U.S. Food and Drug Administration

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The Use of *In Vitro* Bioequivalence as a Regulatory Approach

Public Meeting - Identification of Alternative In Vitro Bioequivalence (BE) Pathways Which Can Reliably Ensure In Vivo Bioequivalence of Product Performance and Quality of Non-Systemically Absorbed Drug Products for Animals
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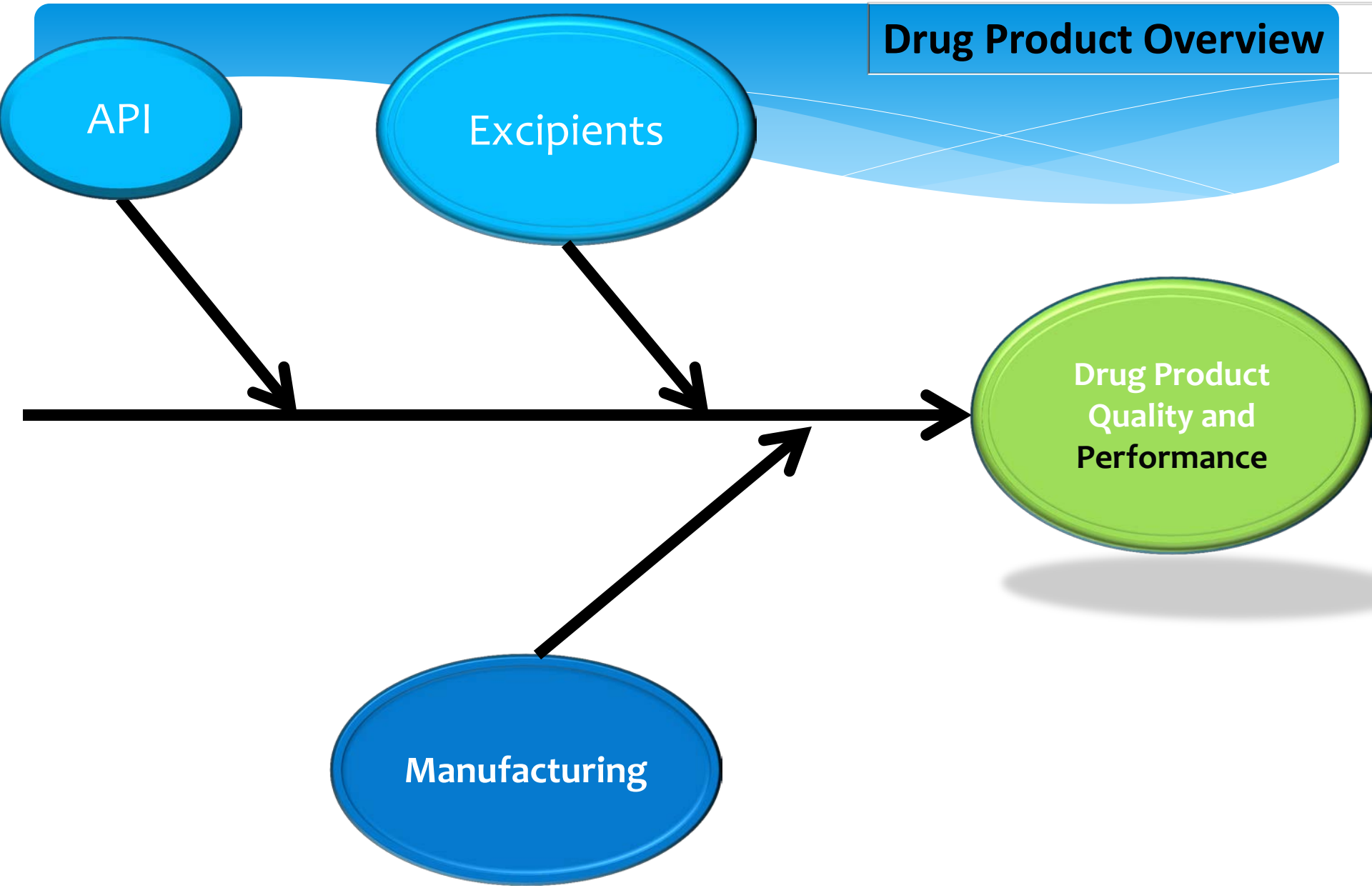
The purpose of the talk is to present a potential pathway for evaluating in vitro bioequivalence. Points being presented are solely intended for discussion and should not be interpreted as guidance.

Outline

Discuss principles of using product formulation and physicochemical characteristics to determine product *in-vivo* bioequivalence (BE) for non-systemically absorbed dosage forms.

Drug Product Overview



In-vitro Bioequivalence

* **Sameness of**
  - ✓ Active ingredient and strength
  - ✓ Dosage form and route of administration
  - ✓ Formulation
  - ✓ **Chemical and physical characteristics**

Points to Consider

* Use a risk based approach that considers the physicochemical properties of the drug product.

* Assessment of sameness of the formulations between the reference listed drug and the proposed product, i.e., Q1, Q2.

* The product should meet the same physicochemical attributes as the RLD, Q3.

DEFINITIONS

Terminology	Abbreviation	Definition
Qualitatively the same	Q1	Test and reference products contain the same active and inactive ingredients
Quantitatively the same	Q2	Test and reference products contain the same amounts of active and inactive ingredients
Physicochemical attributes of a specific dosage form	Q3	Test and reference products have the same physicochemical properties

Examples

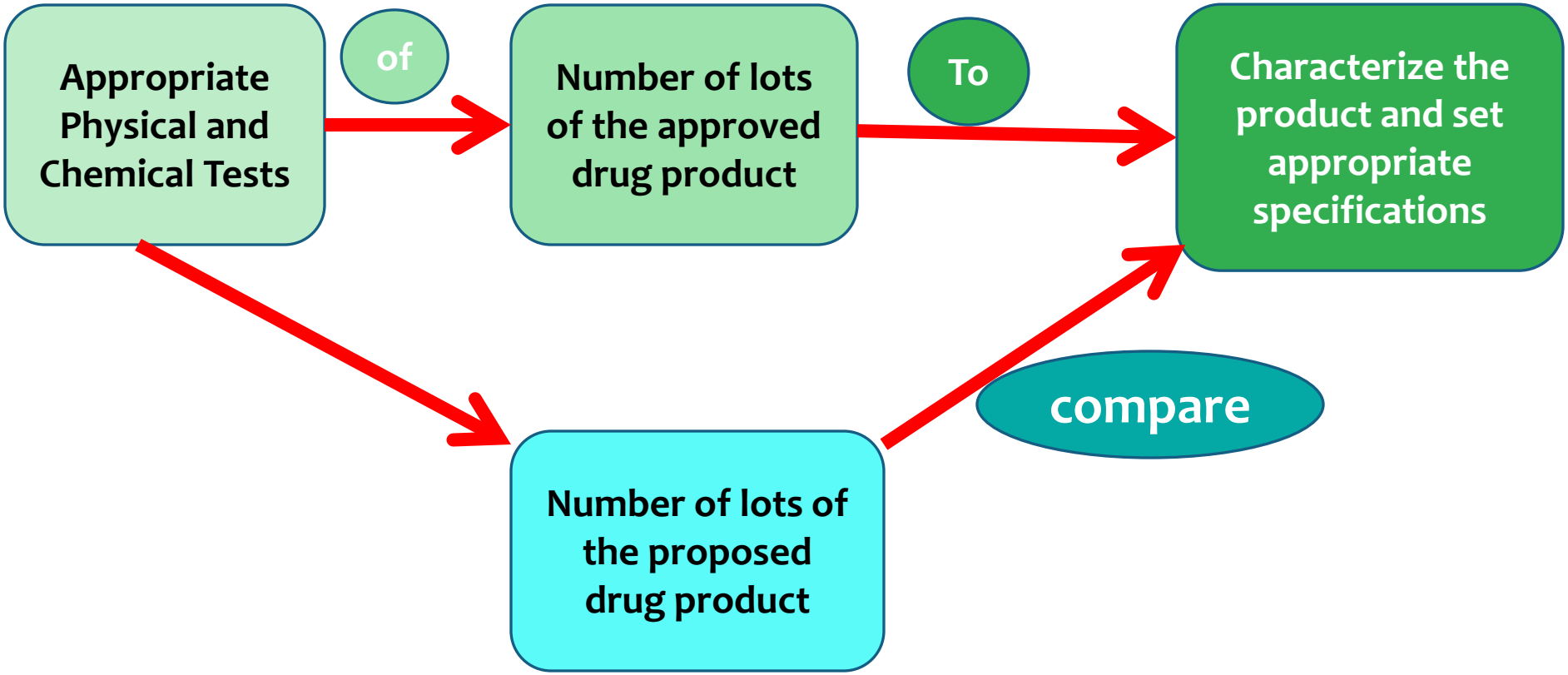
Types of products where the *in vitro* bioequivalence approach can potentially be applied:

- **Type A medicated articles**
- **Locally acting Emulsions, Suspensions, colloids**
- **Topical products that are non-systemically absorbed**
- **Intramammary**

Points to Consider

* Identify and quantify all components of the formulation
* Compare the proposed product formulation to the reference product formulation.
* Determine the critical physicochemical characteristics of the drug product
* Compare the physicochemical characteristics using appropriate validated analytical techniques.

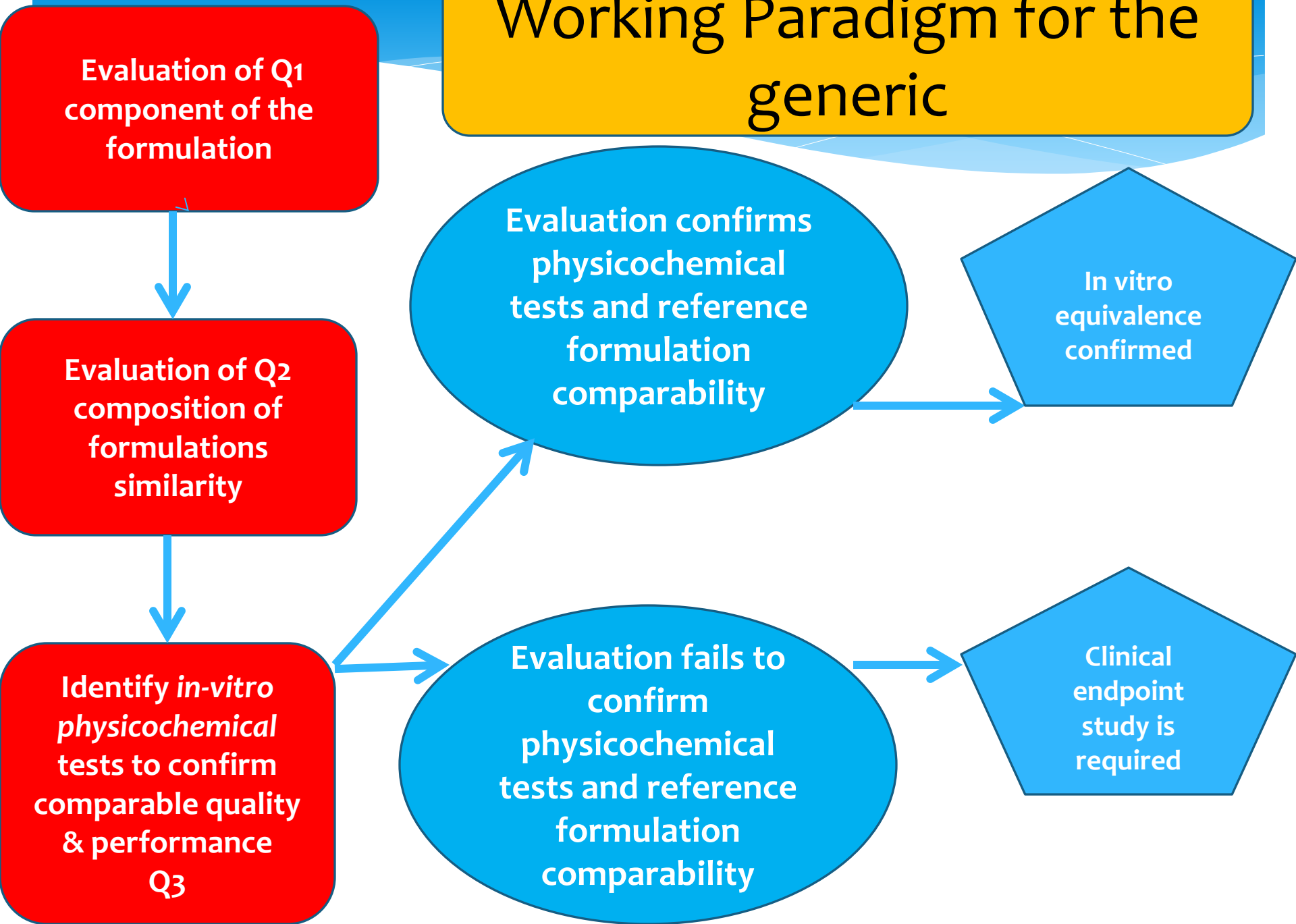
Recommendations



Examples of physicochemical characteristics tests that have been proposed some dosage forms

Dosage form	Suggested *In vitro* Characterizations
Suspension Emulsion Microemulsion Intramammary products	Particle size, particle shape, droplet size distribution, specific gravity, zeta potential, agglomeration, rate of settlement, viscosity, dissolution, pH, assay, impurities, appearance, moisture, surface tension, turbidity, and stability.
Topical products include: Ointment Pastes Creams Gel	pH, thickness, elasticity, plasticity, homogeneity, assay, particle size, rate of in vitro release, and stability.
Type A medicated article	Assay, impurities particle size, loss on drying, dissolution, density, segregation, uniformity, and stability,

Working Paradigm for the generic



Relative Bioavailability

* Applies only to innovators where they have right of reference to the underlying safety and effectiveness data.
* Some changes in formulation or manufacturing process may be acceptable if there is evidence that these changes do not influence the drug quality or performance.
* *In vitro* bioavailability will not be discussed at this forum, rather we will focus on *in vitro* bioequivalence.

Possible Failures

Failure to demonstrate physicochemical comparability.

* Differences in the excipients (amount, type, grade)
* Differences in the API characteristics (different forms or isomers, bio-mass additional characterization may be required)

Possible Failures

Different manufacturing method may lead to different physical and chemical properties of the proposed drug product.

* Critical manufacturing processes were not identified and controlled.
* Control strategy is not appropriate.
* Failure to fully characterize key operating parameters of the process.

Statistical Analysis

The purpose of the *in vitro* test (CMC vs demonstration of in vitro BE) should provide the basis for determining the most appropriate statistical test and for defining the corresponding acceptance criteria. For example:

* CMC tests: the objective is to define the range of values within which a parameter must be contained to legally support batch release. This specification is set on the basis of information generated on that product (e.g., during a BE trial).
* In vitro BE: the objective is to confirm the SAMENESS of the test and reference products. Accordingly, this is an evaluation of two products that compares location (e.g., mean) and dispersion (e.g., %CV) of a given parameter. Both the test and reference products must exhibit comparability for that parameter. The corresponding statistical approach needs to consider parameter distribution and the targeted statistical power.

Additional Considerations

* Are the tests related to the critical quality attributes?
* Number of batches and replicates tested (RLD and proposed)
* Do the tests reflect *in vivo* performance?
* What is the metric and the target of the tests?
* Are the proposed tests practical?
* What level of test variation is acceptable for the approved products?
* Are the methods validated and to what level?

Summary

* The novel *in vitro* BE approach provides a different pathway for demonstrating BE.
* *In vitro* BE compares formulations and physicochemical attributes.
* The *in vitro* BE approach provides an alternative pathway for making certain supplemental changes or pursuing generic and major changes approval.