Connection Between Quality, Safety, and Efficacy

Roger L. Williams, M.D.
United States Pharmacopeial Convention
December 1–3, 2010
Topics

– **Overview**
– **BCS**
– The USP Monograph: Pharmaceutical Equivalence and Bioequivalence
– A National/Global RLD
Federal Food, Drug, and Cosmetic Act
Public Health Service Act

- **FD&C Act**
  - (b)(1)
  - (b)(2)
  - (j)
  - (j)(2)(C)
  - OTC
    - safety/efficacy and identity, strength, quality, purity, potency
    - NDA/ANDA approved

- **PHS Act**
  - PHS: prevention, treatment, or cure of disease
  - safety, purity, potency
  - BLA licensed

- **USP**
  - (Identity), strength, quality, purity

- **ICH**
  - Quality
USP Role Under Federal Law

- **1820** USP—Independent, national pharmacopeia
- **1906** Food & Drugs “Wiley” Act
  - Feds can act if adulterated or misbranded
  - USP *strength, quality & purity*
- **1938** Federal Food, Drug, and Cosmetic Act (FD&C Act)
  - FDA application—safety—but **no preapproval**
  - USP *identity* (drug named in official compendium)
    - USP *packaging & labeling*
- **1962** FD&C Drug Amendments
  - FDA *pre-market approval authority*; safety & efficacy
  - FDA authority to require manufacturing controls:
    - GMPs—assure safety + identity, strength, quality & purity
- **1997** FDA Modernization Act Amendments
  - USP *Positron Emission Tomography (PET) standards*
Pharmaceutical Equivalence and Bioequivalence

- Reference Listed Drug (WHO Comparator Pharmaceutical Product)
  Critical to approach—must be stable via careful post-approval change control

- Pharmaceutical Equivalence
  - Defined at 21 CFR 320
  - BPCI Act: ‘similar’ statements

- BA/BE—harmonization close and could advance further

*Continuing equivalence: Is there an end to the story?*
Class I Drug: Over Discriminating

Metoprolol BE Study

Plasma concentration ug/ml

% release

Reference

Lot #: 931004
Lot #: 931007
Lot #: 931011

Metoprolol BE Study

% release

Plasma concentration ug/ml

Reference

Lot #: 931004
Lot #: 931007
Lot #: 931011
Dissolution Profile of Two Commercial Formations of a Class II Drug in Simulated Intestinal Fluid pH 7.4

From: Lobenberg et al. Pharm Res 2000

Take Aways

- What Is the question?
  - How to assure continuing equivalence
  - Continuing equivalence for chemical drugs: PE, BE and then TE
  - For biosimilars, it’s interchangeability (one-way), not comparability
- The US has a robust system to assure continuing equivalence
- Manufacturers, FDA, USP all play a role
- Process drift is a signal that continuing equivalence may be in jeopardy
Topics

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Biopharmaceutics Classification System: Update

BDDCS BCS

Extensive Metabolism

Gastric emptying determines on-set of absorption

Dissolution likely to be “rate limiting”

Poor Metabolism

Absorption might be:
- incomplete
- sensitive to certain excipients

IV

Generally “problem” molecules

Volume of water (ml) required to dissolve the highest dose strength at pH 1.2 - 8
WHO Essential Drugs

- 325 Medicines
- 260 Drugs
- 123 Oral IR
Take Aways

- 67% of WHO IR drugs at High Solubility
- 68% of US Top 200 drugs are HS
- *BCS Approaches* applicable to the majority of drugs—WHO Essential Medicines and US Top 200
- Allows opportunity to assess impact of process drift on BE at low cost
In Vitro Similarity (IVS)

![Graphs showing in vitro similarity of Zidovudine products from different countries](image)

<table>
<thead>
<tr>
<th>Country</th>
<th>Company</th>
<th>Product</th>
<th>Batch</th>
<th>Exp.</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>GSK USA</td>
<td>Retrovir</td>
<td>TZY1642</td>
<td>10/10</td>
<td>Corn Starch, Mg-Stearate, MCC, Sodium Starch Glycolate</td>
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<tr>
<td>Mexico</td>
<td>GSK (England)</td>
<td>Retrovir</td>
<td>X5953</td>
<td>05/10</td>
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<td>Argentina</td>
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<td>Zetrotax</td>
<td>EMX4V</td>
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<tr>
<td></td>
<td>Laboratoris Filaxix</td>
<td>Zidovudine</td>
<td>12119D1</td>
<td>06/10</td>
<td>Lactose monohydrate, Mg-Stearate, MCC, Cross carmelose Sodium, Silicium Dioxide</td>
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<td></td>
<td>Laboratorio LKM</td>
<td>Crisazet</td>
<td>B853A</td>
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<td>B853A</td>
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<td>Sodium Starch Glycolate, Lactose Monohydrate, Mg-Stearate</td>
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</tbody>
</table>
Amoxicillin

**In Vitro Similarity (IVS)**

**Sanval SGF**
- Sanval Chile
- Sanval Peru
- Sandoz USA 500 mg

**Sanval SIF**
- Sanval Chile
- Sanval Peru
- Sandoz USA 500 mg

**Sanval pH 4.5**
- Sanval Chile
- Sanval Peru
- Sandoz USA 500 mg

Dissolution Profile Comparison:
The US-Product Dissolves >85% in 15 min.
The F2 of the Sanval products is: 64.3

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<thead>
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<th>Batch</th>
<th>Exp.</th>
<th>Excipients</th>
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<td>USA</td>
<td>Sandoz</td>
<td>Amoxicillin</td>
<td>151645</td>
<td>10/09</td>
<td>Silicon dioxide, crospovidone, ethylcellulose aqueous dispersion, hydroxypropylmethylcellulose, magnesium stearate, lactose, triethyleneglycol citrate, titanium dioxide</td>
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<tr>
<td>Peru</td>
<td>Sanval</td>
<td>Amoval 500 mg</td>
<td>122387</td>
<td>07/12</td>
<td>croscarmellose sodium; microcrystalline cellulose; magnesium stearate; titanium dioxide; polycarbophil; Eudragit E100</td>
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<tr>
<td>Chile</td>
<td>Sanval</td>
<td>Amoval 500 mg</td>
<td>033608</td>
<td>11/2012</td>
<td>croscarmellose sodium; microcrystalline cellulose; magnesium stearate; titanium dioxide; polycarbophil; Eudragit E100</td>
</tr>
</tbody>
</table>
Mexico: Metronidazole

**Metronidazole Mexico SGF**

Dissolution Profile Comparison:
The US-Product dissolved very rapidly.
Liomont failed to release 85% in 15 min but dissolved rapidly. Sanofi needed up to 45 minutes to release > 85% of its content.

**Metronidazole Mexico pH 4.5**

Dissolution Profile Comparison:
The US-Product dissolved rapidly.
Liomont dissolved very rapidly. Sanofi released > 85% of its content within 60 minutes; The F2 = 24.1 when compared to the US product in the first 30 min.

**Metronidazole Mexico SIF**

Dissolution Profile Comparison:
The US-Product dissolved not rapidly.
Liomont dissolved very rapidly. Sanofi released > 85% of its content within 45 minutes; F2 = 25.6.

<table>
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<th>Batch</th>
<th>Exp.</th>
<th>Excipient</th>
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<td>Searle Pharmacia</td>
<td>Flagyl</td>
<td>C061228</td>
<td>03/09</td>
<td>Cellulose, Fd&amp;C Blue, Hydroxypropyl Cellulose, Hypromellose, PEG, Stearic Acid, Titanium Dioxide</td>
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<tr>
<td>Mexico</td>
<td>Sanofi Aventis</td>
<td>500 mg</td>
<td>B88575</td>
<td>03/11</td>
<td>Excipients</td>
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<td>Flagenase</td>
<td>P07009</td>
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<td>Country</td>
<td>Manufacturer</td>
<td>SGF</td>
<td>pH 4.5</td>
<td>SIF</td>
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<tr>
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<td>+</td>
<td>-</td>
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<td>Lazar</td>
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<td>Austral</td>
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</tbody>
</table>
Topics

- Overview
- BCS
- The USP Monograph: Pharmaceutical Equivalence and Bioequivalence
- A National/Global RLD
Productivity:

- **370** New Official Monographs
- **1,201** Revised Official Monographs
- **43** New Official General Chapters
- **89** Revised Official General Chapters
## Ronitavir

**Drug Substance Monographs**

**Official Monographs / Ronitavir 1**

#### Analysis

**Solution:** Dilute, Identity solution, Standard solution 2, and Sample solution

1. Calculate the percentage of Ritonavir in the Sample solution

2. Calculate the percentage of each impurity in the impurity solution

3. Impurity Table 1

<table>
<thead>
<tr>
<th>Impurity</th>
<th>Retention Time (min.)</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria (%.%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.07</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>B</td>
<td>0.24</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>C</td>
<td>0.29</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td>D</td>
<td>0.43</td>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>E</td>
<td>0.64</td>
<td>0.7</td>
<td>0.1</td>
</tr>
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</table>

**SPECIFIC TESTS**

- **Water Determination:** Method I (921): NMT 0.5%, Other 0.75%

- **Residue on Ignition:** Method II (921): NMT 0.1%

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Store in tight, light-resistant containers. Store at 2⁰–30⁰.

**USP Reference Standards (1):**

- USP Ritonavir RS
- USP Ritonavir Related Compound reference RS
Drug Product Monographs and General Chapters

Metformin Hydrochloride Extended-Release Tablets

DEFINITION
Metformin Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metformin hydrochloride (C$_7$H$_{14}$NO$_2$·HCl).

IDENTIFICATION
- The retention time of the major peak from the Sample solution corresponds to that from the Standard solution, as obtained in the Assay.

ASSAY
- Procedure
  - Buffer solution: 0.5 g of sodium dihydrogenphosphate and 0.5 g of sodium chloride in water. Prior to final dilution, add with 0.06 M phosphoric acid to a pH of 6.8. Use within 24 hr.
  - Mobile phase: Acetonitrile and buffer solution (1:2). The composition of acetonitrile and buffer solution may be changed to 1:1, if necessary.
  - Diluent: 1% solution of acetonitrile in water
  - Standard solution: 30 mg/mL of USP Metformin Hydrochloride RS in Diluent, where 1 mL of the labeled amount, in mg, is equivalent to 5 mg of USP Metformin Hydrochloride RS in Solution.
  - Mobile phase: 10 M sodium phosphate buffer (pH 4.9) in water. Adjust with 0.04 M sodium hydroxide to a pH of 6.8. Use within 24 hr.
  - Sample solution: 10 mg/mL of Tablets labeled to contain 50 mg.

PERFORMANCE TESTS
- Change to read:

  [Details not provided in the image]

Chart 4. Noncomplex Active Drug Products

[Diagram of noncomplex active drug products with specific tests and methods]

[Details not provided in the image]
Glutathione Example: Assay

**DEFINITION**
Glutathione contains NLT 97.0 percent and NMT 103.0 percent of C₅H₇N₂O₅S, calculated on the anhydrous basis.

**IDENTIFICATION**
- A infrared Absorption <197K>

**ASSAY**

- **PROCEDURE**
  - **Standard solution:** USP Glutathione RS in an appropriate diluent [Note: Neat determination may be substituted where appropriate]
  - **Sample solution:** Glutathione in an appropriate diluent [Note: Neat determination may be substituted where appropriate]
  - **Analytical System:** Use a procedure validated as directed in <10> Criteria Defined Procedures, Assay
  - **Sample:** Standard solution

**Performance Requirements**
- **Precision and Accuracy, Assay <10>: Six independent analyses of the Standard solution:** meets the requirements

**Analysis**
- **Sample:** Sample solution and Standard solution
  - Calculate the percentage of Glutathione found in the Sample solution using the following calculation:
    
    \[ \text{Result} = \left( \frac{R_u}{R_s} \right) \times \left( \frac{C_s}{C_u} \right) \times F \times 100\% \]
  - \( R_u \) = Response for the Sample solution
  - \( R_s \) = Response for the Standard solution
  - \( C_s \) = Concentration of the Standard solution
  - \( C_u \) = Concentration of the Sample solution
  - \( F \) = Correction factor(s)

**Acceptance criteria:** 97.0% - 103.0% of C₅H₇N₂O₅S

**SPECIFIC TESTS**
- **Water Determination**

**COMPENDIAL PROCEDURES**
[Note: This procedure may be used to evaluate a material if verified for their intended purpose (see Verification of Compendial Procedures <1226>).]
USP Reference Standards

- USP Offers More than 2,500 Reference Standards for Use in the Full Range of *USP–NF* Tests and Procedures
- USP Reference Standards Have Been Rigorously Tested by USP, Industry, and Government Scientists

**Productivity:**
- 728 New Reference Standards
- 931 Replacement/Continuing Reference Standards
Take Aways

- FDA does BA/BE
- USP does Performance test (with PVT and reference materials)
- Other countries—Performance test may not signal BA/BE (continuing equivalence)
- BA/BE needs GMPs and careful clinical/in vitro studies to establish/document
- In countries without GMPs and BA/BE requirements, USP Performance test signals performance but may not signal BA/BE
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Most important selection criteria in order of preference:

- **USP RLD**
  - Defined in Orange Book
  - Typically Innovator

- **WHO**
  - Approval in ICH and associated countries
  - Pre-qualified by WHO
  - Extensive, documented use in clinical trials
  - Reported in peer-reviewed scientific journals
  - Long and unproblematic post-market surveillance.
Would/Could USP Do This?

- Obtain from US market
- Five years in advance of patent expiry
- Study in USP laboratories—characterization and dissolution in three media
- Prepare and release as Certified Drug Product Reference Material—packages for national/international BE studies
- Could lead to only one BE study for many markets
- Pros/Cons: to be considered (e.g., what about non-US national comparator pharmaceutical product)
Every pharmaceutical ingredient or formulated product, together with its packaging materials, has unique characteristics or ‘fingerprints’ that can be probed using various regions of the electromagnetic spectrum.
Take Aways

- Manufacturers
  - QbD undergirds continuing equivalence

- FDA and USP
  - Create standards that assure continuing equivalence (law, regulations, guidances, compendial monographs)

- Monitoring is key to success
  - Process drift
  - Periodic studies for PE and BE
  - BCS and USP monographs are low cost ways to monitor
  - Change brings in requirement for further study/FDA involvement

- Reference Listing Drug
  - The link to clinical trial material and documentation of safety and efficacy
Acknowledgements

- Nádia Araci Bou-Chacra
- Raimar Löbenberg
- Erika Stippler
- Vinod Shah
USP Across the Globe
Thank You