Integrated biopharmaceutical approach in pharmaceutical development and drug characterization: general concept and application

Sandra V. Cvijić, Svetlana R. Ibrić and Jelena V. Parojčić

Faculty of Pharmacy, Department of Pharmaceutical Technology and Cosmetology, University of Belgrade, Belgrade, Serbia

Abstract

The importance of biopharmaceutical considerations in pharmaceutical development and drug characterization has been well recognized both by pharmaceutical industry and regulatory authorities as a tool to establish predictive relationships between drug product quality attributes (*in vitro* data) and its clinical performance (*in vivo* data). In the present paper, contemporary biopharmaceutics toolkit including *in vivo* predictive dissolution testing, Biopharmaceutics Classification System, physiologically based pharmacokinetic and biopharmaceutics modeling and simulation, *in vitro-in vivo co*rrelation and biowaiver, are reviewed with regards to relevant general principles and applicability. The recently introduced innovative strategy for patient-centric drug development using an integrated systems approach grounded in fundamental biopharmaceutics concepts, clinical insights and therapeutic drug delivery targets, described as Biopharmaceutics Risk Assessment Roadmap (BioRAM) is also presented. Further development in the field will benefit from joint efforts and exchange of knowledge and experiences between pharmaceutical industry and regulatory authorities for the common goal to accelerate development of effective and safe drug products designed in accordance with patients' needs and expectations.

Keywords: biowaiver; clinical performance; dissolution testing; *in vitro-in vivo* correlation; physiologically based pharmacokinetic/biopharmaceutics modeling.

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1. INTRODUCTION

The importance of biopharmaceutical considerations in drug product development have been emphasized in the seminal work of Stanley Kaplan in the early 1970s [1,2]. It has been recognized that „*the biological availability of a drug is the result of many processes. Factors such as low solubility, slow dissolution or release rate, poor permeability, gastrointestinal degradation, and rapid biotransformation may all contribute to poor availability*", and that „*in the development of the new drug, a sequentially designed biological availability study does not begin with a drug formulation, it results in a drug formulation*" [1]. Furthermore, drug solubility in the gastrointestinal lumen and permeability across the gastrointestinal wall were identified as „*critical parameters associated with drug absorption*" following oral dosage form administration [2]. This was further elaborated and employed as the basis of the Biopharmaceutics Classification System introduced by Amidon et al in 1995 [3]. More recently, John Hodgson [4] provided a lively definition of a drug stating that "*A chemical cannot be a drug, no matter how active nor how specific its action, unless it is also taken appropriately into the body (absorption), distributed to the right parts of the body, metabolized in a way that does not instantly remove its activity, and eliminated in a suitable manner – a drug must get in, move about, hang around, and then get out*."

The importance of biopharmaceutical considerations in pharmaceutical development has been incorporated in the relevant Quality-by-Design (QbD) and Biopharmaceutics Risk Assessment Roadmap (BioRAM) concepts. These contemporary approaches which put the patient at the centre of the drug product development by exploring the specific patient needs, expectations and the desired therapeutic outcome, aim to link drug product physicochemical and biological properties (*i.e.* Critical Quality Attributes, CQA) with its clinical performance [5-9].

Corresponding author: Jelena Parojčić, University of Belgrade – Faculty of Pharmacy, Belgrade, Serbia
E-mail: jelena.parojcic@pharmacy.bg.ac.rs
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In the present paper, different biopharmaceutical tools and principles governing application of the integrated biopharmaceutical approach in pharmaceutical development and drug characterization are reviewed.

2. BIOPHARMACEUTICS TOOLKIT

Modern biopharmaceutics toolkit, which is used in drug product development, characterization and regulatory approval includes relevant *in vitro*, *in vivo* and *in silico* approaches, which can be combined to explore, model, and predict the rate and extent of oral drug delivery. Although long sought after as a surrogate for *in vivo* studies (*i.e.* such as in biowaiver), *in vitro* dissolution testing is increasingly accepted as a reliable indicator of the drug product clinical performance when used complementary with physiologically based pharmacokinetic/biopharmaceutics modeling (PBPK/PBBM) and *in vitro-in vivo* correlation (IVIVC).

2. 1. *In vivo* predictive dissolution testing

In vitro dissolution testing is generally accepted as the most important test for dosage form characterization, which is used in different phases of the product life-cycle, starting from the early development stages, through product optimization, including stability assessment, technology transfer, routine quality control and post-approval changes justification. Within the integrated biopharmaceutical approach in pharmaceutical development and drug characterization, dissolution testing is expected to serve as a substitute for *in vivo* testing, and the focus is placed on the discriminatory *in vivo* predictive dissolution test development and establishment of clinically relevant dissolution specifications [10-12]. While the most often used dissolution equipment for oral dosage form characterization includes compendial rotating paddle/rotating basket apparatus, extensive research efforts are directed towards design of dynamic apparatus which would more closely mimic hydrodynamics and transit times encountered *in vivo*, including the use of complex media, which simulate composition of physiological fluids in different parts of the gastrointestinal tract [13-16]. Two distinct approaches have been recognized: (i) biorelevant dissolution method which attempts to mimic complex factors, which are encountered under the physiological conditions *in vivo*, and may be useful in guiding formulation development and identification of food effects, and (ii) *in vivo* predictive (or, biopredictive) dissolution (iPD) method which includes a set of testing conditions that enable prediction of relevant pharmacokinetic profile, and is typically based on the established IVIVC [17]. The dissolution setup, which provides meaningful relationship between the data obtained *in vitro* and *in vivo* would enable evaluation of the impact of formulation factors and process parameters on the drug product clinical performance and identification of clinically relevant specifications. This implies that a clinically relevant dissolution method may be performed by using biorelevant dissolution conditions, but also that more simple experimental conditions may suffice as long as the method and acceptance criteria are capable of confirming or predicting *in vivo* drug performance [17-19].

2. 2. Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) has been introduced in 1995. as a theoretical framework to classify drug substances based on their gastrointestinal solubility and permeability as fundamental parameters controlling the rate and extent of drug absorption [3]. It has been widely accepted as an important biopharmaceutical tool in drug development and regulatory evaluation [20,21]. However, drug classification based on solubility and permeability is not straightforward and currently established low/high solubility and permeability boundaries are a subject of the ongoing scientific discussions. More recently, it also received considerable criticism for being overly conservative with respect to the established pH-solubility criteria, available media volume, applicability for the specific patient groups (such as paediatric population), veterinary applications, and applicability for other routes of drug administration (*i.e.* inhalation route, topical application), so that several modified classification systems have been proposed to address these limitations [22- 31].

2. 3. Physiologically based pharmacokinetic and biopharmaceutics modeling and simulation

A growing concern for biopharmaceutical characterization of drugs/pharmaceutical products prompted the development of *in silico* models for the prediction and mechanistic interpretation of the drug *in vivo* performance. One may find

various terms describing these modeling tools such as physiologically based pharmacokinetic (PBPK) models, physiologically based biopharmaceutics models (PBBM) or model informed drug development (MIDD) tools, but they all refer to the same object - a wide range of quantitative models used in drug development to understand absorption, distribution, metabolism, excretion and toxicity (ADMET) of drugs, and consequently, to facilitate the decision-making process.

PBPK models are basically mathematical models that integrate physiological parameters of humans (or animals) with drug and formulation properties to predict the expected pharmacokinetic outcome. They evolved rapidly, starting from a simple model of human gastrointestinal (GI) tract [32] to current complex models that integrate a number of parameters, able to simulate complex physiological mechanisms and drug disposition through different tissues [33-36]. Some of these models have been integrated in commercial software packages like GastroPlus™ (SimulationsPlus Inc, USA), Simcyp Simulator (Simcyp Limited, Certara, Inc. UK) and PK-Sim® (Bayer Technology Services GmbH, Germany). Furthermore, new knowledge about human physiology and disease-related changes enabled *in silico* estimation of drug performance in different patients and population groups [37-40]. PBPK models can conform different dosing routes, but major efforts have been directed to predict pharmacokinetics of orally administered drugs. A schematic representation of a PBPK model describing drug transport, absorption and disposition following oral administration is provided in Figure 1.

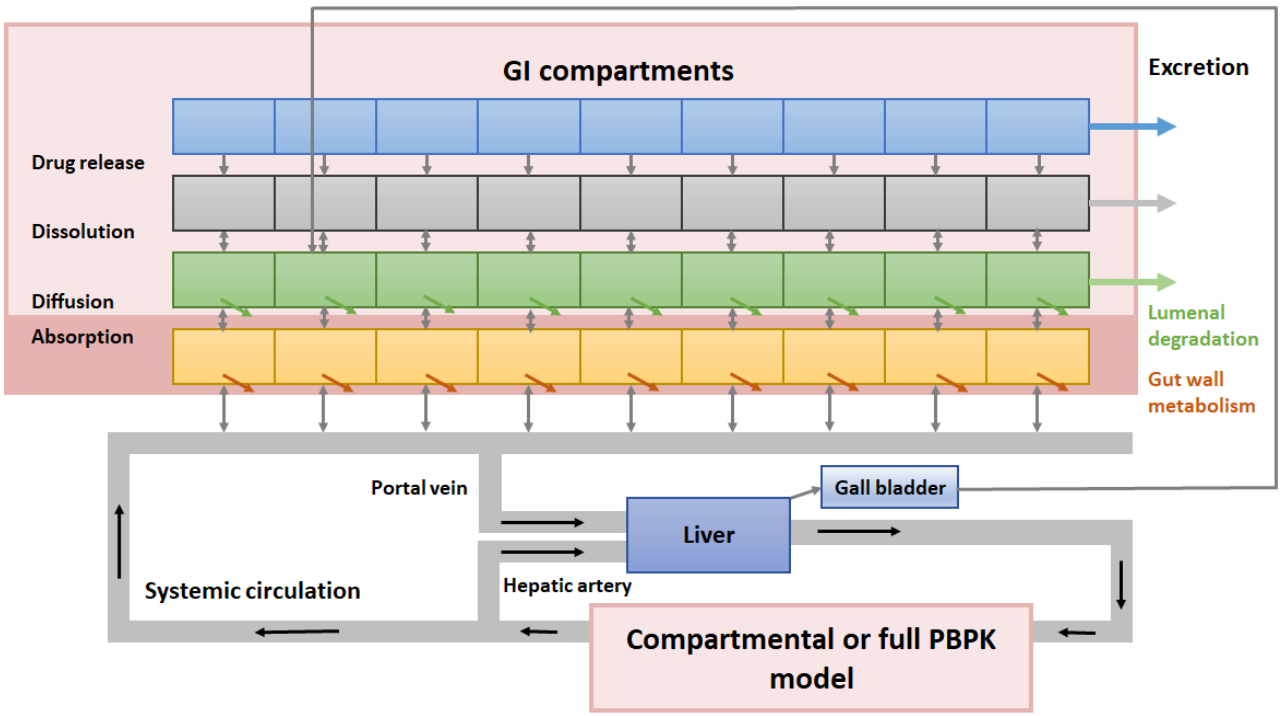

Figure 1. Representation of a PBPK model that describes drug transport, absorption and disposition following oral drug administration

PBPK models integrate a vast number of input parameters which need to be carefully selected and justified. Depending on available data, different modeling approaches can be used. Bottom-up approach is generally used for early predictions, based on drug physicochemical and some pharmacokinetic properties. But if clinical data are available, one can use the top-down approach and, for example, test hypotheses about the mechanisms governing drug absorption. The middle-out approach uses human *in vivo* data to confirm the model or make further refinements, such as parameter optimization.

The examples of PBPK modeling applications are numerous, ranging from sensitivity analysis and mechanistic interpretation of drug absorption to food effect evaluation, biowaiver justification, IVIVC development and virtual trials, including virtual bioequivalence studies. One of the fundamental modeling utilities is the possibility to mechanistically interpret oral absorption patterns of drugs with different biopharmaceutical properties, and understand the influence of drug properties, formulation factors and patients' physiological characteristics on the predicted pharmacokinetic profiles. Also, PBPK modeling can elucidate the combined mechanisms responsible for the positive or negative food effect on drug

absorption. Other modeling features include prediction of pharmacokinetic outcomes for different drug doses, different dosage forms, different patients *etc.* Moreover, virtual population studies enable estimation of the expected variability in drug performance in the selected group of subjects. It should be also noted that these models offer a distinctive opportunity to test hypotheses and explore "what-if" scenarios in cases when clinical studies are not feasible.

However, besides "pros", there are certain "cons" related to PBPK modeling, such as the lack of information on drug biopharmaceutical properties and and/or lack of *in vivo* data for model verification in some cases. Furthermore, our knowledge of human physiology is still rather limited. And finally, PBPK/PBBM modeling tools are sophisticated and complex, so adequate level of proficiency is required for their appropriate use.

2. 4. *In vitro-in vivo* correlation

An *in vitro* - *in vivo* correlation (IVIVC) is a mathematical model describing the relationship between an *in vitro* property of a dosage form (mainly dissolution or drug release) and a relevant *in vivo* response (mainly drug plasma concentration or amount absorbed) [41]. Within the new pharmaceutical quality paradigm and QbD, IVIVC is seen as a bridge linking pharmaceutical quality of the product and its clinical relevance [42,43]. This type of relationship may be expected for products containing poorly soluble drugs, and when the formulation controls the rate of appearance of drug in plasma, such as in the case of modified/extended release dosage forms. Development of meaningful IVIVC is the ultimate goal of biopharmaceutics drug characterization, which facilitates the formulation development, discriminatory dissolution method development and provides support for a clinically relevant dissolution specification establishment and biowaiver justification in different phases of the product life-cycle.

Although different levels of IVIVC have been described, including levels A, B, C and the multiple level C, the most useful and acceptable from both the industrial and regulatory points of view is the level A IVIVC. The level A IVIVC represents a point-to-point correlation between the predicted and *in vivo* observed plasma concentration - time profiles (*e.g.* convolution approach), or between the drug release profile observed *in vitro* and the relevant *in vivo* drug delivery input estimated by using different deconvolution approaches. In order to develop a meaningful IVIVC, at least three formulations with different drug release rates (*i.e.* slow, medium and fast) should be obtained and thoroughly characterized both *in vivo* and *in vitro*. *In vivo* study in the group of healthy volunteers should also include administration of the relevant reference dosage form with high bioavailability, such as intravenous bolus, oral solution or oral immediate release dosage form in order to obtain a unit impulse response (UIR) for deconvolution. Although conventional pharmacokinetic analysis based on the Wagner-Nelson method (in the case of one-compartment), and Loo-Riegelman method (in the case of a two-compartment pharmacokinetic model) can be employed to estimate the *in vivo* drug delivery input (*i.e.* hypothetical rate of drug absorption, or drug dissolution *in vivo*), the preferred and most frequently used is a two-stage approach based on numerical deconvolution [43]. Comprehensive *in vitro* characterization of the investigated formulations should be performed, using different experimental conditions with regards to media composition and hydrodynamics/agitation employed. The relationship between the estimated *in vivo* and *in vitro* profiles is then evaluated by using the linear regression analysis, or the applicable non-linear model. In order to compensate the eventual disproportion between the *in vivo* and *in vitro* profiles, appropriate time shifting/scaling may be employed. The concept of IVIVC development is schematically presented in Figure 2.

Introduction of PBPK/PBBM modeling, which integrates anatomical and physiological parameters of the gastrointestinal tract with the physicochemical properties of the drug substance and drug product properties enabled a model independent, mechanistic estimation of the *in vivo* drug delivery input based on the drug substance physicochemical and biopharmaceutical properties, thus overcoming certain limitations of the conventional deconvolution-based approach [43]. The increased applicability of PBPK/PBBM in IVIVC development has been demonstrated in several published studies [44-49].

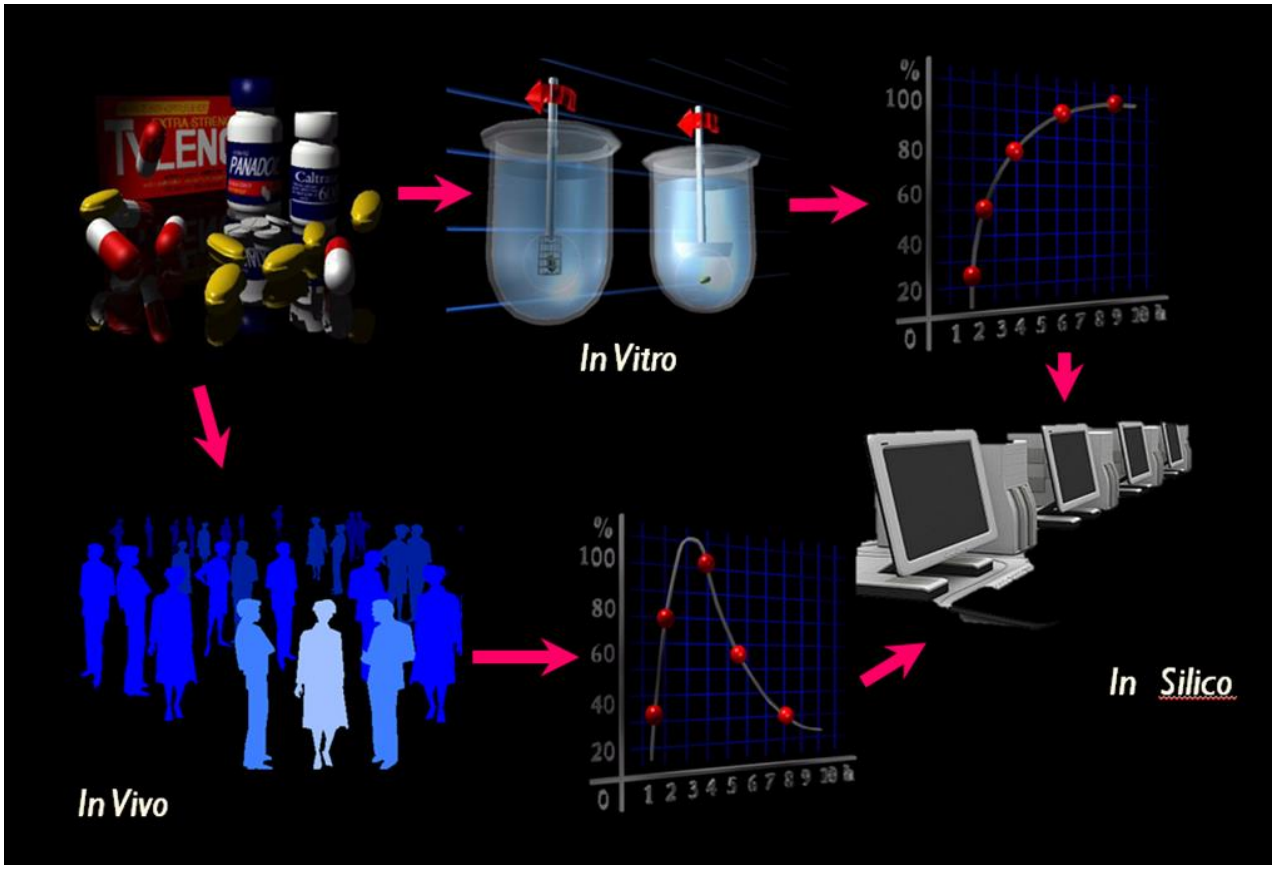

Figure 2. Schematic presentation of the IVIVC concept

2. 5. Biowaiver

Within the integrated biopharmaceutical approach in the pharmaceutical development and drug characterization, the term "biowaiver" is used to denote the regulatory drug approval process in which the dossier (application) is approved based on evidence of equivalence other than the *in vivo* bioequivalence test. The regulatory exemption from the *in vivo* bioequivalence studies must be based on the sound justification of the drug substance and drug product properties and the results obtained by comparative dissolution testing. At present, biowaiver is applicable for additional/lower strengths of proportionally similar formulations, immediate release solid dosage forms containing high solubility compounds (BCS class 1 and 3 drugs) and modified/extended release formulations with established IVIVC [21,50-52].

3. OPTIMIZATION OF A DRUG PRODUCT CLINICAL PERFORMANCE

Drug product *in vivo* performance is affected by a number of factors reflecting drug substance and dosage form properties, as well as the patient physiological status. Therefore, a thorough assessment of the potential factors that may influence the drug clinical performance is a priority in the pharmaceutical development. Formulation scientists use different tools to assess drug substance/drug product biopharmaceutical properties including *in vivo* clinical studies, biopredictive *in vitro* experiments, as well as computer-aided (*in silico*) modeling and simulations. Optimal clinical performance refers to accomplishment of the desired therapeutic response, drug safety, adequate product stability and minimization of inter-patient variability.

The innovative strategy for the patient-centric drug development using an integrated systems approach grounded in fundamental biopharmaceutics concepts, clinical insights and therapeutic drug delivery targets is described as the Biopharmaceutics Risk Assessment Roadmap (BioRAM) [7-9]. The aim of the BioRAM and the BioRAM Scoring Grid is to facilitate optimization of drug products clinical performance. In the 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. The integrated

product development starts with exploration of specific patient needs and desired therapeutic outcome and employs all available resources to secure clinical understanding of the impact and utility of new molecules in pharmacotherapy. The key items and impact that have to be considered include: understanding of the molecular mechanistic target for the intended therapeutic outcome; development of the relevant drug delivery approach taking into account patient needs; assessment of drug substance physicochemical and biopharmaceutical properties; identification of PK or PD effects leading to characterization of the target input profile (*i.e. in vitro* and *in vivo* dissolution/release profiles), development of a suitable formulation approach and robust and reliable assessment tools [7].

4. INDUSTRIAL APPLICATION AND REGULATORY RECOGNITION

Majority of available biopharmaceutics tools have been embraced within the pharmaceutical industry as an integral part of a drug development strategy aimed to support and accelerate regulatory approval of new drug products. Pharmaceutical companies act as a driving force for further development in the field. Recent advances related to the integrated biopharmaceutics approach in drug development and characterization resulted from the joint efforts of industry and academia working together on the major global projects and initiatives (such as the IMI funded OrBiTo project, UNGAP Cost action, International Consortium for Innovation and Quality in Pharmaceutical Development). With the accumulated scientific knowledge and experience, regulatory authorities tend to increasingly confide in the advanced biopharmaceutics tools. The regulatory recognition is reflected in the increased number of relevant submissions, as well as the recent scientific guidelines issued by the EMA and FDA [21,41,53-55].

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SAŽETAK

Integrisani biofarmaceutski pristup u razvoju i karakterizaciji lekova: opšti koncept i primena

Sandra V. Cvijić, Svetlana R. Ibrić I Jelena V. Parojčić

Univerzitet u Beogradu – Farmaceutski fakultet, Beograd, Srbija

(Stručni rad)

Značaj biofarmaceutskih razmatranja u razvoju i karakterizaciji lekova s ciljem uspostavljanja korelacije i mogućnosti predviđanja odnosa između *in vitro* podataka, odnosno karakteristika kvaliteta leka i njegovog *in vivo* ponašanja/kliničkog učinka, prepoznata je kako od strane farmaceutske industrije, tako i od strane odgovarajućih regulatornih tela. U radu je dat pregled savremenih biofarmaceutskih alata, uključujući prediktivno ispitivanje brzine rastvaranja lekovite supstance iz farmaceutskog oblika leka, Biofarmaceutski sistem klasifikacije, fiziološki zasnovano farmakokinetičko i biofarmaceutsko modelovanje i simulacije, *in vitro-in vivo* korelaciju i mogućnost izostavljanja *in vivo* studija bioekvivalencije (engl. biowaiver) iz aspekta opštih principa i mogućnosti primene u razvoju i karakterizaciji lekova. Predstavljena je i nedavno osmišljena inovativna strategija za razvoj leka usmerena ka pacijentu, uz primenu integrisanog sistemskog pristupa zasnovanog na osnovnim biofarmaceutskim konceptima, uvidu u kliničku situaciju i definisanim terapijskim ciljevima označena kao Plan aktivnosti za procenu biofarmaceutskog rizika (engl. Biopharmaceutics Risk Assessment Roadmap, BioRAM). Očekuje se da će daljem razvoju u ovoj oblasti najviše doprineti združene aktivnosti i razmena znanja i iskustava između farmaceutskih kompanija i regulatornih agencija sa zajedničkim ciljem da se ubrza razvoj efikasnih i bezbednih lekova dizajniranih u skladu sa potrebama i očekivanjima pacijenata.

Ključne reči: izostavljanje *in vivo* studija; klinički učinak; ispitivanje brzine rastvaranja; *in vitro-in vivo* korelacija; fiziološki zasnovani farmakokinetički/biofarmaceutski modeli