Dissolution Challenges When Blinding Comparator Agents

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Outline

- Study Design When Using Comparators
- Sourcing Issues
- Understanding Comparator Characteristics
- Typical Blinding Strategies
- Testing Strategies
- Analytical Methods
- Method Validation
- Addressing Storage Conditions, Expiry and Specifications
- Is Bioequivalence Testing Necessary?
- Logistics Challenges
- Wrap Up
Study Design When Using Comparators

- Gold Standard
- Able to be blinded
- Available/usable in all target countries with free movement
- Quality assured
- Acceptable expiry dating
Comparator Needs Affected by Study Stage

- **Early Stages**
  - Preliminary evaluation
  - May be several different comparators
  - Speed is major consideration

- **Later stages**
  - Used in pivotal studies
    - Bioequivalence becomes a larger question
    - Greater risk of being challenged
  - Logistics and cost become major considerations
    - Larger quantities – scalability
    - May be more countries – sourcing issues
Sourcing Issues

- In what countries will the studies be run?
- Using EU or Mutual Recognition Agreement (MRA) country supplies in EU is generally not an issue
  - MRA between US and EU is still under evaluation
- Using US supplies in US is generally not an issue
- There is no formal FDA guidance on using EU supplies in the US
  - Generally requires discussion with FDA
  - Describe rationale, reputable source, qualitative composition, dissolution profiles, release data
Sourcing Issues

- Where will you obtain the comparator product?
  - Manufacturer
  - Wholesaler
  - Local pharmacies
  - Internet

- Does the supplier have the appropriate licenses and reliability?

- Are you willing to accept more than one lot, with the attendant complexities?

- How much lead time is required?
Sourcing Issues

- Generally safety is not a concern
- There may be differences between products from different countries
  - Indications
  - Dosage form
  - Potency
  - Appearance
  - Composition
    - Ethical issues: porcine, bovine, TSE, GMO
  - Biopharmaceutics
    - PK: Cmax, AUC
Understanding Comparator Characteristics

- Dosage form: IR, ER, other
- Drug solubility, BCS class
- Drug product stability
Biopharmaceutical Classification System (BCS)

- **I**: High solubility, High permeability
- **II**: Low solubility, High permeability
- **III**: High solubility, Low permeability
- **IV**: Low solubility, Low permeability

<table>
<thead>
<tr>
<th>Volume to Dissolve Max Dose (ml)</th>
<th>Apparent Permeability (X 10^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
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<tr>
<td></td>
<td>1.0</td>
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<tr>
<td></td>
<td>10.0</td>
</tr>
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Need to Address All Five Senses

- **Sight**
  - Size, shape, color, markings, packaging
- **Smell**
  - Odor
- **Sound**
  - Is there rattling of a tablet in the capsule?
- **Taste**
  - Taste-masking necessary?
- **Touch**
  - Feel, coatings, weight
Typical Blinding Strategies

- Over-encapsulation
- Film coating, sugar coating
- De-printing, over-printing
- Similar placebo
- Grind and recompress or encapsulate
Over-encapsulation of Tablets

- Typically 5-10 delay in dissolution
  - May not be ‘similar’ when using f2 calculation
- Impact of back-fill
  - Without back-fill, capsules can collapse and slow dissolution
  - Different back-fills can result in different dissolution profiles
  - Potential for stability or incapability issues
- May need to break tablets
- Potential for gelatin cross-linking and pellicle formation
Impact of Over-encapsulation, With and Without Back-fill

Betzler, K. “Strategies and Practicalities for Comparator Drug Sourcing”
Effect of Different Back-fill Materials

A Concern When Over-encapsulating: Gelatin Cross Linking
Dissolution Slowing Due to Gelatin Cross-linking on Stability

Dissolution Comparison Plot

- **Initial (117844)**
- **024_WKS, 30_65**
- **038_WKS, 30_65**
- **059_WKS, 30_65**
- **078_WKS, 30_65**
Over-encapsulation of Capsules

- High probability of problems
- Delay in dissolution is often greater than 20 minutes
- Generally high variability
De-printing or Over-printing

- Usually done with an alcohol/salt mixture
- May affect dissolution
- Potential for chemical incompatibility issues
- Over-printing has been used for banded capsules
  - Alcohol could affect seal
Film-coating and Sugar-coating

- Non-functional coating not designed to alter dissolution
- May affect dissolution, especially at early time points
- Sugar-coating can be helpful in masking debossing
• The best way to avoid dissolution issues with a comparator is to avoid modifying it
• Similar vs. exact matches
• Lead times may be longer
  ○ Especially if tooling needed
• Care should be taken to address all five senses
What Testing is Required?

- Appearance
- Dissolution
- Identity
- Potency
- Degradation products
- Moisture
<table>
<thead>
<tr>
<th>What Stability Protocol is Appropriate?</th>
</tr>
</thead>
</table>

- Typical initial, 1, 3, 6, 9, 12 months
  - Which tests?
- Conditions: label and accelerated?
- Packaging critical?
- Prospective or concurrent?
What Analytical Methods Should Be Used?

- Check available sources
  - Compendia (USP, EP, JP, BP)
  - FDA website
    - www.accessdata.fda.gov/scripts/CDER/dissolution
  - Freedom of Information Act
  - Literature
  - Contract Labs

- Develop from scratch

- What if reference standard is not available?
Developing a Comparator Dissolution Method

- Check the solubility of the drug
  - pH 1.2, 4.5, 6.8
  - Surfactants if necessary

- Try standard apparatus
  - USP I (Baskets), 100 rpm
  - USP II (Paddles), 50 rpm

- Run dissolution profiles for unmodified and modified comparator
  - Evaluate using FDA f2 similarity factor or other means
Dissolution Profile Comparisons

- **Difference Factor ($f_1$)**
  
  $$f_1 = \left\{ \frac{\sum_{t=1}^{n} | R_t - T_t |}{\sum_{t=1}^{n} R_t} \right\} \times 100$$

  - Should be close to 0; values 0-15 ensure equivalence

- **Similarity Factor ($f_2$)**
  
  $$f_2 = 50 \times \log \{ \left[ 1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \}$$

  - Should be close to 100; values 50-100 ensure equivalence
Method Validation

- **Accuracy**
  - Recovery of drug from the dissolution medium

- **Precision**
  - Repeatability of the dissolution results
  - Repeatability of the determinative step

- **Specificity**
  - Freedom from interference from the placebo

- **Linearity and range**
  - Need to cover the range of expected results

- **Robustness**
  - Impact of small, deliberate changes
Method Validation

- Filter qualification
  - Demonstrate no loss of active
- Carryover
  - Between pots or sampling times
- Solution stability
  - During and after the test
- Validation of automation
  - Manual versus automated sampling
- Ruggedness
  - Impact of lab to lab variations
Storage Conditions and Expiry

- Storage conditions based on label information, stability of the comparator and extent of modification
  - Consider drug product information and potential for gelatin cross linking, hydrolysis, drug/back-fill interaction
  - For stable products with over-encapsulation: stability data may not be necessary, if required concurrent probably acceptable
  - For sensitive products with reformulation: full testing with stress conditions per ICH may be appropriate
- Expiry will be based on available data, but never longer than unmodified drug product
Use compendial or regulatory specification for dissolution (and other tests) if available
If no specification is available, treat as you would any other drug product under development
Setting the specification

- The time point(s) should be carefully selected: typically on or near the plateau for immediate release products. For sustained release products, early, mid and late time points are selected.
- The acceptance criteria are customarily a multiple of 5
- It is helpful to create a histogram of the dissolution data to visualize the distribution of data
- Statistical analysis will aid in the selection of the acceptance criteria
Histogram of Some Dissolution Data

FSFR = 0.0%  SSFR = 0.0%
FSFR = 0.6%  SSFR = 0.0%
FSFR = 42.9%  SSFR = 11.6%

Histogram of Some Dissolution Data

Percent

FSFR = 0.0%  SSFR = 0.0%
FSFR = 0.6%  SSFR = 0.0%
FSFR = 42.9%  SSFR = 11.6%
Is Bioequivalence Testing Necessary?

- Prefer to avoid due to cost and time requirements
- At early phases, company may accept risk and not perform
- At later stages, scientific judgment and company risk-tolerance play a larger role
Bioequivalence Regulatory Guidances

- FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence for Immediate Release Solid Oral Dosage Forms
- EMEA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWPI/1401/98)
- Multisource (generic) pharmaceutical products: guideline on registration requirements to establish interchangeability (WHO Technical Report Series No. 937, Annex 7)
The guidances are generally similar, although there are technical differences

- Biowaivers will be considered for BCS Class I immediate release drug products where dissolution profiles are similar
- Going beyond BCS Class I may be possible, but would be addressed case-by-case
- Most others require demonstration of bioequivalence
Logistical Challenges

- Multiple sources may bring multiple images and/or compositions
- Timing
- Expiry vs. time required to execute the studies
- Recall and retrieval procedure
  - In the event the sourced product is recalled
  - In the event the modified product needs to be recalled
Documentation Challenges

- Manufactured under GMPs
- Certificate of Analysis
- Expiry Date
- BSE/TSE documentation
- Certificate of Conformity
  - Statement from innovator that composition of product is identical in different countries
- MSDS
Wrap Up

- Choosing a comparator starts with the study design
  - Sourcing issues can have significant influence
- Once the comparator is selected, it is important to investigate its characteristics
- Blinding is often necessary, and a goal is to minimize any impact on the drug product
- Developing and validating methods can be challenging, but is often necessary to address expiry and specification issues
- Bioequivalence testing is expensive and time consuming, but can sometimes be avoided
- Logistical challenges are often substantial, but not always considered up front.
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