Product Quality Research Institute

Session 1
In Vitro Approaches to Demonstrating Bioequivalence -Summary of Discussions-

Facilitators

Bing Li, Ph.D., U.S. FDA

David Christopher, M.S., Schering-Plough

Richard Dalby, Ph.D., University of Maryland

Scribes

Mei-Ling Chen and Wallace Adams, US FDA

PQRI
Product Quality Research Institute

This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred.

Facilitators

Bing Li, Ph.D., U.S. FDA
David Christopher, M.S., Schering-Plough
Richard Dalby, Ph.D., University of Maryland

Scribes

Mei-Ling Chen and Wallace Adams, US FDA

Outline

- General comments on in vitro testing
- Test specific comments

Our Approach

- During this breakout session, we tried to elicit opinions on:
  - Which OINDP in vitro testing methods are useful
  - The challenges and barriers to the use of in vitro testing for the assessment of BE.
  - Opportunities and future direction for the use of in vitro studies to demonstrate BE.
  - Which in vitro tools would be useful for determining bioequivalence during development and what is needed to demonstrate an IVIVC (relationship) for inhaled products.

In Vitro Approaches to Demonstrating Bioequivalence

- What's the intended purpose of the test?
- Are the tests discriminating?
- To what extent is the test method validated?
- Are the tests representative of patient use?
- What's the biological significance of the tests?
- Statistics - what is the metric and what is the target (goal post)?
- Are tests practical, not overly onerous and not too expensive?
- Are tests beyond those in the current use likely to be useful?
- Would in silico tests be potentially useful?
- Which tests might be useful for the in vitro part of an IVIVC?

In Vitro Approaches to Demonstrating Bioequivalence

- What approaches do you currently use?
  - Dosage unit sampling apparatus
    - Single actuation content through container life
  - Particle size distribution
    - Laser diffraction
  - Aerodynamic particle size distribution
    - Cascade impaction
  - Drug/aggregate particle size distribution
    - Microscopy
  - Spray Pattern
    - TLC Plate impaction or laser light sheet reflection
  - Plume geometry
    - Photography or laser light sheet reflection
  - Priming and repriming

General Comments On In vitro Bioequivalence

- There is a lot of uncertainty concerning the appropriate statistical comparisons that should to be applied to BE test results.
- The purpose of the in vitro test (CMC or BE) determines the appropriate statistical quantification and the associated value for the limits. The statistical tools must be appropriate so that:
  - They consistently make the “right” decision.
  - They are demonstrably fit for their intended purpose.
    - For example, the Chi Squared plus Impactor Sized Mass (ISM) was not viewed as adequate for supporting a finding of BE
- It is appropriate to set different numerical limits for CMC (QC) tests and BE tests because they have different objectives.

General Comments On In vitro Bioequivalence

- Generally, Population Bioequivalence (PBE) metrics that incorporate reference product scaling were regarded as useful statistical evaluation tools for BE determination.
  - Implementation can be challenging due to potentially large sample size
  - EMEA Guidance is based on Average Bioequivalence Approach (ABE)
  - Sequential study designs deemed acceptable provided alpha level is preserved
    - Firms should submit a protocol to FDA prior to collecting data
- Reference batch samples are potentially older than Test product batches
- For PK, PD, and clinical studies a power analysis is used to estimate how many patients should be evaluated in order to have a reasonable expectation of achieving the necessary discriminating power.

General Comments On In vitro Bioequivalence

- In contrast, in vitro testing is usually approached with a predefined number of replicates.
  - Is this appropriate?
  - For a given test, should a minimum number of T and R batches/units be prescribed?
    - FDA Current Thinking: 10 units from each of 3 batches is an appropriate minimum.
  - Should we limit the number of in vitro test replicates?
    - Do resource issues justify fewer replicates?
  - There may be both real and/or perceived constraints on the number of replicates that can be evaluated.

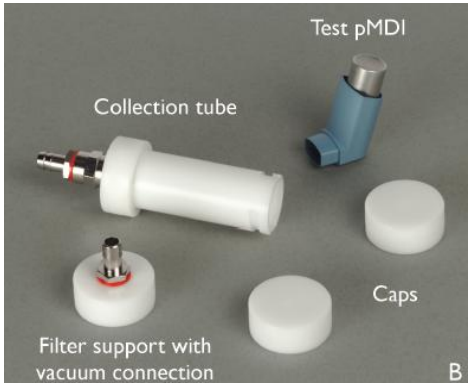
General Comments On In vitro Bioequivalence

- Resources are a bigger consideration for CMC (QC) tests than for one-time BE tests.
- Test methods for BE are generally a subset of CMC tests.
- The goal is avoidance of bias, not blinding
  - Blinding of sample collection is difficult or impossible
  - Automatic actuation can reduce bias
    - Choosing parameters can be a challenge / needs validation
  - Sample recovery and analysis (assay) can be blinded
  - Statistical evaluation need not be blinded (moot point)
- We discussed if consortia of generic companies could collect and share reference data and use the same data in all their ANDA applications
  - Raises exclusivity issues (possibly anticompetitive)
  - Avoids only FDA having access to multiple data sets

General Comments On In vitro Bioequivalence

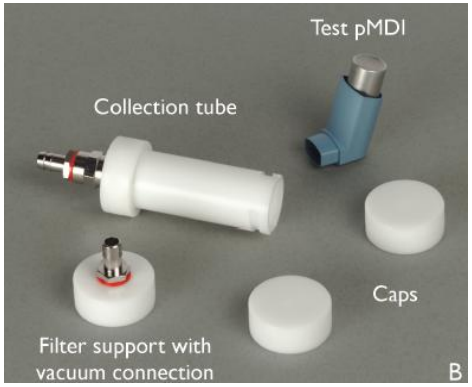
- Is labeled information on R an appropriate target for comparison to T for FPD (Such as Advair labeling)
- Is randomized selection or pre-selection of the reference batch appropriate?

Dosage Unit Sampling Apparatus



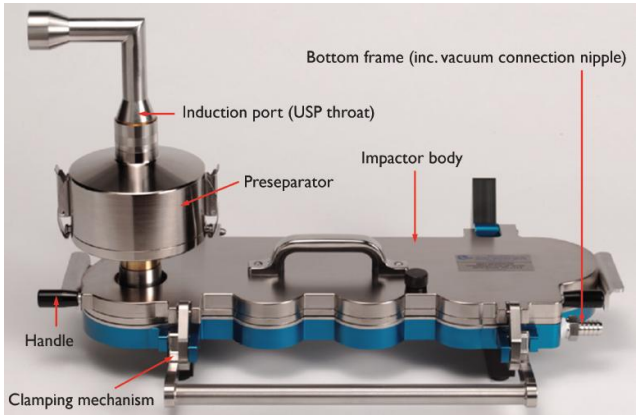
- For solution products, it was generally agreed that spray weight and concentration could be surrogates for emitted dose.
  - Validation necessary to show things like lack of drug adsorption
- Use of the 4kPa pressure drop was judged appropriate for setting test flow rates for T and R DPIs
  - Testing at +/- 10% of the test flow rate was considered necessary.
  - Should emitted dose and APSD be tested at a standard pressure drop-determined flow rate or a fixed flow rate.
  - Is pressure drop-determined flow rate or fixed flow rate more clinically relevant
    - Pressure drop-determined flow rate complicates CI data evaluation

Dosage Unit Sampling Apparatus



- Is simulated inhaled volume critical for testing DPIs?
- Majority favored conducting testing at a flow rate dictated by the resistance of the Reference device (T within a fixed percentage of R's resistance)
  - This was preferred over grouping T & R devices into the same "High", Medium" or "Low" resistance group.

Cascade Impaction



- Viewed as useful and “capturing” the results of other tests
  - If the spray pattern was atypical the group expected that CI results would reflect this.
- No general agreement on test conditions
  - Humidity and Environmental Controls

Spray Pattern & Plume Geometry

- Neither test generally considered useful
  - Spray pattern found isolated supporters.
  - Other test results considered sensitive to the product defects shape tests can identify
    - Off-axis spray detected by increased induction port deposition during CI testing
  - Spraying into open atmosphere not considered useful as a BE metric since it lacks patient-relevance.
  - May have limited value as an incoming QC test on actuators, but not for product testing.

Miscellaneous Comments

- No value perceived for pMDI “plume force” test

Thank You

- We appreciate the interactivity and openness of the audience!