The Biopharmaceutics Risk Assessment Roadmap for Optimizing Clinical Drug Product Performance

ARZU SELEN,[1] PAUL A. DICKINSON,[2] ANETTE MÜLLERTZ,[3] JOHN R. CRISON,[4] HITESH B. MISTRY,[5] MARIA T. CRUAÑES,[6] MARILYN N. MARTINEZ,[7] HANS LENNERNÄS,[8] TIM L. WIGAL,[9] DAVID C. SWINNEY,[10] JAMES E. POLLI,[11] ABU T. M. SERAJUDDIN,[12] JACK A. COOK,[13] JENNIFER B. DRESSMAN[14]

[1]Office of New Drug Quality Assessment, US Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, Maryland
[2]Quantitative Clinical Pharmacology, AstraZeneca, Macclesfield, UK
[3]Faculty of Pharmaceutical Sciences, University of Copenhagen, Copenhagen, Denmark
[4]Bristol-Myers Squibb, New Brunswick, New Jersey
[5]Physiomics PLC, Oxford, UK
[6]Merck & Company, West Point, Pennsylvania
[7]US FDA/CVM, Rockville, Maryland
[8]Department of Pharmacy, University of Uppsala, Uppsala, Sweden
[9]Child Development Center, University of California, Irvine, California
[10]iRND3, Mountain View, California
[11]School of Pharmacy, University of Maryland, Baltimore, Maryland
[12]College of Pharmacy and Health Sciences, St. John's University, Queens, New York
[13]Pfizer Inc., Groton, Connecticut
[14]Institute of Pharmaceutical Technology Biocenter, Johann Wolfgang Goethe University, Frankfurt, Germany

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ABSTRACT: The biopharmaceutics risk assessment roadmap (BioRAM) optimizes drug product development and performance by using therapy-driven target drug delivery profiles as a framework to achieve the desired therapeutic outcome. Hence, clinical relevance is directly built into early formulation development. Biopharmaceutics tools are used to identify and address potential challenges to optimize the drug product for patient benefit. For illustration, BioRAM is applied to four relatively common therapy-driven drug delivery scenarios: rapid therapeutic onset, multiphasic delivery, delayed therapeutic onset, and maintenance of target exposure. BioRAM considers the therapeutic target with the drug substance characteristics and enables collection of critical knowledge for development of a dosage form that can perform consistently for meeting the patient's needs. Accordingly, the key factors are identified and *in vitro, in vivo,* and *in silico* modeling and simulation techniques are used to elucidate the optimal drug delivery rate and pattern. BioRAM enables (1) feasibility assessment for the dosage form, (2) development and conduct of appropriate "learning and confirming" studies, (3) transparency in decision-making, (4) assurance of drug product quality during lifecycle management, and (5) development of robust linkages between the desired clinical outcome and the necessary product quality attributes for inclusion in the quality target product profile. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3377–3397, 2014

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INTRODUCTION

Patient-centric drug development can greatly benefit from a systems approach where drug substance, drug product, and patient health benefit are considered as a system in its entirety, and collection of critical drug development information is carried out according to a "learn and confirm" paradigm. Using systems thinking principles for generating information and knowledge management can facilitate optimization of clinical performance of the drug products for the patient benefit.

The growth and application of systems thinking expanded in early 1940s with individuals including Walter Shewart, W. Edward Deming, Joseph Juran, George Box, and others demonstrating its positive impact on improvement of product quality as well as on product costs.[1–7] Application of systems thinking and the critical value of collaborative efforts has continued to gain awareness over the years. This is evident in numerous publications on systems thinking and its application in diverse fields advocating interdisciplinarity. There are a growing number of pharmaceutical collaborational organizations and partnerships formed by public, academic, industry, government, and private organizations,[8–12] such as those cited here, which seek to develop new tools for accelerating learning

Correspondence to: Arzu Selen (E-mail: arzu.selen@fda.hhs.gov)
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and decision-making. Many collaborative partnerships are exploring not only novel tools but also opportunities for testing and advancing tools in "real organizations" as recommended by Peter Senge and John Sterman for systems thinking and organizational learning.[13]

The biopharmaceutics risk assessment roadmap (BioRAM) described here is one way of applying systems thinking to drug development for patient health benefit and was previously identified as a key element for integration of biopharmaceutics and quality by design (QbD) at the 2009 workshop.[14,15] The patient health benefit is defined as the core driver in the development process. Thus, this approach emphasizes the value of therapy-driven drug delivery scenarios supported with specifically designed dosage form(s) and clinically relevant specification setting. The workshop explored how the knowledge gained from the biopharmaceutics studies using a multidisciplinary approach can be used for drug product specification setting. During the breakout sessions, the workshop participants identified key areas for systematic advances. These areas were grouped into the following four categories and the BioRAM represents a key category enabling integration of all.

1. Quality target product profile (QTPP)-driven specifications
2. BioRAM
3. Advancing and leveraging science and technology including mechanistic understanding, *in silico* tools, statistical approaches, and manufacturing and controls, and
4. Knowledge sharing and collaborations based on multidimensional collaborations, shared database, and glossary development.

The biopharmaceutics risk in this context is defined as the risk of not achieving the intended *in vivo* drug product performance by delivering the drug substance in a manner such that it has the best chance of consistently meeting the patient/consumer needs. According to BioRAM, assessment of suitability of a drug substance for the targeted indication starts early at candidate selection and includes considerations such as how it may be delivered for the intended therapeutic outcome. Initially, there may be limited information on the drug substance and its pharmacologic activity and mechanism of action. Subsequent studies, as guided by the BioRAM, identify the studies that are needed to achieve the steps necessary to meet the therapeutic target.

BioRAM benefits from the richness of biopharmaceutics and related sciences. Some references are provided as examples of the many methods, tools and considerations that might be applied for generating data and decision-making as part of the BioRAM efforts. The application of BioRAM is illustrated by the semi-hypothetical examples in Section *Discussion: Case Studies Using the Basic Roadmap to Illustrate the Scenario-Specific Approaches (Roadmaps)*, where knowledge gained leads to rapid feasibility assessments on the approach taken, and whether additional work may be justified for the specific drug delivery scenario for a particular drug substance. To illustrate the distinction between scenario-specific considerations, the examples developed here start with drug delivery profiles known to be suitable for the intended therapeutic outcome. It is possible that for a novel compound with limited information on the drug substance and its clinical pharmacology, the optimal drug delivery profile may not be immediately apparent early in development. In these instances, the intended therapeutic effect being acute or chronic will drive selection of the delivery pattern (Scenario 1 or Scenario 4, as described in this document). As these examples demonstrate, knowledge gained may lead to a no-go decision or require an alternate delivery route or dosage form to ensure safe and efficacious delivery of the drug substance. The computational, *in silico* modeling and simulation tools may assist in exploring optimization of the drug product, and drug delivery scheme(s) and the boundaries. Regardless of the drug delivery scenario, according to BioRAM, the drug product development process is envisioned as iterative and is supported by predetermined feasibility assessments as the development process advances.

Understanding the mode of action of a drug substance and its optimal delivery for generating the desired therapeutic effect is the central tenet of BioRAM. Based on mechanistic knowledge gained about the drug substance and how it elicits the intended response, BioRAM can help to select the optimal drug delivery scenario and, ultimately, the ideal dosage form.

BioRAM utilizes a "Learn and Confirm" approach for identifying and addressing knowledge gaps and follows the concept originally described and promoted by Lewis Sheiner for clinical trials.[16] Although Sheiner considered the Phase III trials in the clinical setting to be the confirmatory studies, in the BioRAM paradigm, the confirmatory studies for the drug product would ideally be conducted before Phase III trials to enable use of the optimized drug product throughout the late Phase II as well as the Phase III clinical trials. The BioRAM approach can guide selection of the dosage form for the confirmatory studies, and advance development of well-characterized and optimized drug products designed with minimized formulation-related variability. The use of drug products that deliver the intended dose in the intended manner increases the likelihood of a successful outcome in the clinical trials.

It is expected that the application of the BioRAM will enable

1. Feasibility assessment of drug product development for decision-making (such as identification of barriers, selection of dosage form and formulation, and development of a robust/reliable drug product)
2. Generation of the critical knowledge to support product development
3. Development of robust, reliable, and transparent links between drug product and the *in vitro* and *in vivo* performance of drug product leading to identification of drug delivery parameters that are clinically relevant, and
4. Development of a mechanism for multidisciplinary communication and decision-making

Of note, to support the application of BioRAM, a supporting risk assessment tool ("BioRAM scoring tool") will be discussed in subsequent publications. The BioRAM scoring tool is a science- and knowledge-based prognostic tool. Its use can identify the necessary studies to address critical questions, knowledge gaps, the decision points, and improve the likelihood of successful optimization of a drug product for meeting therapeutic objectives. The BioRAM scoring tool is envisioned as a risk assessment/scoring system similar to APGAR that is used as a prognostic scoring approach in pediatrics.[17]