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Dissolution Testing

Maximizing the Use of Novel Dissolution Approaches to Minimize Product Failures

JUNE 25-26, 2007, RADISSON-PLAZA WARWICK, PHILADELPHIA, PA

Featuring Case Studies and Lessons Learned from Industry Experts!

- **Strategies for Developing In Vivo – In Vitro Correlations (IVIVC)**
- **Examining Best Methods for Extended Release and Poorly Soluble Products**
- **Selecting and Implementing Current and Novel Approaches to Dissolution Testing where Traditional Methods Have Failed**
- **Utilizing Computational Fluid Dynamics, Particle Imaging Velocimetry and Laser-Induced Fluorescence to Overcome Product Failures**
- **Understand the Advantages and Limitations of Various Instruments**
- **Control Hydrodynamics and Utilize High-Performance Systems**
- **Selecting the Right Automation Solution for Your Company**

Featuring In-Depth Regulatory Coverage On:

Implementing a Quality by Design (QbD) Approach to Dissolution Testing

Fernando Muzzio, Ph.D., Professor of Chemical Engineering, Rutgers University



Featuring Representation from Leading Companies:

Accelrys
SOTAX Corporation
Primera PharmaLab
Analytical Solutions Inc.

Alcon Research Limited
Merck Research Laboratories
ICON Development Solutions
PharmEng Innovations

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Monday, June 25, 2007

8:30

OPENING WORKSHOP: DISSOLUTION TESTING: IMPLEMENTING A QUALITY BY DESIGN (QBD) APPROACH

Fernando Muzzio, Ph.D., Professor of Chemical Engineering, Rutgers University

8:30: Conference Registration and Coffee

9:00: Workshop Begins

During this in-depth session, we will cover "QbD" approaches for dissolution testing. "Quality by design" is a methodology that generally relies on the development of predictive relationships (whether statistical or fundamental) between inputs (material properties, process parameters) and responses (product attributes) for product optimization and quality control. For dissolution (or more appropriately, bioavailability), application of the methodology is complicated by a number of factors:

- The effect of relevant inputs is poorly understood (in fact, the inputs themselves are sometimes unknown)
- The range of product responses that one wishes to control (from immediate release to sustained release) is quite wide, and the diversity of product architectures used to accomplish these responses is very substantial
- The actual response one wishes to control (bioavailability) is unavailable as a control measurement
- The accepted surrogate measure (dissolution) is only available after long delays, it is unsuitable for real time control, and is affected by substantial technique errors

After cataloguing these barriers, we will review the impact of material and process variables on dissolution (API particle size, MgSt, shear history, hydrophobicity, coating effects). Subsequently, we will cover statistical methodologies for identification and impact assessment of critical material/process variables. The presentation will include worked out examples and DOX templates. Finally, we will focus on application of inferential methods for the development of a predictive framework that bypasses dissolution testing as a routine control method.

12:00: Luncheon

About your workshop leader:

For the last 15 years, pharmaceutical product and process design has been Professor Muzzio's main research and educational focus. As founder of the Rutgers University Pharmaceutical Engineering Program, Dr. Muzzio's accomplishments include the development of the new National Science Foundation Engineering Research Center on Structured Organic Particulate Systems, which represents the largest and most prestigious grant given by the NSF to an engineering organization. FDA and 30 companies are currently partners.

Professor Muzzio has participated in Government-Industry-Academic forums that focused on upgrading the regulations that control drug development. He was the academic member of the PQRI Blend Uniformity working group, which was the source of the proposal that was the basis for the current draft guidance on blend and content uniformity issued by FDA in October 2003. His input is also reflected in the guidance on Process Analytical Technologies, recently issued by the FDA. He is also actively involved in industry/government forums dealing with the FDA's PAT initiative.

1:30 **Chairperson's Welcome and Opening Remarks**

1:45 Selection of Bio-Relevant Dissolution Media for Poorly Water-Soluble Drugs

Lijuan Tang, Ph.D., Director/Formulation Development, Primera PharmaLab

With the new rules from the FDA, ANDA submission now requires both fasted and fed bio-equivalence studies to obtain approval status. It is always a challenge for formulators and analysts to develop a discriminatory and bio-relevant dissolution method suitable for evaluating a poorly water-soluble drug. This case study discusses a selection of dissolution medium on three bio-enhanced formulations of a poorly water-soluble new chemical entity. It will focus on the dissolution data interpretation and analysis; general practice on selecting different dissolution media; and In Vivo bioavailability data.

- What should be considered when selecting a bio-relevant dissolution medium?
- Should we use sink conditions in bio enhanced formulation screening?
- Dissolution results correlated to In Vivo bioavailability data

EXAMINE NOVEL DISSOLUTION APPROACHES AND METHODOLOGIES

2:30 *Current and Novel Applications for USP Apparatus 4 – Flow Through Dissolution Testing*

Marc Finn, Manager, SOTAX Corporation

USP Apparatus 4 or the flow through dissolution system has been employed for many years in the testing of different dosage forms such as tablets and capsules. Historically, it has been the method of choice for extended release and poorly soluble products. However, recent formulations and drug delivery technologies developed by industry have required a newer approach to dissolution testing where traditional USP 1 (Baskets) and USP 2 (paddles) methods have failed. The purpose of this presentation is to briefly discuss the methodology and new applications for such products as Modified Release Tablets, APIs and Powders, Drug Eluting Stents, Medical Devices and Implants, Microsphere, Injection and Suspension formulations, Soft gels and suppositories.

- Methodology of Flow Through Dissolution Testing (open vs closed loop configurations)
- USP requirements for Apparatus 4 including calibration
- Method development parameters for Apparatus 4
- Advantages of USP 4 compared with traditional dissolution methods
- Discussion of usefulness as an alternative method to USP 2 method
- Case study for MR tablets included

3:15 *Refreshment Break*

UTILIZING COMPUTATIONAL FLUID DYNAMICS, PARTICLE IMAGING VELOCIMETRY AND LASER-INDUCED FLUORESCENCE TO OVERCOME PRODUCT FAILURES

3:30 *Assessment of Hydrodynamic Effects in Dissolution Testing* **Fernando Muzzio, Ph.D., Professor of Chemical Engineering, Rutgers University**

In the last five years, work performed at Rutgers University, NJIT, and other academic institutions has

demonstrated that USP II dissolution testing is strongly affected by the wide diversity of hydrodynamic shear environments present within a dissolution vessel under standard conditions. Shear rates are strongly dependent on position, varying by as much as 100% within a small region around the bottom of the vessel. This variability, which is an intrinsic consequence of the symmetric design of the system, can have a strong impact on both the dissolution rate and the disintegration behavior of tablets, among several readily observable effects.

Several commercial methods are available for characterizing, diagnosing, and minimizing these effects, including computational fluid dynamics, particle imaging velocimetry, and laser induced fluorescence. During this presentation, we will cover these methods, illustrate their application for characterizing the aforementioned hydrodynamic effects, and explain how they can be used for overcoming product failures.

NEW STRATEGIES FOR LOW-VOLUME DISSOLUTION TESTING

4:15 *Guide Early Phase Formulation Development Using a Micro-Dissolution Instrument* **Yun Mao, Ph.D., Research Fellow, Merck Research Laboratories**

Dissolution is an important test to guide early phase formulation development. Traditionally, dissolution test is carried out in a standard bath of 500 to 900mL medium. Due to limited API and formulation materials at early phase development, smaller volume dissolution is often desired. In this work, we evaluated a new mDissolution instrument, which utilized an in situ fiber optic UV measurement and allows dissolution to be conducted in volumes from 2mL to 20mL. Dissolution screening of API with different properties and a variety of prototype formulations can be achieved with hundreds fold less materials. We found the instrument useful for API intrinsic dissolution under sink conditions; API solubility measurement; early phase formulation screening in biologically relevant medium; and excipients screening to guide formulation development. The advantages and limitations of the instruments will also be discussed.

5:00 *Close of Day One*

Tuesday, June 26, 2007

CONTROL HYDRODYNAMICS AND UTILIZE HIGH-PERFORMANCE SYSTEMS

8:45

Physicochemical and Bio-Relevance Through Controlled Hydrodynamics

Larry Stevens, Senior Scientist, Alcon Research Limited

On the forefront of dissolution today is its relevance to physical-chemical and especially biological properties. Critical to this, along with needed precision especially between laboratories, is the proper control of hydrodynamics. This session will focus on understanding and controlling hydrodynamics in various systems, and the creation of a fully-automated high-performance system elucidating subtle chemical and in vivo relevant formulation differences, enabling kinetic modeling, and computer simulations for modified delivery systems. The following aspects will be discussed:

- Understanding the critical role of hydrodynamics
- Comparisons between closed and flow-through systems
- Opportunities to optimize / control hydrodynamics
- A fully automated high-performance system approach
- Improved physicochemical and bio-relevance

STRATEGIES FOR PREDICTING SOLUBILITY

9:30

Prediction of Aqueous Drug Solubility, Acidity, and Processability Using Multi-Scale Data Modeling and Analysis Methods

Michael Doyle, Principal Application Scientist, Accelrys

Selections of active pharmaceutical substances and their processability is a core process on the pathway from research laboratory to clinic. Crystalline or amorphous solubility in gastric media or water is of critical importance in designing dosage forms and formulations. If solubility is not well understood in a system, significant additional development resources may be needed to ensure its successful development, or it may be discarded. Therefore it would be desirable to know the solubility at an early stage of development. Experimental

determination of the solubility of drug molecules is unfortunately a very laborious activity. Much time and effort could be saved if solubility could be reliably predicted by computation or at least ranked.

An increasing interest in robust processes has grown in pharmaceutical technology. The ideas of Genichi Taguchi have been used to find one or more optimal combinations of the process variables that would not only lead to the required granulation properties, but also to a stable product of which the properties are not sensitive to noise factors or other causes of variation. The Taguchi approach has been used to prepare an optimal product that is not sensitive to a change in for example impeller speed, because the impeller speed cannot be controlled easily during upscaling of the process. This approach can easily be combined with other responses in a multi criteria optimization procedure for pharmaceutical technological development.

10:15

Refreshment Break

EXTENDED COVERAGE ON THE BENEFITS OF DISSOLUTION TESTING AUTOMATION

10:30

Strategies for and Benefits of Automating Dissolution Testing

YC Lee, Ph.D., Senior Director, PharmEng Innovations

To improve laboratory efficiency, most pharmaceutical companies are focusing on laboratory automation. Often, the efforts of these automation projects focus on the instrumentation (hard ware), but may not pay close strategy. This presentation will focus on the implementation of one of the most popular forms of laboratory automation - dissolution automation.

While it is imperative that the correct automated instrumentation be selected, it is critical to define the user requirements and expectations up front. This presentation will cover different user requirements, as well as vendor selection, and implementation strategy. A detailed cost analysis will be presented to compare all costs and expenses before and after automation to show the real benefits of automation. In addition, a case study will be presented to illustrate the common mistakes in

the implementation process.

- Understanding why you want to automate
- Selecting the right automation solution for your organization
- Providing detailed explanations of implementation strategy
- Comparing all up front costs and hidden costs for automated dissolution testing
- Illustrating the common mistakes in the implementation process

11:45 Luncheon

MAXIMIZING THE USE OF IN VITRO – IN VIVO CORRELATIONS

1:15 *In Vitro-In Vivo Correlations (IVIVC): Maximizing Their Use in Product Development*
Stuart Madden, Senior Vice President, ICON Development Solutions

The presentation provides the details of In Vitro-In Vivo Correlations and how they are developed. Their use as a tool in the product development process is then described and examples provided with respect to their use in aiding specification setting, prototype selection and scale up post approval changes. The audience will:

- Gain an understanding of the overall approach to how an IVIVC is developed,
- Gain an understanding of how an IVIVC can be a valuable tool for product development
- Gain an understanding of how an IVIVC can be useful to support post approval changes

2:00 *Predicting in vivo Performance of BCS II/IV Compounds By Dissolution on USP 4 Apparatus*
Michael Wang, Senior Research Scientist, Merck and Company

In vitro dissolution for several compounds was conducted on USP 4 apparatus in biorelevant media to support their clinical formulation development. The results were successfully applied in the prediction of their in vivo performance i.e. in ranking formulations and food effect. In addition, the in vitro tests on USP 4 apparatus have been demonstrated an important tool in understanding of possible in vivo dissolution mechanism for the formulations. An IVIVR was established for a compound based on the dissolution and animal study results.

2:45 Refreshment Break

DEVELOPING AND VALIDATING THE RELEASE TEST

3:00 *Considerations in Developing and Validating Release Tests*

Kailas Thakker, Ph.D., President and CEO, Analytical Solutions Inc.

Dissolution of semisolid and some novel dosage forms is determined using diffusion of the active pharmaceutical ingredient into an appropriate receiving medium. Several different types of diffusion cells/apparatus are in use, Franz diffusion cells being one of the more popular apparatus. Some considerations in developing and validating the release test will be discussed with appropriate examples. Some application of Franz diffusion cells for novel solid oral dosage forms will be described.

3:45 *Novel In-Vitro Screening of Excipients for Early Development of Low-Solubility Compound Formulations*

Maria T. Cruanes, Sandy Robertson, Henry Wu and Wei Xu, Pharmaceutical Research and Development, Merck and Co.

A novel approach that relies on dose- and bio-relevant measurements of solubility, dissolution or physical dispersion of low solubility compounds to select key formulation excipients will be presented. This approach, which is alternative to conventional dissolution, aims to rationally probe and address the compound's physical chemical properties that might control in vivo absorption. Additionally, this approach allows for miniaturization of experiments and saves API, an important advantage during early stage development. Case studies that include in vivo data and relationship with in vitro data will be discussed.

- Rational formulation design
- API sparing measurements
- IVIVC

4:30 *Panel Discussion: Examining Current Technologies and Dissolution Strategies: Current Developments and Considerations*

During this interactive discussion, hear faculty members discuss new developments and technologies available that have recently changed industry approaches to dissolution testing. Key considerations including novel approaches, IVIVC and regulatory considerations will be addressed.

5:00 Close of Conference



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The Radisson-Plaza Warwick is located in the heart of downtown Philadelphia, and adjacent to beautiful Rittenhouse Square. From the conference venue, you can access many points of interest in Philadelphia including Independence Hall, the Kimmel Center and the Avenue of the Arts and numerous shops, hotels and excellent restaurants!



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VENUE INFORMATION:

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