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Clinical Trials and Translational Medicine Commentary

Optimizing Clinical Drug Product Performance: Applying Biopharmaceutics Risk Assessment Roadmap (BioRAM) and the BioRAM Scoring Grid

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ABSTRACT

The aim of Biopharmaceutics Risk Assessment Roadmap (BioRAM) and the BioRAM Scoring Grid is to facilitate optimization of clinical performance of drug products. BioRAM strategy relies on therapy-driven drug delivery and follows an integrated systems approach for formulating and addressing critical questions and decision-making (*J Pharm Sci*. 2014,103(11): 3777-97). In BioRAM, risk is defined as not achieving the intended *in vivo* drug product performance, and success is assessed by time to decision-making and action. Emphasis on time to decision-making and time to action highlights the value of well-formulated critical questions and well-designed and conducted integrated studies. This commentary describes and illustrates application of the BioRAM Scoring Grid, a companion to the BioRAM strategy, which guides implementation of such an integrated strategy encompassing 12 critical areas and 6 assessment stages. Application of the BioRAM Scoring Grid is illustrated using published literature. Organizational considerations for implementing BioRAM strategy, including the interactions, function, and skillsets of the BioRAM group members, are also reviewed. As a creative and innovative systems approach, we believe that BioRAM is going to have a broad-reaching impact, influencing drug development and leading to unique collaborations influencing how we learn, and leverage and share knowledge.

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Introduction

Pharmaceutical drug development has many success stories, but there are also numerous instances of lengthy development experiences with inconclusive or unsatisfactory outcomes. Despite collaborative efforts and partnerships, which explore approaches for improving efficiency, address delays, and shorten decision times, drug development costs are increasing while the high attrition rates of drug candidates during development remain.[1-8]

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The challenges and outcomes in some cases may be attributed to the drug development process that is generally linear and sequential, is more operational than strategic, and often relies on an additive time line.[9] This, coupled with the narrow focus on what is necessary for the next study or stage of development and need for quick resolutions, may postpone identifying and addressing the critical issue(s) for development of the drug product (DP) candidate. Furthermore, by following the sequential approach, key drivers for progression become the routine process with established timelines. Although a body of knowledge is generated over several years, timelines do not allow teams to take the opportunity to review data and reassess strategy, leading to missed opportunities. For example, too often optimal dose regimens are assumed early in the development process only to be proven wrong when postmarketing dose changes are necessary.[10-12]

In this commentary, the Biopharmaceutics Risk Assessment Roadmap (BioRAM) strategy is briefly reviewed, and the newly developed BioRAM Scoring Grid is presented. Together BioRAM and the BioRAM Scoring Grid offer a novel and an alternate strategy to drug development, in which systems thinking is integrated into drug development, utilizing fundamental biopharmaceutics concepts and therapeutic drug delivery as the framework. The use of systems thinking as a strategy in global organizational development and learning,[13-16] as well as in health care research and policy development is continuing to receive wide application.[17,18] By providing an integrated systems strategy, BioRAM facilitates development of critical questions that support targeted knowledge generation, feasibility assessments, and decision-making throughout the development process, including development of new candidates and life-cycle management of existing products, resulting in optimized DPs (see Glossary). To demonstrate the practical application of the BioRAM Scoring Grid, a worked example based on literature data is presented, and suggestions for applying BioRAM in a real-life drug development setting are provided.

The Background of BioRAM

BioRAM was first presented at its very early concept stage at the AAPS workshop[19] on "Developing A Biopharmaceutics Risk Assessment Road Map" in 2013; subsequently, BioRAM and a BioRAM Scoring Grid were presented through use of examples at the 2015 workshop[20] (Rockville, MD). In the 2014 BioRAM commentary,[21] 4 drug delivery scenarios (therapy-driven drug delivery; Fig. 1) and the BioRAM strategy (Fig. 2) were described and exemplified. It should be noted that they are not intended as a classification system of drugs based on different delivery scenarios or as an exhaustive list of possible drug development strategies or scenarios. Rather, the concept of a therapy-driven drug delivery scenario forces one to consider, at every stage of development, the clinical needs and the expected outcomes for a particular drug and how can the DP be developed and optimized to meet those clinical needs and achieve desired outcomes. Biopharmaceutics risk is defined as not achieving the intended *in vivo* DP performance.[21] Three types of studies—Learning, Learning and Confirming, or Confirming[22]—are conducted depending on the critical knowledge needs and the stage of the drug development program.

The BioRAM[21] (Fig. 2) depicts integrated drug development and outlines a sequence of events (such as conducting targeted studies for knowledge generation and assessments for decision-making) during product development. The dashed horizontal line in the figure symbolizes fluid integration of efforts; above the dashed line, the boxes represent decision steps and stages where data and knowledge are assessed and whether gained knowledge addresses the potential issues and is sufficient to advance the program. Below the dashed line are the Learn, and Learn and Confirm studies (including clinical studies) conducted which generate critical knowledge to support decision-making and feasibility assessments. The first Box is Basic Knowledge at the very left bottom corner of the roadmap and in left-to-right stepwise fashion,

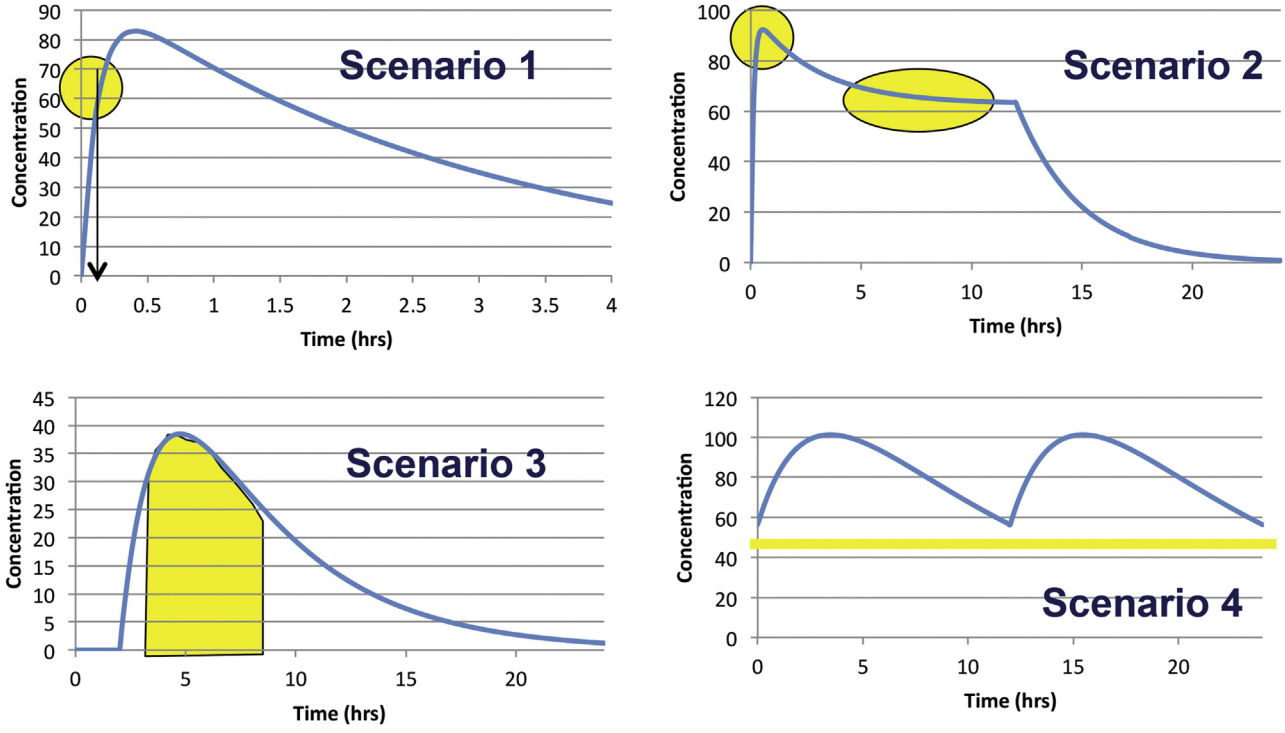

Figure 1. Depiction of plasma drug concentration-time profiles according to the 4 therapy-driven drug delivery scenarios: rapid therapeutic onset (Scenario 1), multiphasic delivery (Scenario 2), delayed therapeutic onset (e.g., chronotherapy; Scenario 3), and maintenance of target exposure (Scenario 4). Figure reproduced with permission from Elsevier, March 2016 (original 2014 publication in *J Pharm Sci*. Available at: http://onlinelibrary.wiley.com/doi/10.1002/jps.24162/full).