Evolution of Dissolution Testing: Toward Prediction of In Vivo Performance

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M-CERSI Workshop: The Evolution of Biopharmaceutics: Risk Assessment and Clinical Relevance – April 30 – May 1, 2026

In Vitro Dissolution Testing: Objectives

- Assure batch to batch consistency
- Provide “process control” and quality assurance
- Guide development of new formulations
- Ascertain the need for bioequivalence studies
  - BCS-based Biowaiver
  - Generic Drugs
  - Different strengths
  - Post-approval changes

In Vitro Dissolution Testing Serves Dual Roles

- Assure batch to batch consistency
- Provide “process control” and quality assurance

Process Control Dissolution

- Guide development of new formulations
- Ascertain the need for bioequivalence studies
  - BCS-based Biowaiver
  - Generic Drugs
  - Different strengths, scale-up or site transfers
  - Post-approval changes

Biodiscriminating Dissolution

The AAPS Journal, Vol. 19, No. 6, November 2017 (© 2017)
DOI: 10.1208/s12248-017-0117-1

White Paper

Approaches for Establishing Clinically Relevant Dissolution Specifications for Immediate Release Solid Oral Dosage Forms

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Abstract. This manuscript represents the perspective of the Dissolution Analytical Working Group of the IQ Consortium. The intent of this manuscript is to highlight the challenges of, and to provide a recommendation on, the development of clinically relevant dissolution specifications (CRS) for immediate release (IR) solid oral dosage forms. A roadmap toward the development of CRS for IR products containing active ingredients with a non-narrow therapeutic window is discussed, within the context of mechanistic dissolution

Biodiscriminating Dissolution

- Biodiscriminating Dissolution
  - A dissolution test is biodiscriminating when it distinguishes drug product variants that are bioequivalent from those that are not.
  - Biodiscriminating methods typically require an external anchor, defined as evidence that in vitro differences translate to meaningful in vivo outcomes (e.g., plasma exposure, onset of action, or pharmacodynamic response); however, this requirement may not be necessary in all cases.

Conceptual Shift: From Process Control to Biodiscriminating

- Process control dissolution ensures process consistency, which refers to how reproducibly the manufacturing process operates—batch after batch.
- Biodiscriminating dissolution ensures product quality, which refers to what the product is and whether it is fit for its intended use in patients.

Process Control and Biodiscriminating Dissolutions Can Diverge

A highly consistent process can still produce poor-quality product if it is centered on the wrong target or built on incorrect assumptions. The withdrawal of Budeprion illustrates the importance of selecting tests that are predictive of in vivo performance. Otherwise, the consequences can range from redevelopment of the product to patient harm

The NEW ENGLAND JOURNAL of MEDICINE

Withdrawal of Generic Budeprion for Nonbioequivalence

Janet Woodcock, M.D., Mansoor Khan, R.Ph., Ph.D., and Lawrence X. Yu, Ph.D.

The Food and Drug Administration (FDA) has completed a head-to-head bioequivalence study of single doses of the generic drug Budeprion XL 300 mg (extended-release bupropion hydrochloride,

manufactured by Impax Laboratories and distributed by Teva Pharmaceuticals) and the brand-name drug Wellbutrin XL 300 mg.

Budeprion XL 300 mg became the subject of intense media coverage describing adverse events in patients being treated for major

Evaluation and Rese
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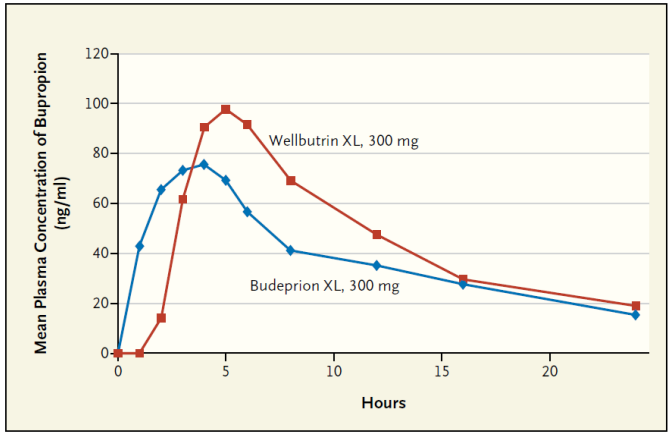
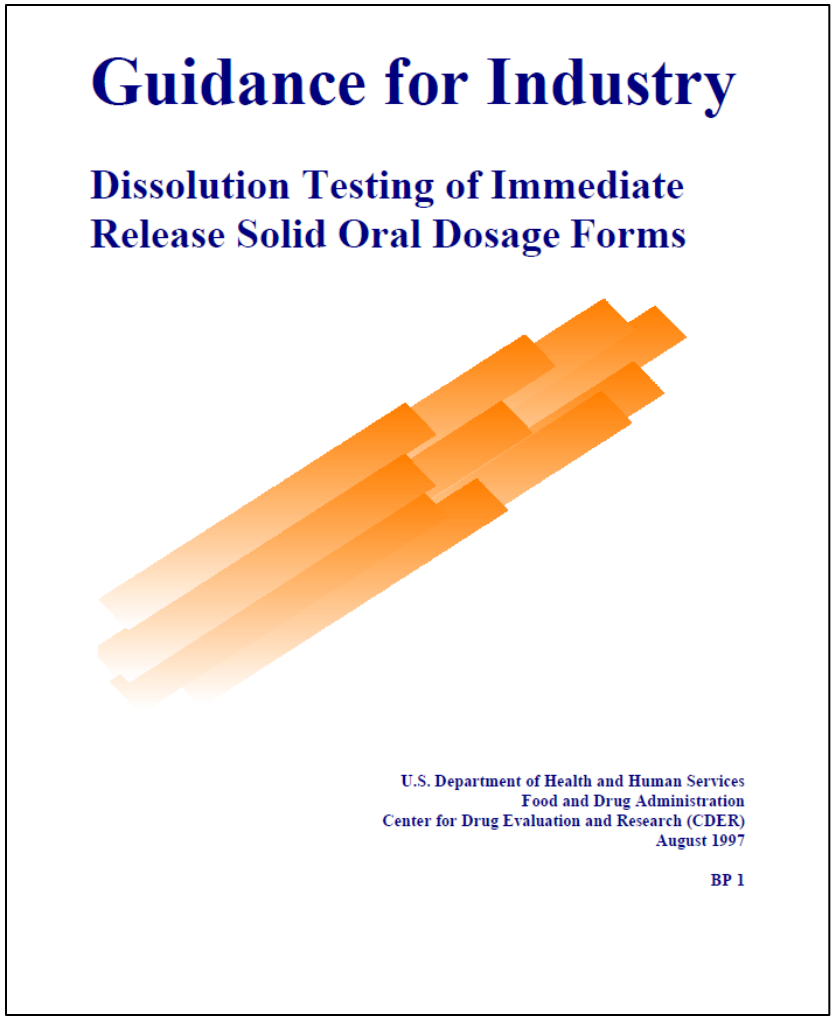
alence limits of 8



Mean Plasma Concentration of Bupropion (Budeprion XL and Wellbutrin XL) as a Function of Time in 24 Fasting Healthy Volunteers.



The concept of biodiscriminating dissolution testing is not new

"The in vitro test serves as a tool to distinguish between acceptable and unacceptable drug products. Acceptable products are bioequivalent, in terms of in vivo performance, whereas unacceptable products are not"

Quality by Design (QbD)

- ICH Q8(R1): 2006
  - "quality cannot be tested into products, i.e., quality should be built in by design."
- ICH Q8(R2): 2009
  - Quality by Design (QbD): : A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management
  - QTPP and CQA

Pharmaceutical Research, Vol. 25, No. 4, April 2008 (© 2007)
DOI: 10.1007/s11095-007-9511-1

Research Paper

Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control

Lawrence X. Yu[1,2]

Received September 9, 2007; accepted November 26, 2007; published online January 10, 2008

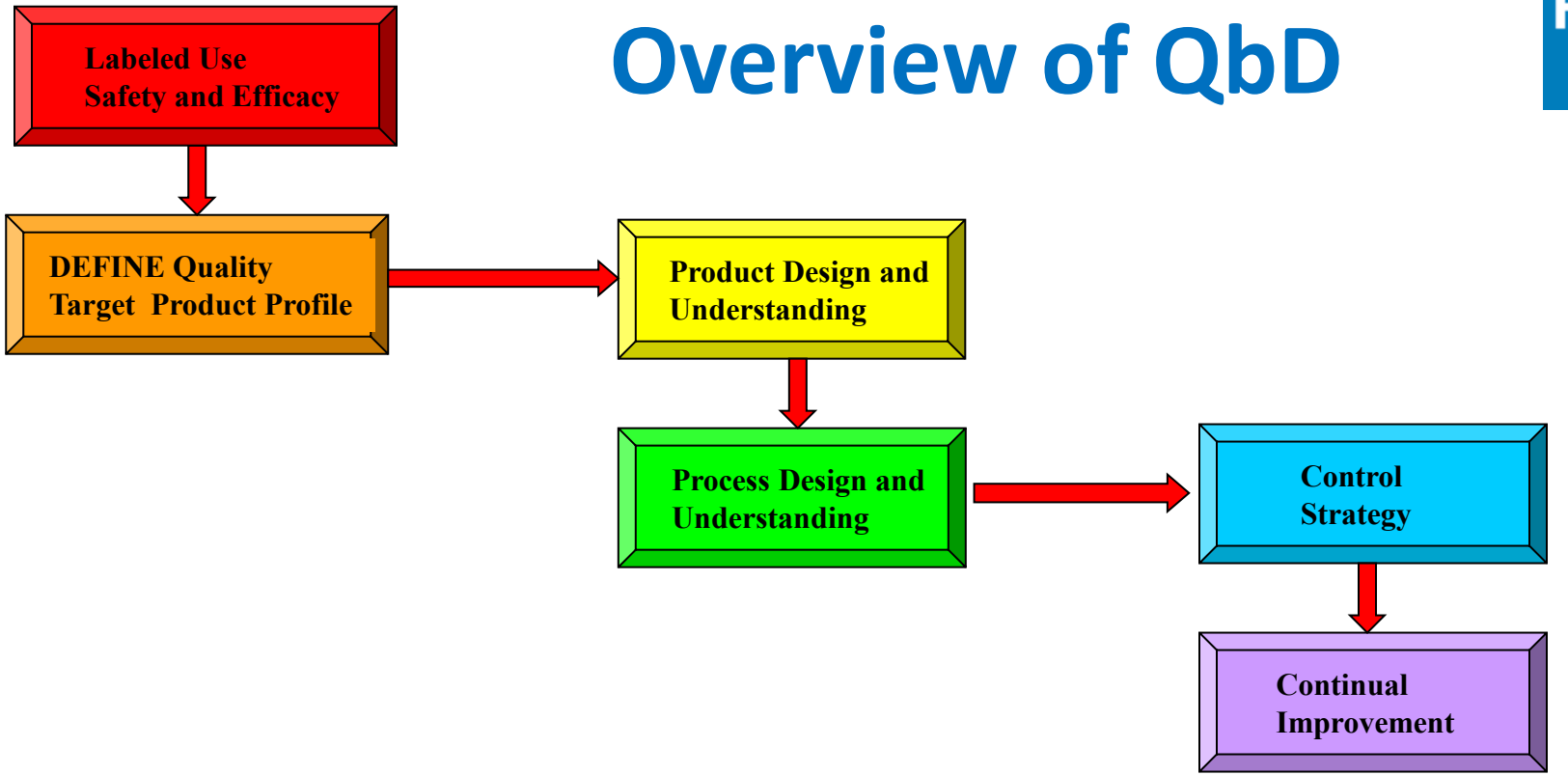
Purpose. The purpose of this paper is to discuss the pharmaceutical Quality by Design (QbD) and describe how it can be used to ensure pharmaceutical quality.
Materials and Methods. The QbD was described and some of its elements identified. Process parameters and quality attributes were identified for each unit operation during manufacture of solid oral dosage forms. The use of QbD was contrasted with the evaluation of product quality by testing alone.
Results. The QbD is a systemic approach to pharmaceutical development. It means designing and developing formulations and manufacturing processes to ensure predefined product quality. Some of the QbD elements include:

- Defining target product quality profile
- Designing product and manufacturing processes
- Identifying critical quality attributes, process parameters, and sources of variability
- Controlling manufacturing processes to produce consistent quality over time

Conclusions. Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. Product testing confirms the product quality. Implementation of QbD will enable transformation of the chemistry, manufacturing, and controls (CMC) review of abbreviated new drug applications (ANDAs) into a science-based pharmaceutical quality assessment.

KEY WORDS: pharmaceutical quality by design; pharmaceutical quality by testing; process control; process design; process parameter; process variability; product design; quality attribute; question-based review.

Overview of QbD



TARGET
(CQAs: Dissolution)

DESIGN and
UNDERSTANDING
(CMAs and CPPs)

IMPLEMENTATION

QbD Product and Process Understanding: Linking CMAs and CPPs to CQAs

The AAPS Journal (© 2014)
DOI: 10.1208/s12248-014-9598-3

Review Article

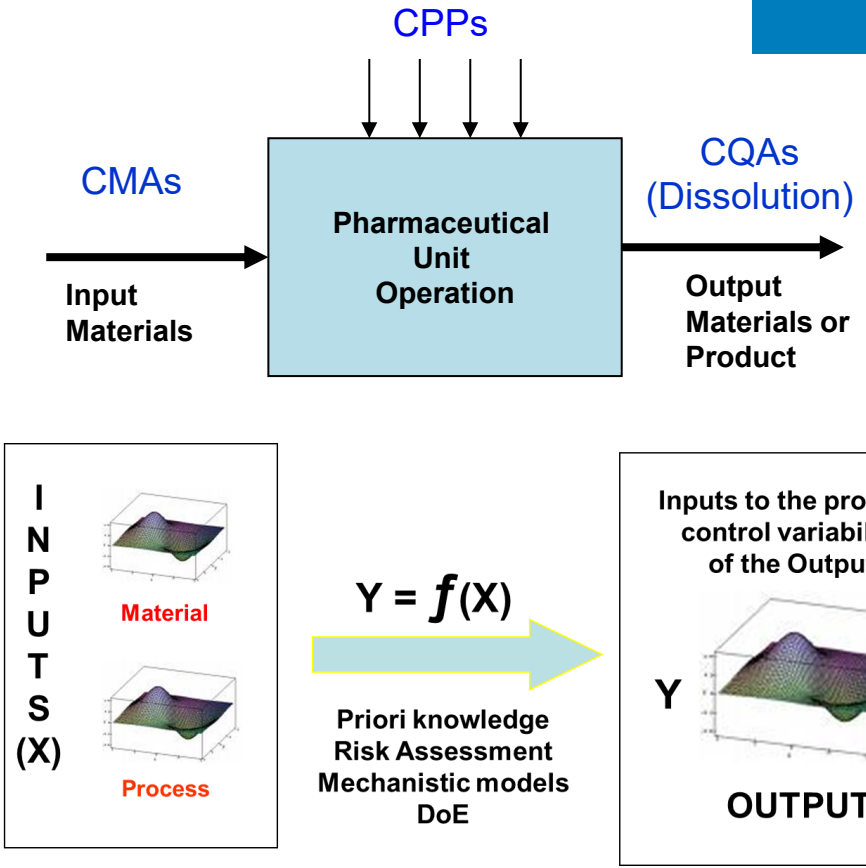
Understanding Pharmaceutical Quality by Design

Lawrence X. Yu,[1,6] Gregory Amidon,[2] Mansoor A. Khan,[1] Stephen W. Hoag,[3] James Polli,[3] G. K. Raju,[4,5] and Janet Woodcock[1]

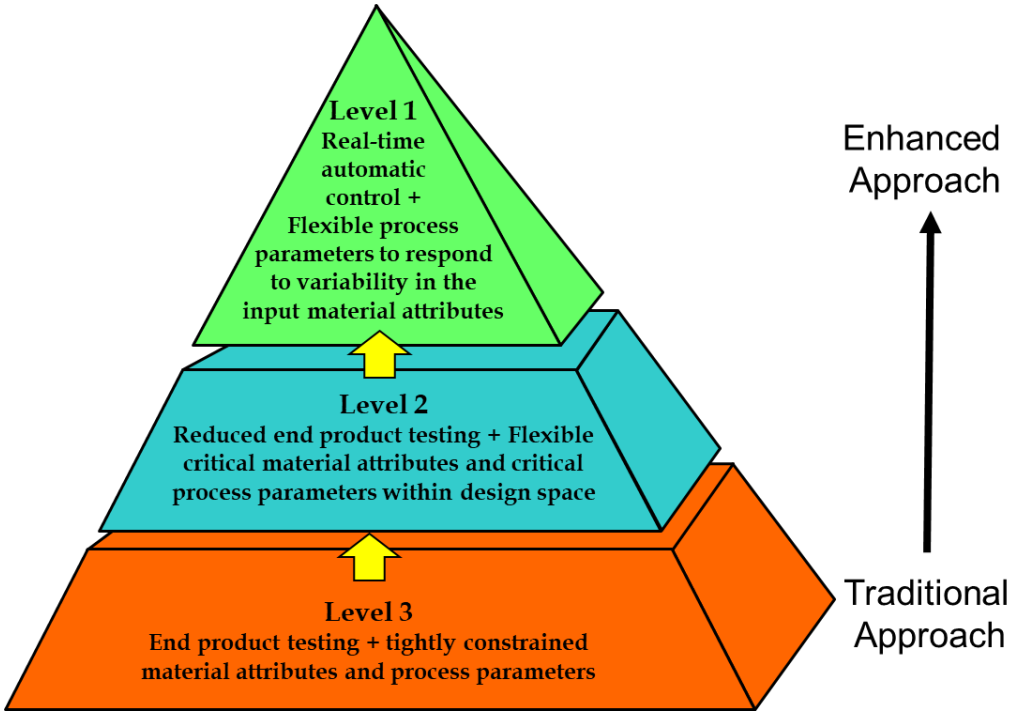
Received 17 November 2013; accepted 24 March 2014

Abstract. This review further clarifies the concept of pharmaceutical quality by design (QbD) and describes its objectives. QbD elements include the following: (1) a quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product; (2) product design and understanding including identification of critical material attributes (CMAs); (3) process design and understanding including identification of critical process parameters (CPPs), linking CMAs and CPPs to CQAs; (4) a control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process; and (5) process capability and continual improvement. QbD tools and studies include prior knowledge, risk assessment, mechanistic models, design of experiments (DoE) and data analysis, and process analytical technology (PAT). As the pharmaceutical industry moves toward the implementation of pharmaceutical QbD, a common terminology, understanding of concepts and expectations are necessary. This understanding will facilitate better communication between those involved in risk-based drug development and drug application review.

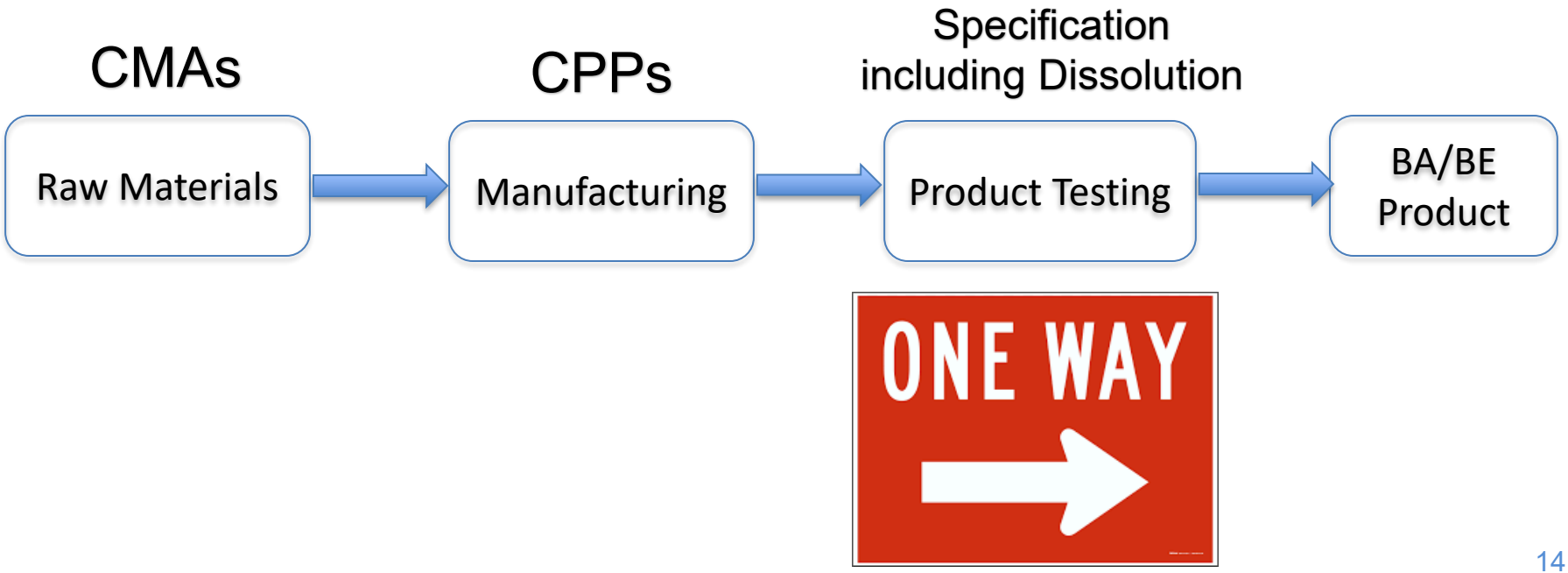
KEY WORDS: control strategy; critical quality attributes; pharmaceutical quality by design; process understanding; product understanding.



Biodiscriminating Dissolution Enhances Control Strategy in QbD



Focusing Dissolution's Role Solely on Assuring BA/BE

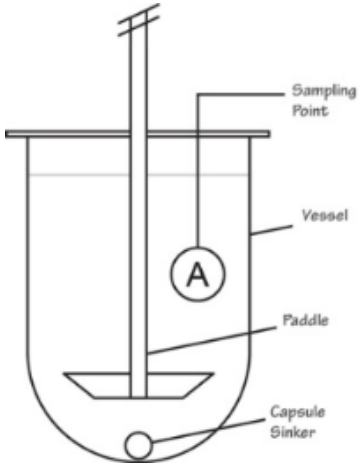


Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Biopharmaceutics



"For immediate-release solid oral drug products containing a high solubility drug substance (as defined herein), the dissolution criterion is Q=80% in 30 minutes"

The AAPS Journal (2021) 23: 113
DOI: 10.1208/s12248-021-00639-0

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Research Article

Theme: Integrating In Vitro Systems and Physiologically-Based Pharmacokinetics Modeling to Optimize Drug Product Development

Guest Editors: Rodrigo Cristofoletti and Lawrence Yu

Understanding *In Vivo* Dissolution of Immediate Release (IR) Solid Oral Drug Products Containing Weak Acid BCS Class 2 (BCS Class 2a) Drugs

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Abstract. *In vivo* drug dissolution kinetics of BCS Class 2a IR solid oral drug products remains largely unknown. An understanding to what extent the solubility influences *in vivo* dissolution is needed to design appropriate *in vitro* dissolution methods. In this study, non-steroidal anti-inflammatory drugs (NSAIDs) are used to investigate the *in vivo* dissolution of BCS Class 2a drugs based on numerical deconvolution analyses. The PK data were obtained from published literature or drug applications submitted to the FDA. It has been hypothesized that the *in vivo* drug dissolution rate would likely correlate to the solubility of NSAIDs in the media at gastrointestinal pH. Our findings show a short lag time of absorption (T_{lag}), comparable to the liquid gastric emptying time and independent of the solubility and formulation. *In Vivo* drug dissolution of NSAIDs was generally rapid and complete within the regular drug residence time in the small intestine while multi-phase absorption was observed in some subjects for all the NSAIDs. The comparisons of *in vivo* drug dissolution rate, which was characterized by *in vivo* dissolution half-life (T_{half}), indicate that solubility has a minimal impact on *in vivo* drug dissolution rate for NSAIDs. Gastric emptying regulated by migrating motor complex (MMC) under fasted state most likely governs drug dissolution and absorption of NSAIDs. For BCS Class 2a IR solid oral drug products, large variability of gastric emptying and MMC as well as the strong driving force of intestinal absorption probably outweigh the impact of solubility on drug *in vivo* dissolution.

KEY WORDS *In vivo* dissolution · BCS class 2a · NSAID · Deconvolution · Gastric emptying

FDA

Gastric emptying…most likely governs drug dissolution and absorption of NSAIDs. For BCS Class 2a IR solid oral drug products, large variability of gastric emptying and MMC as well as the strong driving force of intestinal absorption probably outweigh the impact of solubility on drug in vivo dissolution.

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Perspective

Physiologically Based Biopharmaceutics Modeling (PBBM): Best Practices for Drug Product Quality, Regulatory and Industry Perspectives: 2023 Workshop Summary Report

Published as part of Molecular Pharmaceutics virtual special issue "2023 PBBM Workshop for Drug Product Quality".

Claire Mackie,* Sumit Arora, Paul Seo, Rebecca Moody, Bhagwant Rege, Xavier Pepin, Tycho Heimbach, Christer Tannergren, Amitava Mitra, Sandra Suarez-Sharp, Luiza Novaes Borges, Shinichi Kijima, Evangelos Kotzagiorgis, Maria Malamatari, Shereeni Veerasingham, James E. Polli, and Gregory Rullo

Cite This: *Mol. Pharmaceutics* 2024, 21, 2065−2080

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ABSTRACT: Physiologically based biopharmaceutics modeling (PBBM) is used to elevate drug product quality by providing a more accurate and holistic understanding of how drugs interact with the human body. These models are based on the integration of physiological, pharmacological, and pharmaceutical data to simulate and predict drug behavior in vivo. Effective utilization of PBBM requires a consistent approach to model development, verification, validation, and application. Currently, only one country has a draft guidance document for PBBM, whereas other major regulatory authorities have had limited experience with the review of PBBM. To address this gap, industry submitted confidential PBBM case studies to be reviewed by the regulatory agencies; software companies committed to training. PBBM cases were independently and collaboratively discussed by regulators, and academic colleagues participated in some of the discussions. Successful bioequivalence "safe space" industry case examples are also presented. Overall, six regulatory agencies were involved in the case study exercises, including ANVISA, FDA, Health Canada, MHRA, PMDA, and EMA (experts from Belgium, Germany, Norway, Portugal, Spain, and Sweden), and we believe this is the first

Future State of Dissolution Testing

- An in vitro dissolution test that provides predictive insight to in vivo performance. This ensures high quality drug products that maintain safety and efficacy throughout the product lifecycle. With an in vivo predictive dissolution, the impact of critical material attributes and critical process parameters on in vivo performance can be quantitatively assessed by in vitro dissolution. This provides scientific and risk-based knowledge to support patient-centric quality standards.