Advisory Committee for Pharmaceutical Science

Research Update
Office of Testing and Research
Product Quality Research Institute, Inc.

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Director (Act.), Office of Testing and Research
OPS, CDER, FDA

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Mission

- Advance the scientific basis of regulatory policy
- Assure that regulatory policy and decision making are based on the best available science
- Provide scientific and laboratory support for review, postmarketing surveillance, and compliance activities

Collaborations

- Product Quality Research Initiative (PQRI)
- Advisory Committee for Pharmaceutical Science (ACPS), Nonclinical Studies Subcommittee (NCSS)
- Other government organizations such as NIH, NIEHS, NCTR
- Academia
- Industry

OTR Organization

OFFICE OF TESTING AND RESEARCH
Aja S. Hussain, Ph.D., Director (Act.)

Research and Analytics
Director: Aja S. Hussain, Ph.D.

Laboratory of Clinical Pharmacology
Director: Joo S. H. Seo, Ph.D.

Programs:
- Division of Product Quality Research
  - Robert C. Oder, Ph.D.
  - Acting Director
- Division of Regulatory Affairs Research
  - CAPT. Franz J. Schmitt, Ph.D.
  - Director
- Division of Pharmaceutical Planning
  - Richard A. N. Noyes, Ph.D.
  - Director

OTR Program Focus

Key Multidisciplinary Focus Areas that address important areas of CDER's mission:

- Nonclinical/clinical linkage
- Product quality - improved methodology
- Database availability and monitoring
- Regulatory analytical support to CDER and FDA

OTR Topics

- Regulatory contributions
  - Science base
  - Regulatory policies and decisions
- Re-engineering efforts
  - Further enhance the ability to meet the needs of the CDER
    - Multidisciplinary team concept
    - Strengthening linkages with review
Background: Sorbitol

- Widely used excipient in oral liquid dosage forms
- Hexahydrate alcohol related to mannose and is isomeric with mannitol
- Low intestinal permeability
- Metabolized in liver to fructose and glucose
- Reports of adverse reactions largely due to its action as an osmotic laxative (>20g)
  - Sorbitol/Mannitol: Impact on Bioavailability
- Two tablespoons (adult dose) of some commercial syrups contain up to 23g of sorbitol

Sorbitol/Mannitol: Impact on Bioavailability

- 2.3 grams of mannitol in a tablet reduced bioavailability of cimetidine (a low permeability drug, per FDA's BCS Guidance) compared to a tablet containing the same amount of sucrose
  - AUC, Cmax, and Tmax ratios of the mean values were 77%, 46%, and 167%, respectively
  - Spurrell et al. J. Pharm. Sci. 84: 1425-1430, 1995
- About 10 grams of sorbitol had no (minimal) effect on bioavailability (Cmax and AUC) of theophylline (a high permeability drug)
  - Results et al. J. Pharm. 72: 178-183, 1999

Formulations

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Test Formulation</th>
<th>Reference Formulation</th>
<th>BCS Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine</td>
<td>0.15 g</td>
<td>0.15 g</td>
<td>Low</td>
</tr>
<tr>
<td>Sucrose</td>
<td>6 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbitol</td>
<td>5 g</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Water</td>
<td>15 ml</td>
<td>15 ml</td>
<td>High</td>
</tr>
</tbody>
</table>

* Rapidly metabolized into the intestinal wall in glucose and fructose, both exhibit complex absorption

Results: Average Profiles (n=40)

Study Objectives

- Published and in-house data suggests that low permeability excipients such as sorbitol (or mannitol), in amounts used in typical syrup formulations, can significantly reduce bioavailability of drugs that also exhibit low intestinal permeability
  - Bioavailability of drugs that exhibit high intestinal permeability may be less likely to be affected by these excipients
- In this study bioequivalence of a ranitidine (low permeability model) solution containing sorbitol (5%) were assessed using as reference a ranitidine solution containing sucrose (5%)
Results: Average Profiles (n=20)

Average Profiles (n=20)

Individual Bioequivalence

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sucrose</th>
<th>Sorbitol</th>
<th>AUC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>6.04</td>
<td>4.17</td>
<td>0.64</td>
</tr>
<tr>
<td>AUCI</td>
<td>0.19</td>
<td>0.18</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Subject-by-Formulation Interaction?

**Estimate = 0.15 for AUCI**

Bioequivalence: Average Criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln(Cmax)</td>
<td>64%</td>
<td>74%</td>
</tr>
<tr>
<td>Ln(AUCI)</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Ln(AUC)</td>
<td>52%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Note: Solution containing sucrose was used as the reference

Results

- On average, bioavailability of ranitidine from sorbitol solution was about 50% that of sucrose solution
  - Mean Tₘₓ for the two treatments were within 10%
- Although estimated value for Subject-by-formulation interaction was 0.15 for AUCI, it was not statistically significant (CI included 0) in this study

Conclusion

- A significant risk of bioequivalence exists between sucrose and sorbitol based syrups
  - In this study, this risk was demonstrated for a low permeability model drug
  - In addition to literature reports and this study results, similar trends have been observed in data available to FDA on other low permeability drugs (e.g., furosemide and atenolol)
- Literature and in-house submission data on drugs such as theophylline suggests that the risk of bioequivalence is lower for drugs that exhibit high intestinal permeability
Generalization of these results?

- To address this question a study was carried out with metoprolol as a model high permeability drug.
- Preliminary results suggest that difference in bioavailability between sorbitol and sucrose solution is significantly less than what was observed for ranitidine.

PQRI Recommendations to FDA

- Once a project is completed by a Working Group, the outcome will be presented by the Technical Committee to the Steering Committee for dissemination to FDA and the public.
- If a vote is required on the research outcomes, FDA representatives on the Steering Committee will not vote.
- The Steering Committee will forward policy development recommendations and related research data to FDA.

FDA

- FDA is not obligated to implement policy based on Institute information/recommendations and may accept or reject any information/recommendations at its discretion.
- FDA has the sole statutory responsibilities for developing regulatory policy and guidance and may not delegate this responsibility.
Safety, Efficacy and Product Quality Linkages

Desired Outcome

- Reduce time and cost for implementing manufacturing changes (industry)
- Reduce the number of CMC/Biopharm supplements
- Reduce review load - one time review by CDER (FDA)
- Facilitate introduction of new technology and maintain the competitive edge of US industry
- Ensure that quality is "built-in"

FDA Perspective: CMC

- Release testing at the time of manufacture does not provide information that assures "shelf-life"
- Stability commitment may identify stability problems at a later time when the product is already in use by the patients, recall takes time and may be incomplete

Regulatory Hypothesis Approach

- Drug Product Technical Committee
  - H0: Adherence to CGMP's, which include validation, and appropriately established product specifications are sufficient to assure consistent quality and performance (or equivalence) of drug products that are manufactured at different locations using alternate pharmaceutical unit operations, excipients, and container/closure systems
  - Initial Projects: IR Dosage Forms
  - Outcome: ???

Different Perspectives

- SUPAC-IR
  - CGMP's, which include validation, and product specifications are NOT sufficient to assure consistent quality and performance (or equivalence) of MOST IR drug products that are manufactured at different locations using alternate pharmaceutical unit operations, excipients, and container/closure systems
  - Why? AHS
  - Why not? Sid Goldstein, Arsi Repta, and Steve Byrn

Major Reasons For “Recall”*

- Sub-potency
- Dissolution failures
- Super-potency
- Stability data generated did not support expiry date
- Failure to meet established impurity or degradant limits

*Barry Rothman, Office of Compliance, CDER, FDA, 1999
FDA Perspective: CMC

• A combination of long term and accelerated stability testing (and PAS) are currently the only means for assuring correct expiry date
  - principles of accelerated stability may not be appropriate for predicting "physical" stability

FDA Perspective: Biopharm

• In Vitro dissolution specification may not assure bioequivalence
  - dissolution test is for QC only
  - media and hydrodynamic conditions may not reflect in vivo conditions
  - IVIVC needed - tends to be "formulation specific"
  - excipients may alter absorption

Current Research Focus

• Drug Product Technical Committee
  - Chairperson: Sid Goidstein
  - Adherence to CGMP's, which include validation, and appropriately established product specifications are sufficient to assure consistent quality and performance (or equivalence) of drug products that are manufactured at different locations using alternate pharmaceutical unit operations, excipients, and container/closure systems
  - Blend uniformity
  - Manufacturing changes to IR Solid Dosage forms
  - Packaging changes

Rational Approaches for Powder Blend Uniformity Testing for Solid Dosage

• Problem
  - Current regulatory policies require demonstration of adequacy of mixing or in-process powder blend homogeneity
  - Blend uniformity testing using sampling thives is the only accepted method
  - For most powder blends, blend testing for every production batch is not necessary and can cause sampling, using sampling thives, can cause significant problems.
  - The gap in the scientific understanding and regulatory policies is a source of continued debate and, from an industry perspective, undermine regulatory actions.
  - Current policies may be draining industry and FDA time and resources to address a redundant question.

Blend Uniformity Testing

• Approach
  - Identify when blend uniformity tests are needed to assure product quality
  - Seek to enhance confidence in end product content uniformity tests to assure batch-to-batch content uniformity without the need for an in-process blend uniformity test
  - Develop and validate a more effective method for testing blend uniformity when such tests are necessary

• Outcome
  - Science based recommendations for development of new guidance document that will identify when and how powder blend uniformity should be tested.
  - This guidance will save development time and resources and may also reduce the number of unfavorable regulatory actions (e.g., 483's) associated with this issue.
Current Research Focus

- Biopharmaceutics Technical Committee
  - Chairperson: Elizabeth Luce
  - In vitro drug release and other appropriate physicochemical product tests can be developed to assure equivalent rate and extent of drug absorption from pharmaceutical equivalent dosage forms
    - In Vivo Methods for Bioequivalence Assessment of IR Solid Dosage Forms (extension of NCS-based bioequivalence)

Current Research Focus

- Science Management Technical Committee
  - Chairperson: Vacant
  - The goal of this technical committee is to develop strategies that maximize the efficiency of the processes that produce an optimally performing drug product that meets public health objectives for identity, strength, quality, purity, and potency (SMTG Meeting 4 November 1998).
    - Process mapping (CMC & Biopharms.)

Current Research Focus

- Drug Substance Technical Committee
  - Chairperson: Steve Bym
  - Adherence to CGMPs and a critical comparison of the analytical results encompassing specifications, impurity profiles, and relevant physical properties will be adequate to show unchanged identity, strength, quality, purity, and potency of a drug substance in the presence of pre- and post approval changes in 1) manufacturing scale, site, equipment, controls and process; 2) route of synthesis; 3) packaging; 4) supplier(s) of drug substance

Additional Information

- WWW.PQRI.ORG
Product Quality (Pharmaceutical Chemistry and Biopharmaceutics)


The following presentations were made at the American Association of Pharmaceutical Scientists Annual Meeting, Indianapolis, Indiana, November 2, 2000

Detection of Betamethasone 21-butyrate 17-propionate as an Undeclared Corticosteroid in Topical Pharmaceutical Products by LC-MS. Reepmeyer, J.C.

Characterization of Conjugated Estrogens by LC-MS. Reepmeyer, J.C., Doub, W.H.

"Comparative Analysis of Common Particle Sizing Techniques for Pharmaceutical Powders". Hullahalli R. Prasanna¹, Everett H. Jefferson¹, Jeb S. Taylor¹, Ajaz S. Hussain¹, Richard F. Karuhn², Robbe C. Lyon¹. FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD; ²Particle Technology Labs, Downers Grove, IL

"Lot-To-Lot Variability In Extended Shelf Life Of Selected Drug Products". Jeb S. Taylor¹, Ajaz S. Hussain¹, Eric B. Sheinin², Robbe C. Lyon¹. FDA, Division of Product Quality Research,
Nicholson Research Center, Kensington, MD and Office of Pharmaceutical Science, Center for Drug Evaluation and Research, FDA, Rockville, MD

“Detecting Hydration of Active Components In Solid Oral Dosage Forms by Near Infrared Spectroscopy”, Everett H. Jefferson, Charles R. Brownell, H.R. Prasanna, Ajaz S. Hussain, Smita Debnath, Raj Suryanarayanan, Robbe C. Lyon, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD; "Department of Pharmaceutics, University of Minnesota, Minneapolis, MN

“When Is the Solid-State Of Drug Relevant To Its Performance? Smita Debnath, S., Robbe C. Lyon, R., Ajaz S. Hussain, and Raj Suryanarayanan, "Department of Pharmaceutics, University of Minnesota, Minneapolis, MN, Division of Product Quality Research, Center for Drug Evaluation and Research, FDA, Nicholson Research Center, Kensington, MD

“Determination of Acetaminophen in Tablets by Near-Infrared Reflectance Spectroscopy”. Jack A. Spencer, Everett H. Jefferson, T. BoClair, and J. Chan, Division of Pharmaceutical Analysis, FDA, St. Louis, MO and Division of Product Quality Research, FDA, Nicholson Research Center, Kensington, MD

“Determination of Drug Solubility Using A Potentiometric Acid-Base Titration Method Compared To the Saturation Shake-Flask Method”. A. Avdeef, M. A. Strafford, C.R. Brownell, R.C. Lyon, P. Artursson, C.A.S. Johansson, K. Luthman, pION INC, Woburn, MA, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD; Uppsala University, Uppsala, Sweden; University of Tromso, Tromso, Norway

“Ex-Vivo Solubilization of Ketoprofen, Carbamazepine and Griseofulvin in Dog Gastric and Jejunal Fluids and Comparison to In-Vitro Solubilization in Aqueous Solutions of Sodium Lauryl Sulfate”. Nehal A. Kasim, John R. Crison, Michal L. Vieira, Aly H. Nada, Youssef E. Hammouca, A. Hussain and Gordon L. Amidon, College of Pharmacy, University of Michigan, Ann Arbor, MI; Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt; PORT Systems, LLC 540 Avis Drive, Ann Arbor, MI, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

“Intra- And Inter-Manufacturer Variability of In Vitro Dissolution of Metoprolol Tablets: Relevance to In Vivo”. Jin T. Wang, William N. Worsley, Lawrence X. Yu, and Ajaz S. Hussain, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

“Effect of Compression Force, Dissolution Medium Volume, Disc Position, and Rotational Speed on Intrinsic Dissolution Rate”. Alan S. Carlin, Lawrence X. Yu, and Ajaz S. Hussain, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

“Feasibility Studies of Intrinsic Dissolution Rate as an Alternative Method to Determine BCS Solubility Membership”. Lawrence X. Yu, Alan S. Carlin, and Ajaz S. Hussain, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

“Application of USP Dissolution Apparatus III for the Dissolution Testing of Rapidly Dissolving Dosage Forms of Highly Soluble Drugs”. Lawrence X. Yu, Jin T. Wang, William N. Worsley, and Ajaz S. Hussain, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

“Effect of Common Excipients on Caco-2 Permeability of Class III/IV Drugs in Biopharmaceutic Classification System”. B.D. Rege, Lawrence X. Yu, Ajaz S. Hussain, James E. Polli, University of Maryland, Baltimore, MD; FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD
"Artificial Neural Network Analysis of Experimental Conditions on The In Vitro Permeability of Mannitol". Donna A. Volpe and Ajaz S. Hussain, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

"Correlating Absorption Rate-Limiting Processes to Drug Substance and Drug Product Attributes". Lawrence X. Yu, Christopher D. Ellison, Larry J. Lesko, and Ajaz S. Hussain, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD; FDA, Office of Pharmaceutical Sciences, Rockville, MD

"A Physiologically Based Absorption Model to Predict Oral Absorption and Double Peak Phenomenon of Plasma Concentration-Time Profile". Christopher D. Ellison, Lawrence X. Yu, and Ajaz S. Hussain, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

"Development of a Novel Mechanistically Disintegration and Dissolution Model". Lawrence X. Yu, Christopher D. Ellison, Jin T. Wang, William N. Worsley, Alan S. Carlin, and Ajaz S. Hussain, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

"Predicting Human Oral Bioavailability: Comparison of Animal Models with Theoretical Approach". Huailiang Wu, Lawrence X. Yu, and Ajaz S. Hussain, University of Michigan, College of Pharmacy, Ann Arbor, MI; FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

"Can Human Oral Bioavailability Of A Compound Be Quantitatively Predicted?" C. Webster Andrews, Lee Bennett, Lawrence X. Yu, GlaxoWellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709, National Institute of Environmental Health Sciences, 111 Alexander Drive, MS D2-04, Research Triangle Park, NC 27709. FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

"Fluid Mechanical Analysis of Topical Vaginal Formulations". D.H. Owen, A.M. Plenys, A.S. Hussain and D.F. Katz, Department of Biomedical Engineering, Duke University, Durham, NC, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD


Pharmacology and Toxicology

Publications:


vascular injury without consistent evidence of direct infection of the vascular wall. *Circulation* 100 1569-1575.


**Book Chapters**


**Abstracts**


Lester, D.L. Potential applications of noninvasive imaging in toxicology research. (Annual meeting on alternative toxicology) (11/28-12/1/00), in press, 2000


Herman E, Zhang J, Rifai N, Lipshultz S, and Sistare F. Serum cardiac troponin T is a sensitive biomarker of anthracycline-induced myocardial damage and dexrazoxane cardioprotection. Toxicologist, in press, 2000


Clinical Pharmacology


Kitchen B.J., Moser A., Lowe E., Balis F.M., Widemann B., Anderson L.,


