Advisory Committee for Pharmaceutical Science

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

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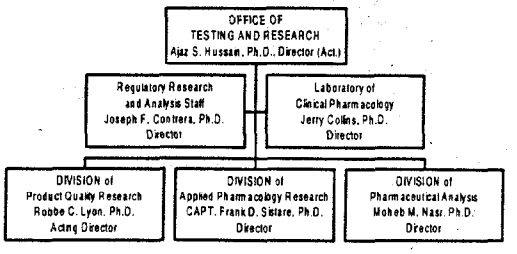
OPS, CDER, FDA

16 November 2000

# OTR Organization




# 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**

# 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**

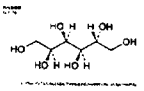
# Collaborations

- **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 Topics

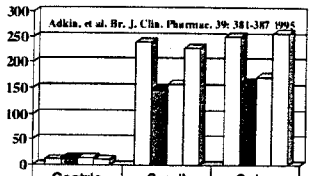
- Regulatory contributions
  - Science base
  - Regulatory policies and decisions
- Re-engineering efforts
  - Further enhance the ability to meet the needs of the CDER
    - Multidisciplinary team concept
    - Strengthening linkages with review

## Background: Sorbitol



- Widely used excipient in oral liquid dosage forms
  - Hexahydric 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)
    - 5.48% W/V aqueous solution is iso-osmotic with serum
      - » Handbook of Pharmaceutical Excipients, APhA, PhP.
  - Two tablespoons (adult dose) of some commercial syrups contain upto 23g of sorbitol

## Effect on Gastro-Intestinal Transit Time (minutes)




| | Gastric Emptying | Small Intestinal | Colon Arrival |
|---|---|---|---|
| Water | 11 | 240 | 251 |
| SAPP (1.1g) | 14 | 147 | 161 |
| Mannitol (2.264 g) | 14 | 158 | 172 |
| Sucrose (4.08 g) | 11 | 229 | 258 |

## 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 71%, 46%, and 167%, respectively
    - Sparrow et al. J. Pharm. Sci. 84: 1405-1409, 1995)
- About 10 grams of sorbitol had no (minimal) effect on bioavailability (Cmax and AUC) of theophylline (a high permeability drug)
  - Fassihi et al. Int. J. Pharm. 72: 175-178, (1991)

## Study Objectives

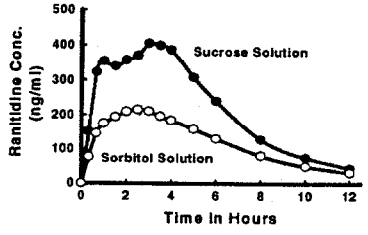
- Published and in-house data suggests that low permeability excipients such as sorbitol (or mannitol), in amounts used in typical syrup formulations, can significantly reduce bioavailability of drugs that also exhibit low intestinal permeability
  - Bioavailability of drugs that exhibit high intestinal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

## Formulations

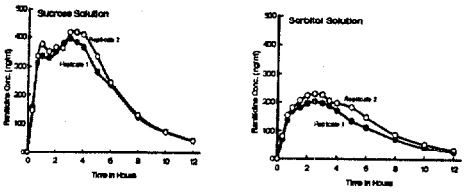
| Ingredient | Test Formulation | Reference Formulation | BCS Permeability |
|---|---|---|---|
| Ranitidine | 0.15 g | 0.15 g | Low |
| Sucrose | - | 5 g | High* |
| Sorbitol | 5 g | - | Low |
| Water | 15 ml | 15 ml | High |

* Rapidly metabolized at/in the intestinal wall to glucose and fructose, both exhibit complete absorption

## Results: Average Profiles (n=40)



## Results: Average Profiles (n=20)




## Bioequivalence: Average Criteria

| Parameter | Lower 90% CI | Upper 90%CI |
|---|---|---|
| Ln (Cmax) | 44% | 54% |
| Ln(AUCL) | 50% | 60% |
| Ln(AUCI) | 52% | 62% |

Note: Solution containing sucrose was used as the reference

## Individual Bioequivalence

| Parameter | Intra-subject Std. dev. | | | S-F-I* | 95% Upper Confidence Bound | |
|---|---|---|---|---|---|---|
| | Sorbitol | Sucrose | Ratio | | Constant Scaled | Reference Scaled |
| Ln(Cmax) | 0.24 | 0.24 | 1.0 | 0.13 | 0.58 (Null) | 0.61 (Null) |
| Ln(AUCL) | 0.19 | 0.17 | 1.1 | 0.14 | 0.46 (Null) | 0.41 (Null) |
| Ln(AUCI) | 0.2 | 0.16 | 1.2 | 0.15 | 0.42 (Null) | 0.38 (Null) |

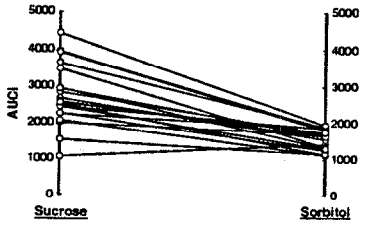
*S-F-I: Subject-by-formulation interaction

## Results

- On average, bioavailability of ranitidine from sorbitol solution was about 50% that of sucrose solution
  - Mean Tmax 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

## Subject-by-Formulation Interaction?

Estimate = 0.15 for AUCI



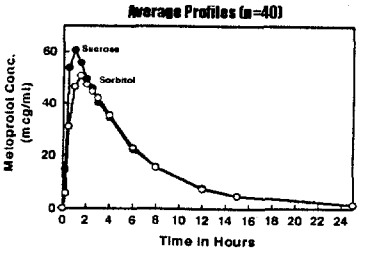

## Conclusion

- A significant risk of bioINequivalence 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 bioINequivalence is lower for drugs that exhibit high intestinal permeability

## Generalization of these results?

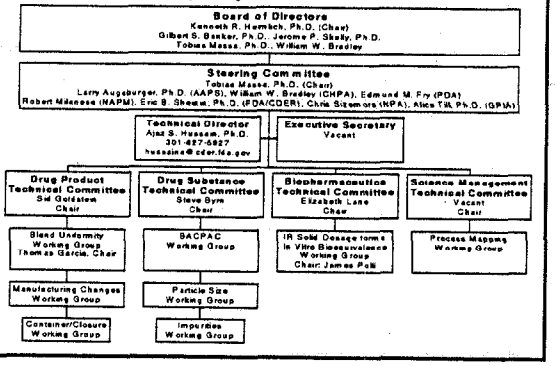
- To address this question a study was carried out with metoprolol as a model high permeability drug
  - Preliminary results suggest that difference in bioavailability between sorbitol and sucrose solution is significantly less than what was observed for ranitidine

## Metoprolol Study: Preliminary Data




## PQRI

Product Quality Research Institute




## Founding Members

- **The Institute is comprised of eight founding member organizations:**
  - **AAPS; the Consumer Healthcare Products Association (CHPA), the Generic Pharmaceutical Industry Association (GPIA); the National Association of Pharmaceutical Manufacturers (NAPM); the National Pharmaceutical Alliance (NPA), the Parental Drug Association (PDA), the Pharmaceutical Research and Manufacturing Association (PhRMA), and the Center for Drug Evaluation and Research (CDER) of FDA.**
  - **AAPS is responsible for the day-to-day management of the Institute.**

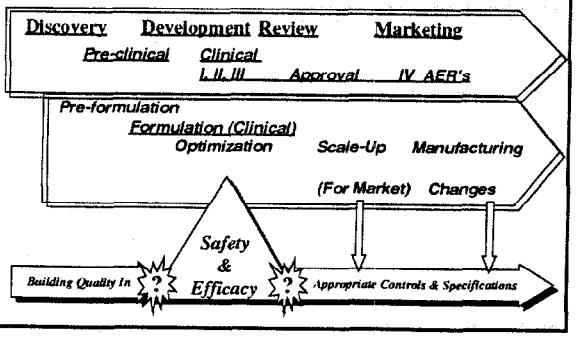
## PQRI Recommendations to FDA

- **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




## Regulatory Hypothesis Approach

- **Drug Product Technical Committee**
  - **Ho: 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: ????**



## 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"



## 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, and excipients** (container/closure systems not covered under SUPAC-IR)
  - **Why? Ajaz Hussain**
  - **Why not? Sid Goldstein, Arni Repta, and Stve Byrn**



## 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



## 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
    - one point acceptance criterion
    - 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 Goldstein
  - ***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 thieves is the only accepted method
  - For most powder blends, blend testing for every production batch is not necessary and that unit dose sampling, using sampling thieves, can pose significant problems.
  - The gap in the scientific understanding and regulatory policies are a source of continued debate and, from an industry perspective, undesirable regulatory action.
  - Current policies may be diverting industry and FDA time and resources to address a redundant question.

## Blend Uniformity Testing

- **Approach**
  - Identify if/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

## Blend Uniformity Testing

- **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 Lane
  - ***In vitro drug release and other appropriate physico-chemical product tests can be developed to assure equivalent rate and extent of drug absorption from pharmaceutical equivalent dosage forms***
    - ***In Vitro Methods for Bioequivalence Assessment of IR Solid Dosage Forms (extension of BCS based biowaivers)***

## Current Research Focus

- Drug Substance Technical Committee
  - Chairperson: Steve Byrn
  - ***Adherence to CGMPs and a critical comparison of the analytical results encompassing specifications, impurity profile, 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***

## 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 (SMTC Meeting 4 November 1998).***
    - ***Process mapping (CMC & Biopharm.)***

## Additional Information

- WWW.PQRI.ORG

# Center for Drug Evaluation and Research
# Office of Pharmaceutical Science
# Office of Testing and Research

## Publications and Presentations 1999 - 2000

### Product Quality (Pharmaceutical Chemistry and Biopharmaceutics)

Screening for Corticosteroids in Topical Pharmaceuticals by High – Performance Liquid Chromatography with a Scanning Ultraviolet Detector. Reepmeyer, J.C. *Journal of Liquid Chromatography and Related Technologies.* In press.

Mahayni, H., Rekhi, G. S., Uppoor, R. S., Marroum, P., Hussain, A. S., Augsburger, L. L., and Eddington, N. D. Evaluation of External Predictability of an In vitro – In Vivo Correlation for an Extended Release Formulation Containing Metoprolol Tartrate. J. Pharm. Sci. (in press).

Near – Infrared Reflectance Spectroscopic Determination of Acetaminophen in Tablets. Jefferson, E.H., Spencer, J.A., BoClair, T., Chan, J. *Journal of Association of Official Analytical Chemists International.* In press.

The FDA Regulatory Methods Validation Program for New and Abbreviated New Drug Applications. Layloff, T., Nasr, M., Baldwin, R., Caphart, M., Drew, H., Hanig, J., Hoiberg, C., Koepke, S., Lunn, G., MacGregor, J.T., Mille, Y., Murphy, E., Ng, L., Rajagopalan, R., Sheinin, E., Smela, M., Welschenbach, M., Winkle, J., Williams, R. *Pharmaceutical Technology,24*(1), 30 – 42, (2000).

A. Adveef, C.M. Berger, and C. Brownell "pH-Metric Solubility. 2: Correlation between the Acid-Base Titration and the Saturation Shake-Flask Solubility pH Methods". *Pharm. Res.* 17, 85-89 (2000).

Pharmaceutical Fingerprinting in Phase Space. 1. Construction of Phase Fingerprints. Aksenova, T.I., Tetko, I.V., Ivakhnenko, A.G., Villa, A.E.P., Welsh, W.J., Zielinski, W.L. *Analytical Chemistry*, 71, 2423-2430 (1999).

Pharmaceutical Fingerprinting in Phase Space. 2. Pattern Recognition. Tetko, I.V., Aksenova, T.I., Patiokha, A.A., Villa, A.E.P., Welsh, W.J., Zielinski, W.L., Livingstone, D.J. *Analytical Chemistry*, 71, 2431-2439 (1999).

Algorithms for Validating Chiral Properties of Insulins. Purdie, N., Province, D.W., Layloff, T.P., Nasr, M.M. *Analytical Chemistry*, 71, 3341-3346(1999).

Dowell, J. A., Hussain, A. S., Devane, J. and Young, D. Artificial Neural Networks Applied to the In Vitro - In Vivo Correlation of an Extended-Release Formulation: Initial Trials and Experience. *J. Pharm. Sci. 88: 154-160 (1999).*

Kaus, L. C., Gillespie, W R., Hussain, A. S. and Amidon, G. L. The Effect of In Vivo Dissolution, Gastric Emptying Rate and Intestinal Transit Time on the Peak Concentration and Area Under-the-Curve of Drugs with Different Gastrointestinal Permeabilities. *Pharm. Res. 16:272-280 (1999).*

Hussain, A. S., Lesko, L. J., Lo, H, Y., Shah, V. P., Volpe, D. and Williams, R. L. The Biopharmaceutics Classification System: Highlights of the FDA's Draft Guidance. *Dissolution. Technology. 6: 5-9 (1999).*

X. Wang, T. Sakuma, E. Asafu-Adjaye, G.K. Shiu. Determination of ginsenosides in plant extracts from Panax ginseng and Panax quinquefolius L. by LC/MS/MS. *Anal. Chem.* 71:1579-1584 (1999).

L.Yu, A. Bridgers, J. Polli, A. Vickers, S. Long, A. Roy, R. Winnike, M. Coffin. "Vitamin E-TPGS increases absorption flux of an HIV protease inhibitor by enhancing its solubility and permeability". *Pharm. Res.* 16:1812-1817 (1999)

C. W. Andrews, L. Bennett, and L.X. Yu. "Predicting human oral bioavailability of a compound: Development of a novel quantitative structure-bioavailability relationship". *Pharm. Res.* 17:639-644 (2000)

L.X. Yu. "An integrated model for determining causes of poor oral drug absorption". *Pharm. Res.* 16:1883-1887 (1999)

L X. Yu and G.L. Amidon. "A compartmental absorption and transit model for estimating oral drug absorption". *Int. J. Pharm.* 186:119-125 (1999)

L.X. Yu, L.A. Gatlin, and Gordon L. Amidon. "Predicting gastrointestinal drug absorption in humans". In G. L. Amidon, P. L. Lee, and E. M. Topp (Eds.). Transport Processes in Pharmaceutical Systems. Marcel Dekker, Inc., 1999, pp. 377-409

**Abstracts:**

Consistency Measures for Recombinant Protein Drugs: Single and Couple - Column HPLC Retention and Peak Dimensions of Insulin Variants. Brower, J.F., Doub, W.H., Jefferson, E.H., Zielinski, W.L., Layloff, T.P. *22nd International Symposium on High Performance Liquid Phase Separations and Related Techniques*, St. Louis, Missouri, May 1999. [Abstract]

Characterization of Various Forms of Insulin by Protease Digestion followed by HPLC. Doub, W.H., Feldman I., Senderovich, D. *22nd International Symposium on High Performance Liquid Phase Separations and Related Techniques*, St. Louis, Missouri, May 1999. [Abstract]

Development and Application of Simple Fingerprinting Strategies for Ensuring Quality and Consistency of Drug Products. Drew. H.D. *A.O.A.C. International 113th Annual Meeting and Exposition*, Houston, Texas, September 1999. [Abstract]

*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. Prasanna[1], Everett H. Jefferson[1], Jeb S. Taylor[1], Ajaz S. Hussain[1], Richard F. Karuhn[2], Robbe C. Lyon[1], [1]FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD; [2]Particle Technology Labs, Downers Grove, IL

"Lot-To-Lot Variability In Extended Shelf Life Of Selected Drug Products". Jeb S. Taylor[1], Ajaz S. Hussain[1], Eric B. Sheinin[2], Robbe C. Lyon[1], [1] FDA, Division of Product Quality Research,

Nicholson Research Center, Kensington, MD and [2]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[1], Charles R. Brownell[1], H.R. Prasanna[1], Ajaz S. Hussain[1], Smita Debnath[2], Raj Suryanarayanan[2], Robbe C. Lyon.[1], [1] FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD; [2]Department of Pharmaceutics, University of Minnesota, Minneapolis, MN

"When Is the Solid-State Of Drug Relevant To Its Performance? Smita Debnath, S.[1], Robbe C. Lyon, R[2], Ajaz S. Hussain[2], and Raj Suryanarayanan[1], [1]Department of Pharmaceutics, University of Minnesota, Minneapolis, MN, [2]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[1], Everett H. Jefferson[2], T. BoClair[1], and J. Chan[1], [1]Division of Pharmaceutical Analysis, FDA, St. Louis, MO and [2]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[1], M. A. Strafford[1],C.R. Brownell[2], R.C. Lyon[2], P. Artursson[3], C.A.S. Johansson[3], K. Luthman[4], [1]pION INC, Woburn, MA, [2]FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD; [3]Uppsala University, Uppsala, Sweden; [4]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*[1,2], John R. Crison[3], Michal L. Vieira[3], Aly H. Nada[2], Youssef E. Hammouda[2], A. Hussain[4] and Gordon L. Amidon[1], [1]College of Pharmacy, University of Michigan, Ann Arbor, MI; [2]Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt; [3]PORT Systems, LLC 540 Avis Drive, Ann Arbor, MI, [4] 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[1], Lawrence X. Yu[2], Ajaz S. Hussain[2], James E. Polli[1], [1]University of Maryland, Baltimore, MD; [2] 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[1], Christopher D. Ellison[1], Larry J. Lesko[2], and Ajaz S. Hussain[1], [1]FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD; [2]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[1], Lawrence X. Yu[2], and Ajaz S. Hussain[2], [1]University of Michigan, College of Pharmacy, Ann Arbor, MI; [2] FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

"Can Human Oral Bioavailability Of A Compound Be Quantitatively Predicted?" C. Webster Andrews[1], Lee Bennett[2], Lawrence X. Yu[3], [1]GlaxoWellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709, [2]National Institute of Environmental Health Sciences, 111 Alexander Drive, MS D2-04, Research Triangle Park, NC 27709. [3] FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

"Fluid Mechanical Analysis of Topical Vaginal Formulations". D.H. Owen[1], A.M. Plenys[1], A. S. Hussain[2] and D.F. Katz[1], [1]Department of Biomedical Engineering, Duke University, Durham, NC, [2]FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

"Replicate Design Bioequivalence Study Evaluation of an Oral Solution of Ranitidine Containing Sorbitol". Ajaz S. Hussain[1], Marvin Meyer[2], Arthur Straughn[2], Anthony Ciavarella[1], Patrick Faustino[1], Mei-Ling Chen[1], Rabindra Patnaik[1], and Larry Lesko[1]., [1]CDER, FDA: Rockville, MD; [2]University of Tennessee: Memphis, TN

"Solubilization Characteristics of A Commercial Ginseng Product". Ebenezer B. Asafu-Adjaye, Jin T. Wang, William Worsley, Patrick Faustino, Lawrence X. Yu and Ajaz S. Hussain, FDA, Division of Product Quality Research, Nicholson Research Center, Kensington, MD

**Pharmacology and Toxicology**

**Publications:**

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