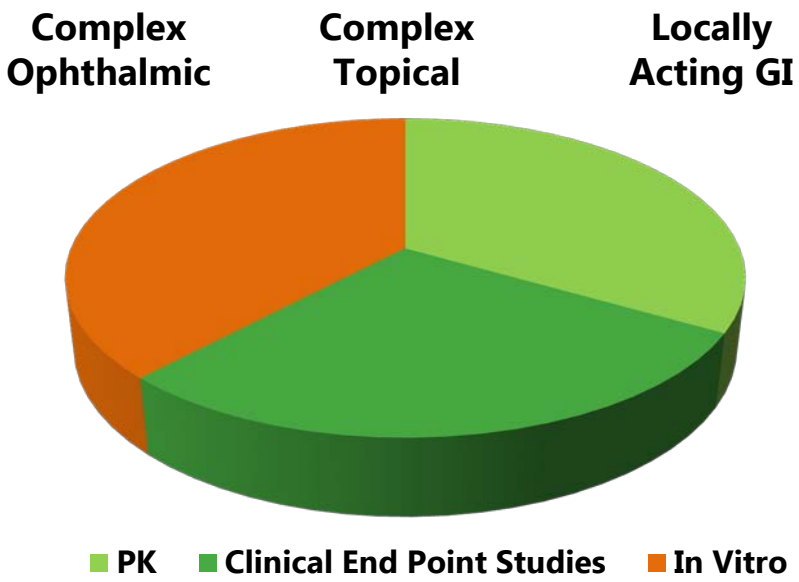
Limited Access; Limited Success

Attributed to lack of generic-

- Topicals
- Ophthalmics
- Locally Acting GI
  + additional CDPs

Slow down of unique generic drug product approvals

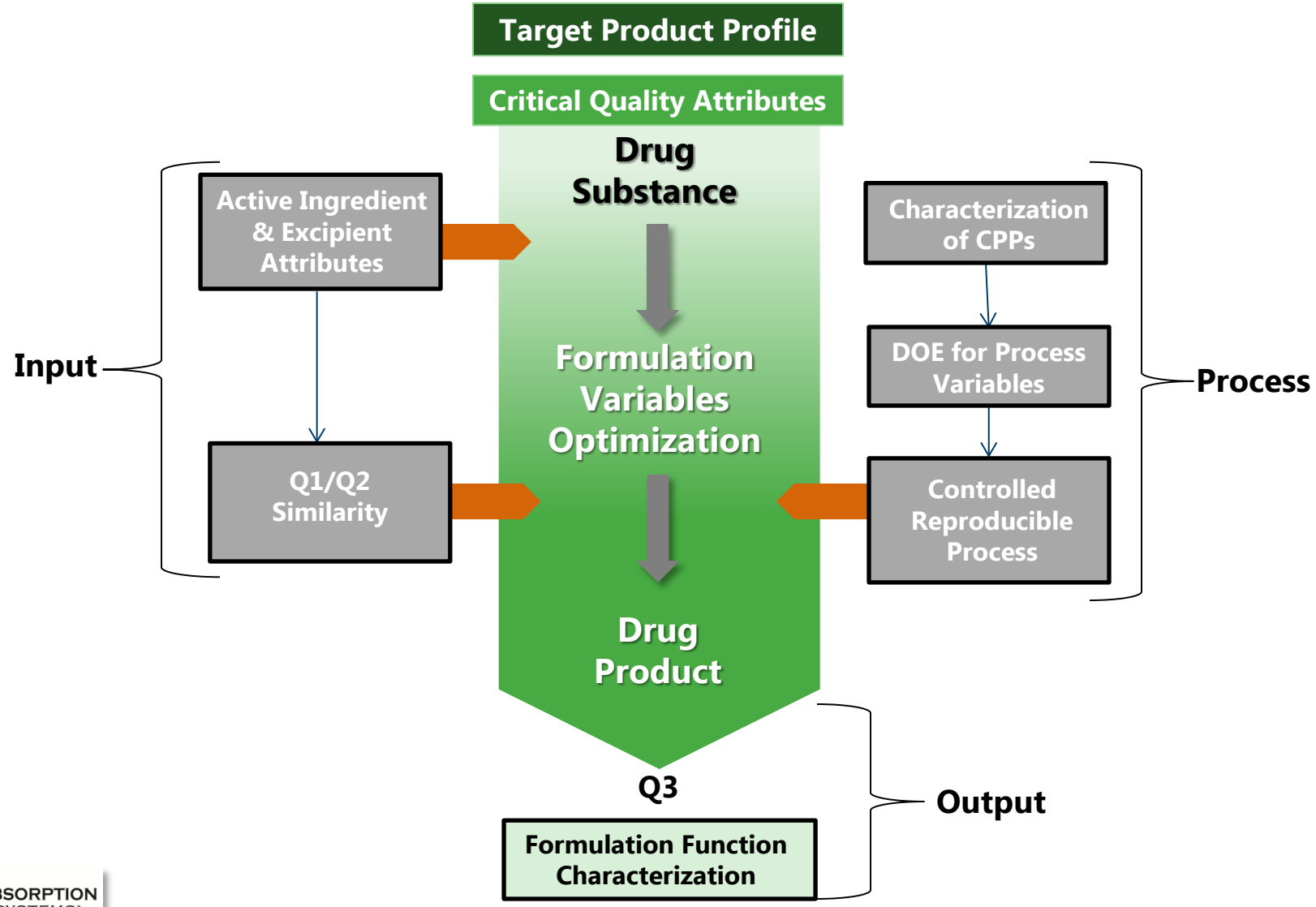
IMS Report: Declining Medicine Use and Costs: For Better or Worse? May 2013 and AAPS Local BE Workshop, November 2016



API | RLD | PD Specific

***In Vitro* Based BE**

In Vitro Characterization Based Equivalence



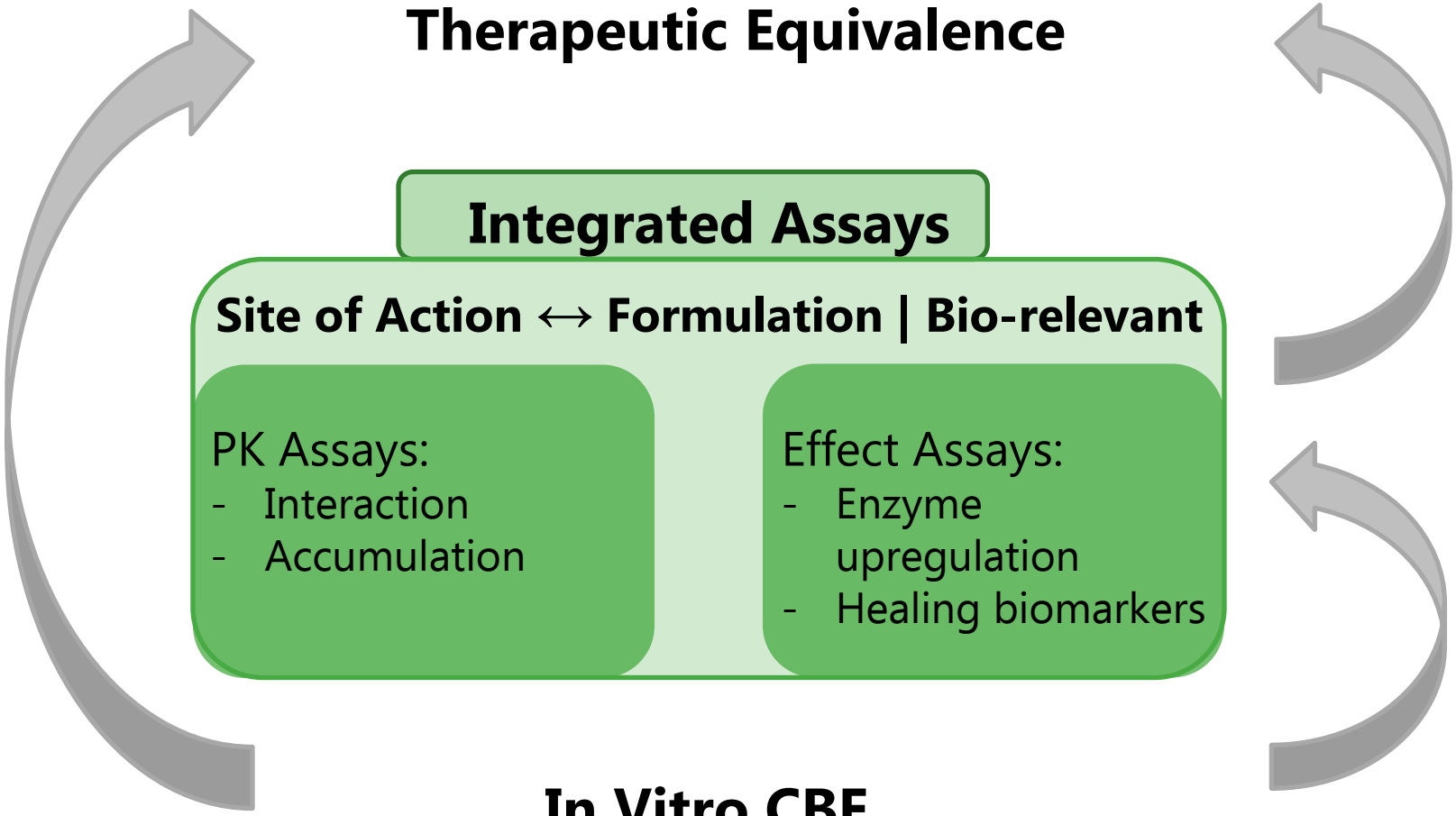
Characterization Based Equivalence

Limitations

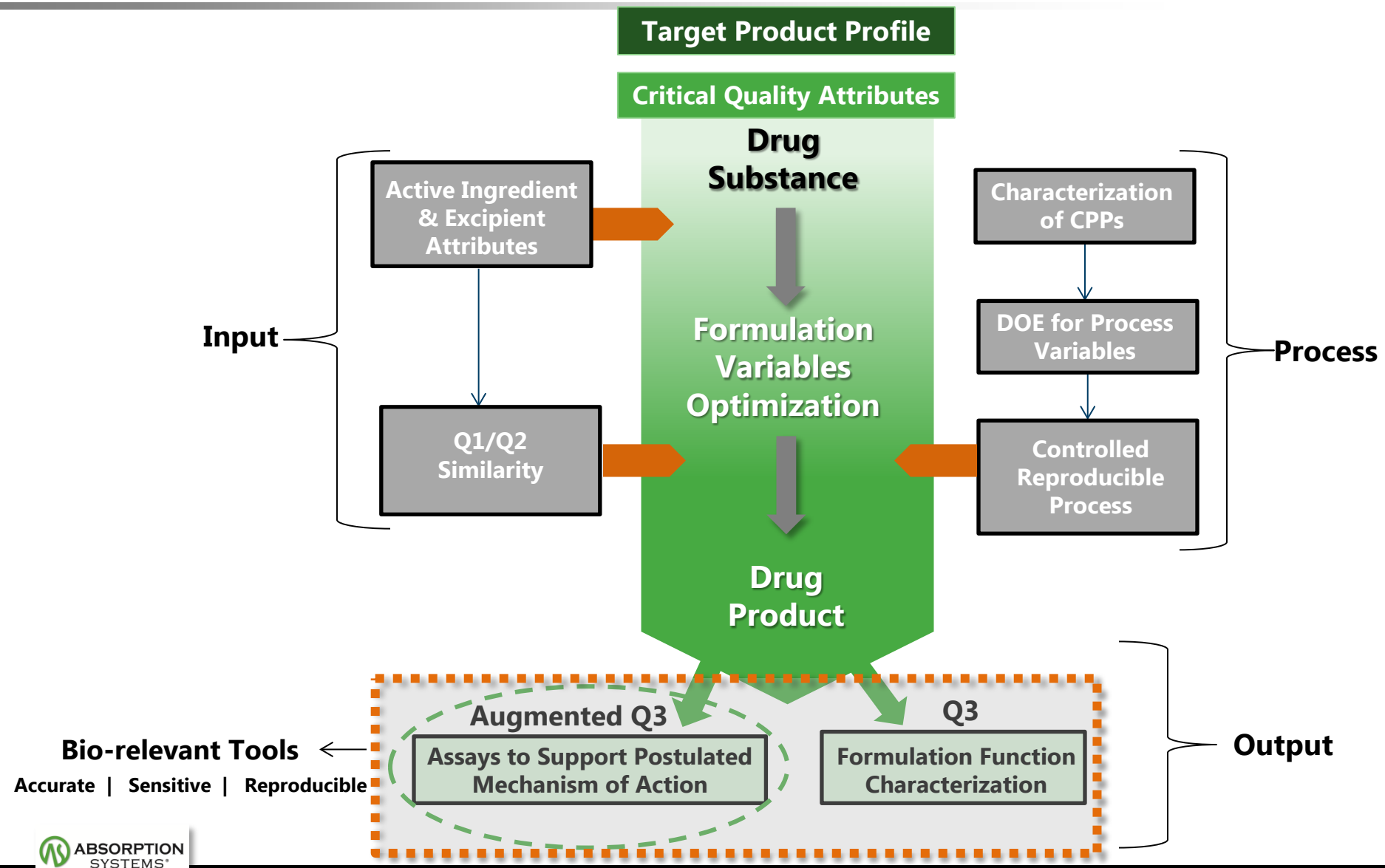
- Which attributes to measure?
  - Identifying key factors that impact BA
- How to perform?
  - Outcome can be methodology dependent
- Open-ended process optimization
  - Interpretation of differences observed; do they matter?
- No insights on site of action vs. formulation interaction
  - Complex, multifactorial and layered biology
  - API molecular diversity or multiphasic formulations
- Q1/Q2 not possible
  - Unable to use approach; Constraint

API | Formulation

Opportunity for Innovation



Augmented Q3 - Bioassays



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

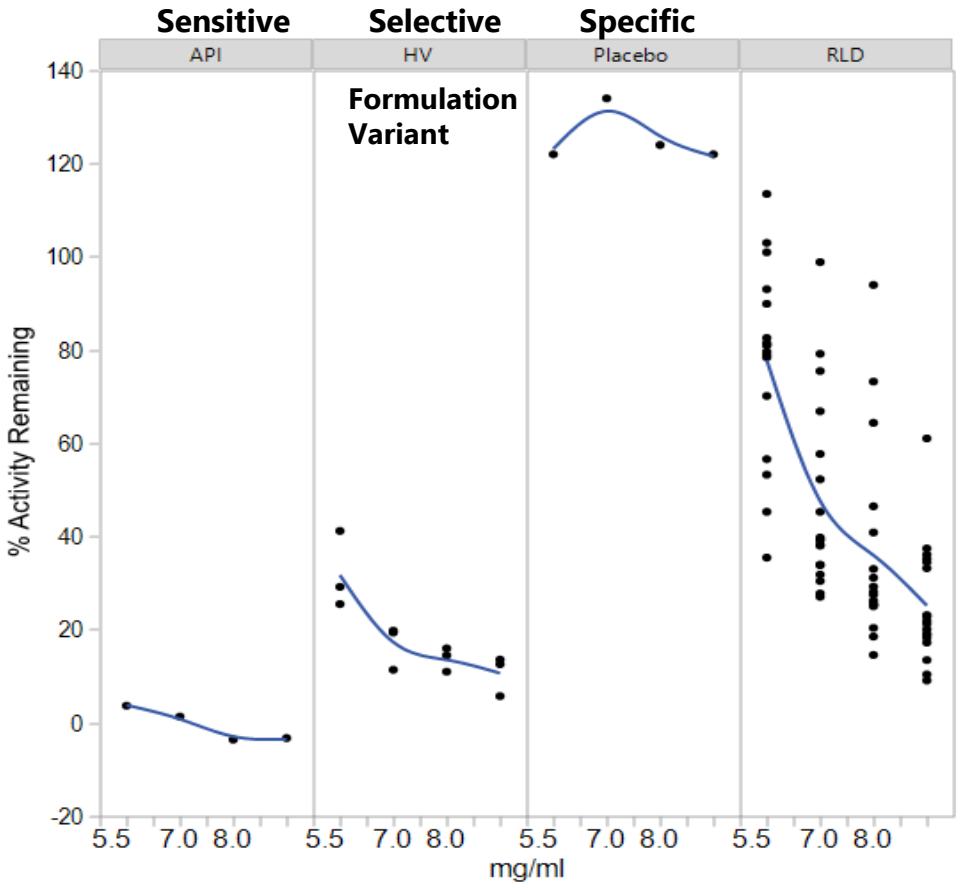
Pivotal Performance assessment

- Multiple lots of RLD and Test formulations
- Quantitative Comparison

Bioassays - Integrated Effect

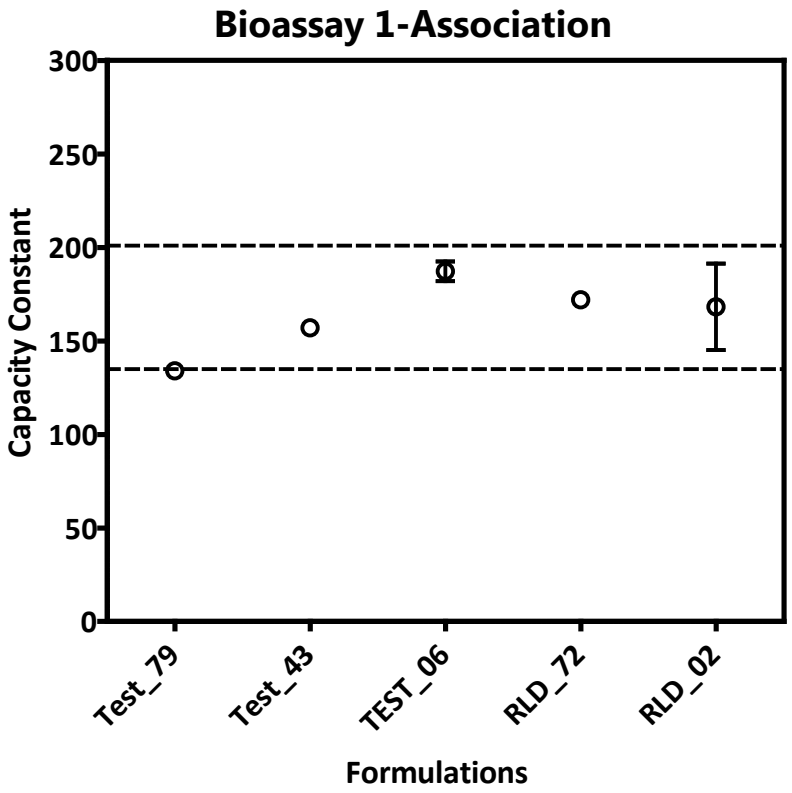
- **Comparative Physicochemical Characterization**
  - **Local GI**
    Dissolution, pH, viscosity, acid neutralizing capacity, re-dispersibility, specific gravity, PSD
  - **Ophthalmic**
    pH, rheology, crystalline habit, re-dispersibility, surface tension, osmolality, buffer capacity, PSD
  - **Topical**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

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



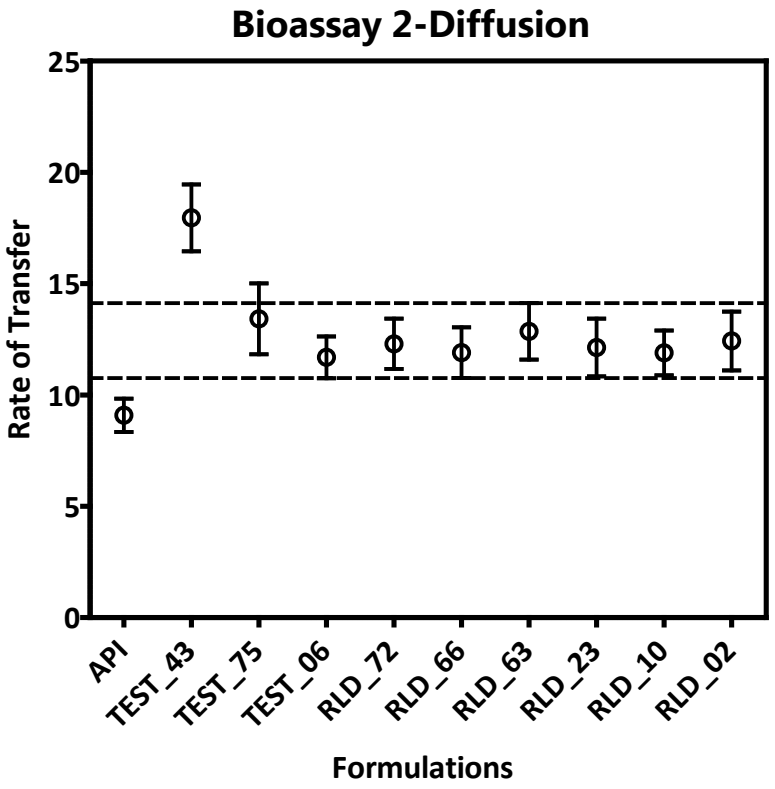
Bioassays - Orthogonal Measures

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



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

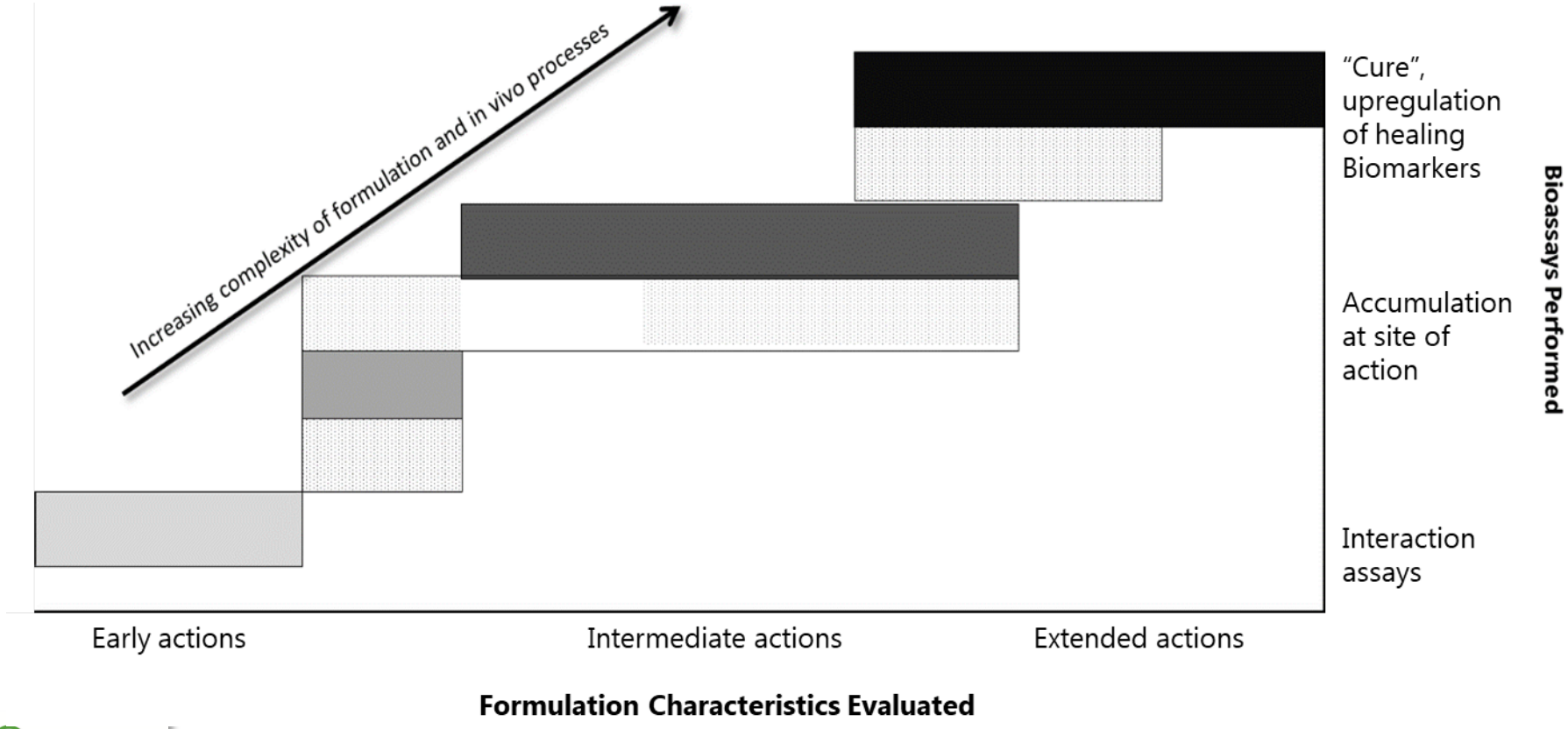
- Assay outcomes are complementary
- Combined selectivity strengthens assurance of overall conclusions



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

Bioassays – Greater Relevance

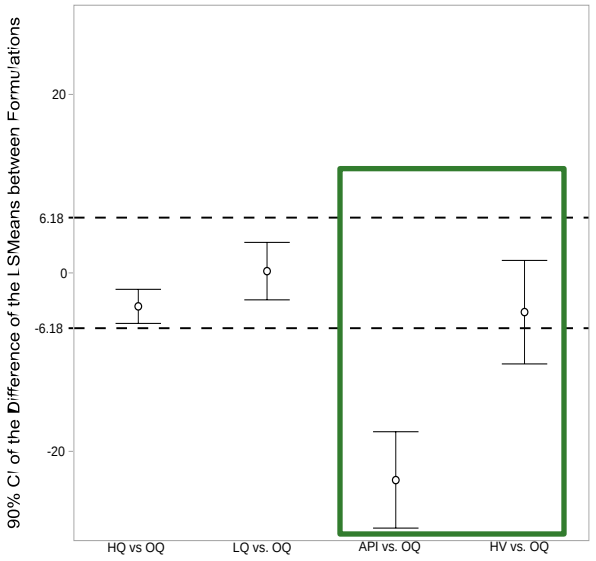
- Quantify a single formulation property
- Evaluate multi-faceted formulation-related effect mechanisms
- Assess relevant interactions between doses



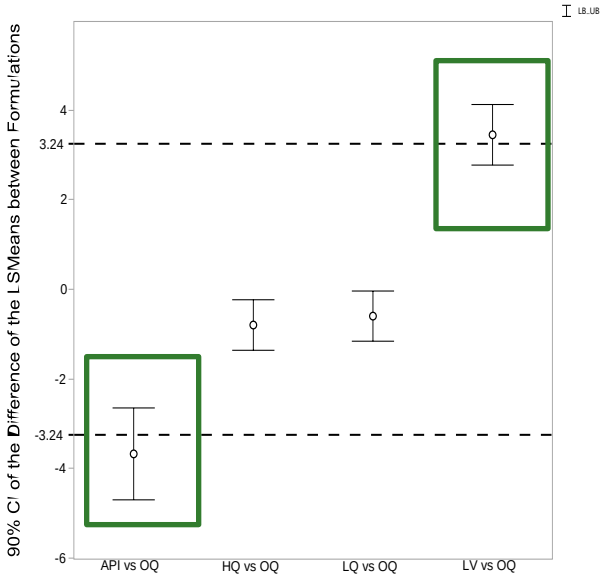
Bioassays – Mitigate Q2 Differences

- 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

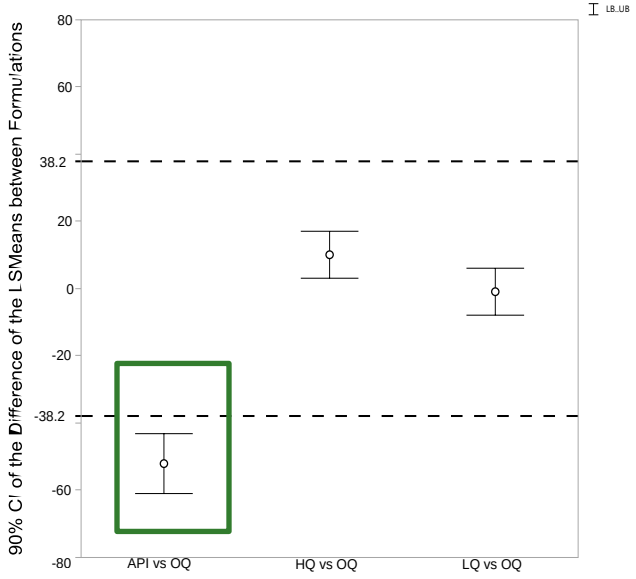
Early Action Bioassay



Intermediate Action Bioassay



Extended Action Bioassay



Pathways to Approval	In Vitro CBE	Bioassays- Integrated Approach that links API to Formulation	Clinical Studies
Approach	▪ Product Specific Guidance is required ▪ Q1/Q2/Q3 ▪ IVRT comparison for test and RLD formulations	▪ Independent of Product Specific Guidance availability ▪ Q1 Similarity ▪ Q2/Q3 differences may be justifiable ▪ Orthogonal bioassays with in vivo relevance that complement physicochemical characterization	▪ Clinical Endpoint ▪ Site of Action PK
Risks & Probability of Success	▪ Knowledge, capability and experience under progress ▪ Frequent revisions to guidance based on new knowledge ▪ Product guidance is a recommendation/guide not a roadmap ▪ Success based on Q1/Q2/Q3 being achieved limits utility	▪ In vitro CBE risks mitigated with a "totality of evidence" approach ▪ Knowledge, bioexemption capabilities and experiences are growing ▪ Wider product development applicability ▪ Possible to overcome Q2 and Q3 differences	▪ Time consuming, expensive, potentially inconclusive ▪ FDA Guidances acknowledge difficulty in approach and requests Sponsors to propose alternative reproducible methods ▪ Opportunity to innovate to enhance patient access