Clin Pharmacokinet (2016) 55:1179–1190
DOI 10.1007/s40262-016-0388-1

CURRENT OPINION

A New Level A Type IVIVC for the Rational Design of Clinical Trials Toward Regulatory Approval of Generic Polymeric Long-Acting Injectables

Mahadevabharath R. Somayaji[1] · Debarun Das[1] · Andrzej Przekwas[1]

Published online: 27 June 2016

Abstract Chronic neuropsychiatric disorders and diabetes mellitus affect millions of patients and require long-term supervision and expensive medical care. Although repeated drug administration can help manage these diseases, relapses and re-hospitalization owing to patient non-adherence and reduced therapeutic efficacy remain challenging. In response, long-acting injectables, which provide sustained drug release over longer periods at concentrations close to therapeutic ranges, have been proposed. Recent advancements include polymeric long-acting injectables (pLAIs), in which the active pharmaceutical ingredient (API) is encapsulated within U.S. Food and Drug Administration (FDA)-approved biocompatible polymers, such as poly(lactic-*co*-glycolic acid), or PLGA. Despite significant progress and development in the global pLAI market, FDA guidance for the approval of complex drug products, such as generic pLAIs, is not clearly defined. Although in vitro to in vivo correlation (IVIVC) can facilitate the identification of critical quality attributes (CQAs), drug formulations, and in vitro test platforms for evaluating drug performance in vivo, the application of IVIVC in order to shortlist time- and resource-intensive clinical trials for generic pLAIs has not been reported. Here, we propose a new Level A Type IVIVC that directly correlates the in vitro outcomes, such as drug dissolution, of candidate generic formulations with the clinical characteristics, such as drug absorption, of a reference listed drug (RLD), to help identify the specific generic pLAI formulations with clinical absorptions that are likely to be similar to that of the RLD, thereby reducing the number of clinical trials required for evaluation of clinical bioequivalence (BE). Therefore, the scope of the proposed method is intended only for the rational design of clinical trials, i.e., to shortlist the specific pLAI generic formulations for clinical BE evaluation, and not necessarily to analyze drug performances (i.e., drug safety and effectiveness) in the shortlisted clinical trials or post-approval. Once validated, this method will be of great value to developers of generic pLAIs and regulatory bodies to accelerate their approval of these generic pLAIs.

Key Points

Polymeric long-acting injectables (pLAIs) play an important role in the long-term treatment of chronic conditions, such as neuropsychiatric diseases and diabetes mellitus. However, the development of generic pLAIs is challenging due to the complexity of the generic formulations, the kinetics of drug release, and the lack of regulatory guidelines for evaluation and approval.

We propose a new Level A Type in vitro to in vivo correlation (IVIVC) to help accelerate the development and approval of generic pLAIs. Whereas a conventional Level A Type IVIVC compares the in vitro and in vivo outcomes of the same generic formulation, our method directly correlates the in vitro outcomes of candidate generic formulations with the clinical absorption characteristics of a reference listed drug, thereby reducing the number of clinical trials required for the evaluation of clinical bioequivalence.

✉ Mahadevabharath R. Somayaji
mrsomayaji@gmail.com;
bharath.somayaji_mr5@outlook.com

[1] Computational Medicine and Biology Division, CFD Research Corporation, 701 McMillian Way NW, Suite D, Huntsville, AL 35806, USA

1 Introduction

Chronic diseases, such as neuropsychiatric diseases and diabetes mellitus, affect millions of people and require long-term supervision and expensive medical care. In the USA, approximately 2.4 million Americans have schizophrenia, with men and women affected equally [1]. Recurrent administration of a drug (oral or parenteral) is required to manage these diseases over a prolonged treatment period. Despite the available treatment options, the likelihood of relapse remains high, primarily because of poor patient adherence to oral drug regimens [2]. For example, approximately two-thirds of patients with schizophrenia are partially non-adherent, and the discontinuation rate for oral antipsychotics ranges from 26 to 44 % [3, 4]. Therefore, the effective treatment of schizophrenia with oral antipsychotic medications poses significant clinical challenges. Consequently, hospital readmission rates and penalties have increased. For instance, approximately 2500 hospitals were penalized by the Centers for Medicare and Medicaid Services in 2015 because an unacceptable number of patients were readmitted soon after discharge (based on readmissions between July 2011 and June 2014) [5].

1.1 Clinical Impact of Long-Acting Injectables

The recurrent administration of oral drugs usually leads to a 'peak-and-valley' pattern in the plasma compartment, in which the achievable drug concentration either exceeds the toxic threshold, leading to undesirable adverse effects, or falls below the therapeutic threshold, sacrificing efficacy (*solid red line* in Fig. 1a). An alternative approach to circumvent this undesirable drug distribution is the use of long-acting injectables (LAIs), which are typically administered into intramuscular (IM) or subcutaneous (SC) spaces [6, 7]. A 'depot' is formed at the injection site to allow for the controlled release of the drug over longer durations, thereby facilitating the maintenance of therapeutic concentrations while reducing unintended toxicity and the required dosage (*solid green line* in Fig. 1a). The intrinsic pharmacokinetics (PK) of LAIs have resulted in improved patient compliance, quality of life, and ease of application and reduced rates of relapse, re-hospitalization, and non-adherence.

1.2 Polymeric Long-Acting Injectables and Drug-Release Kinetics

LAIs were introduced in the 1960s as solutions of simple ester prodrugs in sesame oil [8]. Recent advances include the development of pLAIs, in which the drug, i.e., the active pharmaceutical ingredient (API), is encapsulated within biocompatible polymeric matrices that undergo biodegradation over several weeks, resulting in the formation of biodegradable and biocompatible byproducts, such as lactic and glycolic acids that can be cleared by the Krebs cycle [9]. Several commercially available, synthetic and natural polymer materials are available for synthesizing pLAIs. Poly(lactic-*co*-glycolic acid) or PLGA is a U.S. Food and Drug Administration (FDA)-approved polymer used in many therapeutic devices and medical applications [9–12]. PLGA is synthesized by the copolymerization of two different monomers: cyclic dimers (1,4-dioxane-2,5-diones) of glycolic acid and lactic acid. Other polymer carriers routinely used for clinical applications include natural carriers such as polylactic acid, polyglycolic acid, and polycaprolactone and the synthetic carriers such as chitosan, alginate, gelatin, starch and dextran. The APIs used in pLAIs are usually small molecules or peptides that exert the desired pharmacodynamic (PD) response in the target area once they are released from the polymeric matrix. By modifying the formulation, size, shape, and type of the polymer matrix, the mechanism and kinetics of the API release can be controlled [13]. Therefore, several generic pLAI variants with different release kinetics have been developed by packaging an existing API into polymeric formulations. The drug release from polymeric microspheres primarily depends on the erosion characteristics of the polymer. For example, the release kinetics of the API from PLGA primarily rely on bulk erosion and degradation (Fig. 1b), whereas polymers such as polyanhydrides exhibit surface erosion characteristics via hydrolysis at the polymer-water interface [8, 14].

1.3 Pharmacoeconomics of pLAIs

pLAIs have benefited millions of patients and have found increased relevance as therapeutics, such as antipsychotics, fertility treatment, hormone therapy, protein therapy, antibiotics and antifungals, cancer therapy, treatment during orthopedic surgery, and postoperative pain treatment, chronic pain treatment, vaccination/immunization, and immunosuppression [15]. The annual worldwide market for polymer-based controlled-release systems has therefore increased to US$50 billion in 2014, as illustrated in Fig. 2 [16, 17]. Risperdal Consta, the first pLAI approved for the treatment of schizophrenia and bipolar disorder, was introduced by Janssen Pharmaceuticals, Johnson and Johnson (J&J) in 2003. Currently, six LAI antipsychotics with five unique combinations of molecular form and delivery strategy have been approved and are available on the market [18]. Despite the clinical advantages and market potential of pLAIs, the introduction of their generic variants into the market has been challenging owing to the

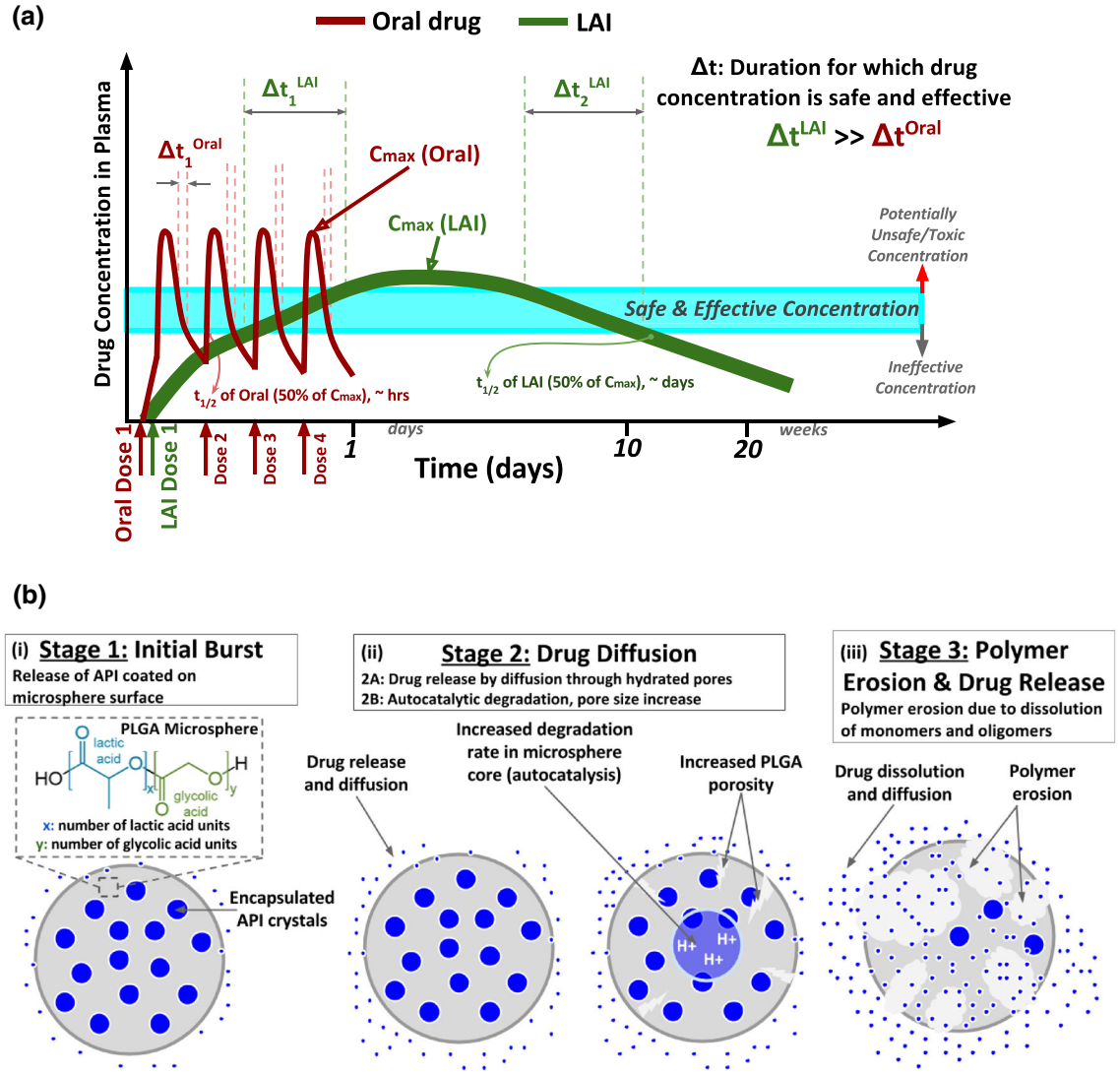

Fig. 1 **a** Conceptual illustration of plasma drug concentrations following repeated administration of conventional oral dosage (*red*) vs. controlled release from polymeric long-acting injectables (LAIs) (*green*). The therapeutic window of the plasma drug concentration is depicted by the *rectangular blue* strip. Δt represents the duration for which the drug concentration in the plasma is safe and effective. Note that in this illustration, LAIs have two therapeutic windows (Δt_1^{LAI} and Δt_2^{LAI}) during which the plasma drug concentration is safe and effective compared to the oral drug, which generally has one therapeutic window (Δt_1^{Oral}). **b** Illustration of different stages of poly(lactic-*co*-glycolic acid) or PLGA microsphere degradation and erosion, leading to sustained drug release and dissolution. The stages include the initial burst (the release of active pharmaceutical ingredient [API] on the microsphere surface), drug diffusion (drug release by diffusion through hydrated expanding pores and autocatalytic degradation), and drug release (due to polymer erosion and dissolution of monomers and oligomers)

complexity of the generic formulations, the lack of regulatory guidelines for the evaluation and approval of such long-acting drug products, and the mutual exclusivity of RLDs. These issues are discussed below.

1.4 Evaluation of Generic Drugs and Challenges to Regulatory Approval

Bioequivalence (BE) and bioavailability (BA) are important elements in the evaluation of generic drugs because they help quantify the release of an API from a drug product and its subsequent absorption into systemic circulation. BE and BA can also help establish therapeutic equivalence to ensure interchangeability between drug products. The FDA defines BE as the "absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed

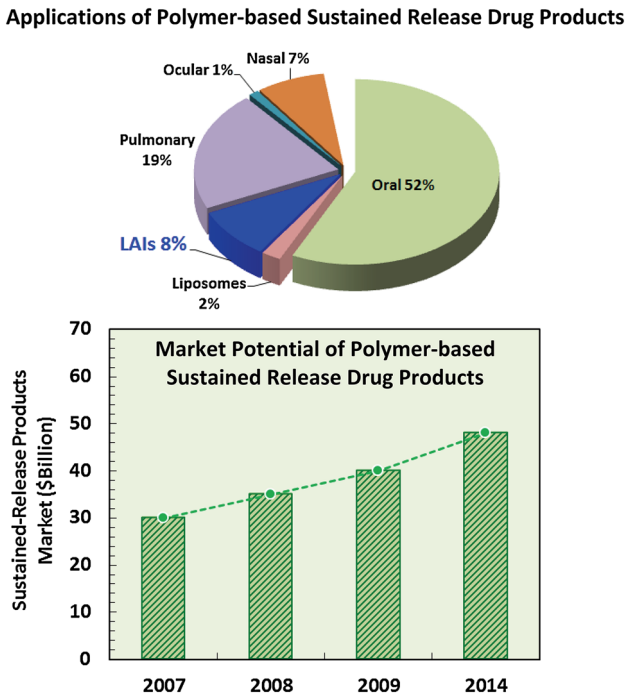

Fig. 2 Illustration of market potential of polymer-based sustained/controlled-release drug products from 2007 to 2014. The market share of the polymer-based sustained-release systems was estimated to be about US$40 billion in 2010 and was administered to over 100 million patients each year. Long-acting injectables (LAIs) are applied as psychiatric medication (antipsychotics), fertility treatments, hormone therapy, protein therapy, infection treatments (antibiotics and antifungals), cancer therapy, treatment following orthopedic surgery, postoperative pain treatment, chronic pain treatment, vaccination/immunization, and immunosuppression [15–17]. Polymeric long-acting injectables account for approximately 8 % of the sustained-release drug market, and there are six approved antipsychotic products with five unique combinations of molecular form and delivery strategy [18]

study" [19]. According to the FDA guidelines for evaluating the BE of orally and non-orally administered drugs, the measurement of the API concentration in systemic circulation is emphasized because measuring the API at the site of action is generally not straightforward [20]. However, these guidelines are not clearly defined for non-oral dosage forms, such as polymeric LAIs [21, 22]. This uncertainty may be attributed to the non-availability of standard in vitro drug-release assays to predict/assess in vivo performance, the nature of the API release kinetics from a polymer matrix, and the complexity and sensitivity of the biomanufacturing processes used to produce pLAIs [23, 24].

To address these challenges, computational approaches combining multiscale models of drug formulation, in vitro drug release, and in vivo physiologically based pharmacokinetic (PBPK) modeling can be indispensable for predicting the BE of candidate generic formulations. In addition to assessing different release characteristics, these models can be used to evaluate in vitro systems and optimize the design and process parameters for improved IVIVC. The model algorithms can serve as precursors for the development of software toolkits that benefit pharmaceutical scientists, drug developers, and the regulatory bodies, such as FDA's Office of Generic Drugs (OGD) that establish product quality standards and to accelerate the review and approval of new drug applications. In this paper, we propose a new Level A Type IVIVC that directly correlates the in vitro outcomes of candidate generic formulations, such as drug dissolution, with the clinical characteristics of a reference listed drug (RLD), such as drug absorption, to help identify the specific generic pLAI formulations with clinical absorptions that are likely to be similar to that of the RLD. This approach may thereby reduce the number of clinical trials required for the evaluation of clinical BE. This idea is based on the first author's response to a proposal solicitation from the FDA for "Pharmacometric modeling and simulation for long acting injectable products" in 2015 [25].

This paper is organized as follows: Sect. 2 introduces the IVIVC methodology and Sect. 3 describes its role in drug design and manufacturing. In Sect. 4, a new Level A Type IVIVC for the rational design of clinical trials (i.e., shortlisting the specific generic pLAI formulations that qualify for clinical testing) toward regulatory approval is discussed. The paper concludes with perspectives on the proposed IVIVC approach in Sect. 5 and insights into future research directions in Sect. 6.

2 In Vitro to In Vivo Correlation: Current Status and Potential Role in Drug Design and Manufacturing Phases

IVIVC, as defined by the FDA, is a "predictive mathematical model describing the relationship between an in vitro property of a dosage form and an in vivo response" [26]. The main goal of IVIVC is to predict the in vivo performance of a drug based on its in vitro drug-release profiles. Because in vitro dissolution is often used as a surrogate for in vivo absorption [20, 27, 28], IVIVC also helps identify the appropriate in vitro platform in which the dissolution profiles are reminiscent of the in vivo absorption profiles for different drug formulations [13, 29–33]. As listed in Table 1, four types of IVIVC have been defined by the FDA: Levels A, B, C, and D [26]. For generic drug approvals, a Level A Type IVIVC is generally required [26, 34, 35] and is established based on the in vitro drug dissolution and in vivo drug absorption [28]. The rationale for comparing the in vitro drug dissolution and in vivo absorption is based on the observation that the rate of drug absorption in vivo is dependent on the rate of drug

Table 1 Classification of IVIVC as defined by the U.S. Food and Drug Administration to establish a correlation between the in vitro dissolution and in vivo drug release of a product. Three or more formulations with different release rates are recommended to establish an IVIVC, with a minimum of three time points covering the early, middle, and late stages of the dissolution profile [26]

Level	Description
A	Point-to-point correlation between in vitro dissolution and in vivo absorption over time, which is considered the highest possible correlation. The Nelson–Wagner approach is used to determine the drug fraction absorbed (F_{abs}) based on the plasma concentration-time data [37]: $F_{abs}(t) = [C(t) + k_e \times AUC_{(0-t)}]/[k_e \times AUC_{(0-inf)}]$, where k_e is the elimination rate constant (time^{-1}), $C(t)$ is the plasma concentration of the drug (API) at time 't', and AUC is area under the curve (of the PK profile) *Remark*: Level A Type IVIVC is descriptive of the complete in vivo plasma PK profile based on the in vitro measurement parameter (dissolution rate) and can satisfactorily predict the biopharmaceutical release rate of a drug product in vivo with different formulations and dosages [75]. This process enables the assessment of changes in manufacturing processes, raw materials used, or minor modifications to the formulation and dose strength of the generic product without conducting additional clinical trials. For these reasons, establishing Level A Type IVIVC is desirable from a regulatory standpoint. The Level A IVIVC can then be used to conduct BE studies between different dissolution profiles, thereby playing an important role in QbD processes [34]
B	Correlation between two different derived quantities (or summary parameters), such as the mean dissolution time in vitro vs. the mean residence time in vivo; not a point-to-point correlation *Remark*: Level B Type IVIVC cannot be used to justify a change in drug formulation, excipient composition, or manufacturing process because it is not a point-to-point correlation [75]. Although this method can be applied to identify potential CQAs associated with a drug product, it cannot help quantify the limits of these attributes and quality-control standards to ensure that the generic product is bioequivalent with the RLD PK profile
C	Single-point comparison of the amount of drug dissolved in vitro at a particular time (e.g., T50 %) and an in vivo pharmacokinetic parameter (e.g., AUC); the correlation is not descriptive of the complete in vivo plasma PK profile *Remark*: This type of correlation is not predictive of actual in vivo performance and therefore has limited application for regulatory biowaivers (BE studies) [26]. This correlation can be used as a reference tool during the early stages of formulation development of the generic drug, when pilot formulations are being shortlisted, or in quality-control reference procedures [75, 76]
D	Rank order correlation; qualitative comparison *Remark*: As a qualitative comparison, Level D is generally not considered during the regulatory approval process. This comparison is not a formal correlation but can aid early formulation development [26, 77]

API active pharmaceutical ingredient, *AUC* area under the curve, *BE* bioequivalence, *CQAs* critical quality attributes, *IVIVC* in vitro to in vivo correlation, *PK* pharmacokinetics, *QbD* quality by design, *RLD* reference listed drug

dissolution (controlled, sustained, or modified release) [27, 36]. Deconvolution techniques, such as the Nelson–Wagner method (Table 1), can be used to estimate the in vivo drug absorption from clinical PK data (plasma drug concentration) [37].

For the approval of generic drugs, the FDA requires IVIVC for different formulations (at least two, but three or more is recommended) that differ significantly in their release rates, i.e., slow, medium, and fast releasing [26]. This process facilitates the early stages of drug formulations by defining the design space and identifying the critical quality attributes (CQAs), which are quality attributes (physical, chemical, biological, or microbiological) that must be controlled (directly or indirectly) to ensure that the final therapeutic product consistently meets safety, efficacy, stability, and performance standards [38, 39]. Typically, CQAs include the drug content, the particle size, and the excipient properties (non-API components in the drug product). In other words, alteration of these attributes can affect the in vivo performance of new drug formulations [39–42]. For complex drug products such as pLAIs, the design space becomes extensive owing to a large number of product attributes, the excipient properties in particular, as illustrated in Fig. 3. Therefore, identifying the CQAs of pLAIs is an important first step toward establishing a control strategy for monitoring critical processes during the manufacturing stage, designing rational clinical trials, and accelerating regulatory approval. Thus, in addition to shortlisting the candidate formulations for which an in vitro to in vivo correlation exists, IVIVC methods can also help determine the CQAs and their allowable variances during manufacturing to provide an understanding of how different formulations and process variables influence product quality [42], governed by the principles of quality by design (QbD) [43–45], as illustrated in Fig. 4. Thus, IVIVC is integral to QbD because the identification of the CQAs associated with the product, and the determination of the extent to which these attributes can be varied without affecting the quality and performance of the final product (i.e., which defines the margin of error) are the first required steps for establishing QbD [46]. The process also enables generic drug

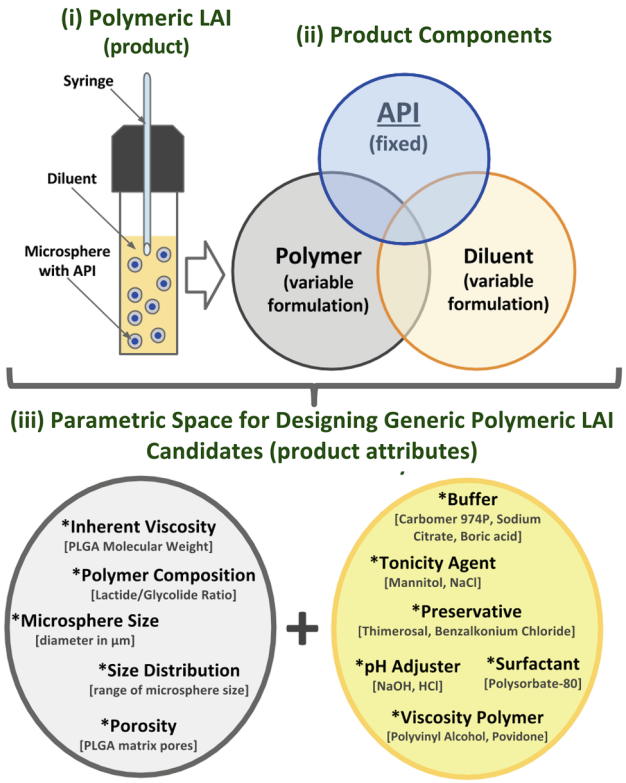

Fig. 3 Product attributes of microsphere-based pLAIs comprising the active pharmaceutical ingredient (API), the polymeric material encapsulating the API, and the diluent in which the polymer microspheres are suspended. Few of these attributes qualify as critical quality attributes (CQAs) that must be controlled (directly or indirectly) to ensure that the product meets its intended safety, efficacy, stability, and performance. Typically, the CQAs include the drug content, particle size, and other excipient properties. Identifying the CQAs of pLAIs is important because altering these attributes can directly affect the in vivo performance of a candidate generic formulation. The CQAs of pLAIs can be identified by varying the excipient properties (e.g., polymer and diluent) and determining their sensitivities using in vitro dissolution studies [41, 78]

developers to take a proactive approach for product development, fulfill FDA requirements for approval, and rapidly identify the root causes for deviations from RLD performance or unexpected toxicity from pLAIs.

3 Current Scope, Application, and Challenges of IVIVC for the Development of pLAIs

The use of IVIVC requires an in vitro and an in vivo system. The in vitro systems include the sample and separation method [47], the continuous flow method [48], and the dialysis membrane-based method [49]. These methods are often used for studying drug release from pLAIs in terms of release kinetics and dissolution characteristics. Currently, animal models (typically rodent) constitute the in vivo counterpart for the IVIVC-based evaluation of candidate generic pLAI formulations [13, 22, 50, 51]. Using a rat model, D'Souza et al. found that the modified dialysis bag [52] was a suitable in vitro platform for characterizing the in vivo performance of olanzapine (originally branded as Zyprexa) encapsulated in PLGA microspheres as this platform yielded a consistent Level A Type IVIVC between the in vitro release rates and the in vivo absorption of different PLGA formulations with varying lactide:glycoside ratios [22]. Although such IVIVC methods can provide insights into the in vivo relevance and performance of in vitro systems and drug formulations, a 1:1 match between the preclinical and clinical outcomes is not readily apparent because of the inherent differences in organ-level physiology and cellular biology [53–56]. Moreover, the size of the in vivo trial sample is typically similar to that of the in vitro experiments during initial development, which in conjunction with the vast number of product attributes can result in a combinatorial explosion of time- and resource-intensive clinical testing. In light of these developmental challenges, we conjecture that IVIVC methods can be intelligently adapted to reduce and optimize the number of clinical trials required to establish the BE of generic formulations, thereby reducing the developmental time required for accelerated approval, and to provide inputs for establishing regulatory guidelines for pLAIs. An instance of such an adaptation with a new Level A Type IVIVC is discussed next.

4 A New Level A Type IVIVC for the Rational Design of Clinical Trials Toward Regulatory Approval of Generic pLAIs

We propose a new Level A Type IVIVC to help accelerate the development of generic pLAIs by shortlisting the candidate generic formulations that are likely to be bioequivalent with the RLD. By subjecting only the shortlisted candidate generic formulations to further clinical testing, the method can help reduce the number of time-intensive clinical trials, resulting in a faster regulatory evaluation and approval. The proposed method is conceptually illustrated in Fig. 5a. Whereas a conventional Level A Type IVIVC compares the in vitro and in vivo outcomes of the same generic formulation, our method directly correlates the in vitro outcomes of candidate generic formulations with the clinical absorption characteristics of a RLD. The application of IVIVC for the rational design of clinical trials, i.e., shortlisting the specific pLAI formulations for the clinical BE evaluation, has not been reported thus far.

Figure 5b mathematically illustrates the proposed idea for three different pLAI formulations by quantifying the relative degrees of correlation between the percentage of drug dissolution in vitro and the percentage of drug

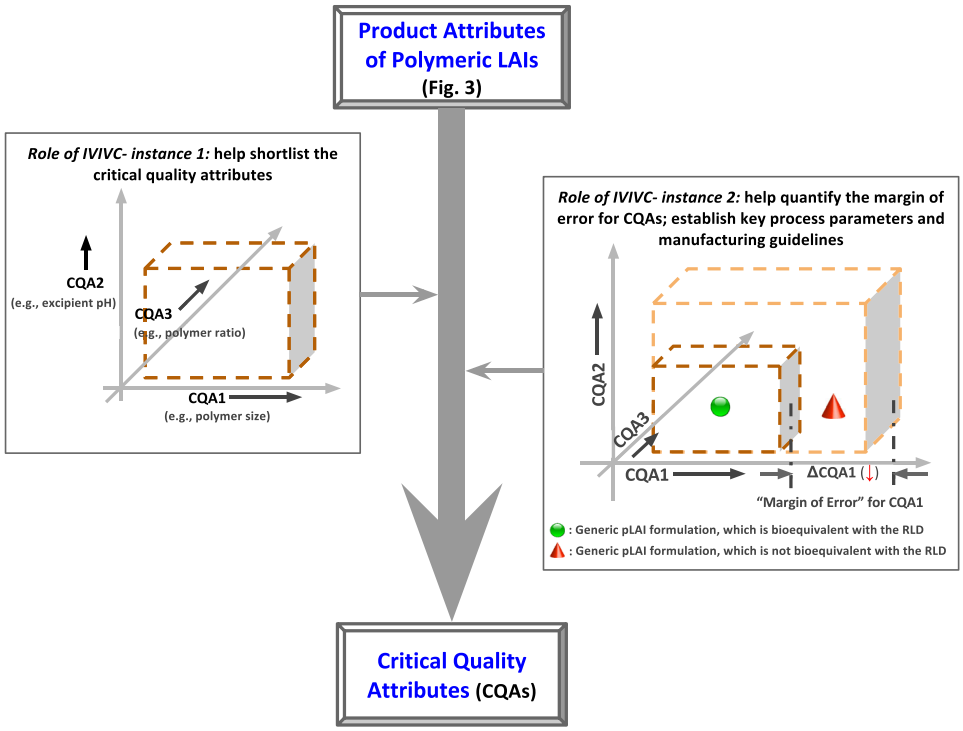

Fig. 4 Broader applications of in vitro to in vivo correlation (IVIVC) methods, which include **a** identifying the critical quality attributes (CQAs) by performing a sensitivity analysis of the product attributes and determining their effects on the in vitro outcomes such as release rates and dissolution; and **b** optimizing the product performance, quality and manufacturing processes by conducting quantitative analyses of the CQAs. For example, the panel on the left illustrates CQA1–3 as the main attributes that determine the quality and performance of a polymeric long-acting injectable formulation, whereas the panel on the right determines the margin of error and acceptable ranges for one of the CQAs (CQA1) in a three-dimensional design space. The IVIVC-identified CQAs and their bounds are linked to manufacturing processes, which are governed by the principles of quality by design

absorption of the RLD in vivo. We posit that the formulation(s) for which the slope of the linear correlation line (m) is closer to unity (i.e., 45° slope) with a high R^2 value (>0.95) during IVIVC are likely to be bioequivalent with the RLD and thus qualify for further clinical testing. Nonetheless, this qualification is contingent upon the availability of RLD PK data and the appropriateness of the in vitro platform to predict the in vivo drug absorption of different formulations. The *thick blue line* (45° line) represents the ideal IVIVC, i.e., the formulations for which the in vitro outcomes are expected to be bioequivalent with the RLD (Fig. 5b, *shaded green region* representing the bounds of the measurement error). For example, of the three candidate formulations, formulation 2 (f2, depicted as solid purple line in Fig. 5b) correlates well with the RLD data and therefore represents the qualifying candidate for clinical BE evaluation. This quantitative alignment suggests that f2 is likely to have the same API release kinetics and similar PK characteristics compared to the RLD. Similarly, other formulations that lie within this shaded green region represent the short-listed candidates that qualify for clinical testing. Conversely, formulations 1 and 3 (f1 and f3, depicted as dotted lines in Fig. 5b) do not align with the RLD data and therefore do not qualify for clinical evaluation. The non-alignment or the offset from the 45° line for these formulations could be attributed to the variations in excipient properties and the effect of these variations on the API release rates from the polymer matrix, culminating in the discrepancies between the in vitro dissolutions and the in vivo absorption of the RLD. In this mathematical illustration, the API release rate from f1 was slower when compared to the RLD, whereas the API release from f3 was relatively faster than the RLD. We conjecture that a priori sensitivity analyses could shed light on the specific product attributes affecting the correlation of the in vitro dissolution rates with the RLD absorption data.

5 Perspectives

Because clinical studies are required by the FDA to demonstrate BE before generic drug candidates can achieve regulatory approval, extensive and unpredictable number of clinical trials for BE evaluation entails additional time and costs, particularly for complex drug products such as pLAIs that have a large number of design parameters. Ad hoc in vitro experiments and time-intensive clinical trials can significantly

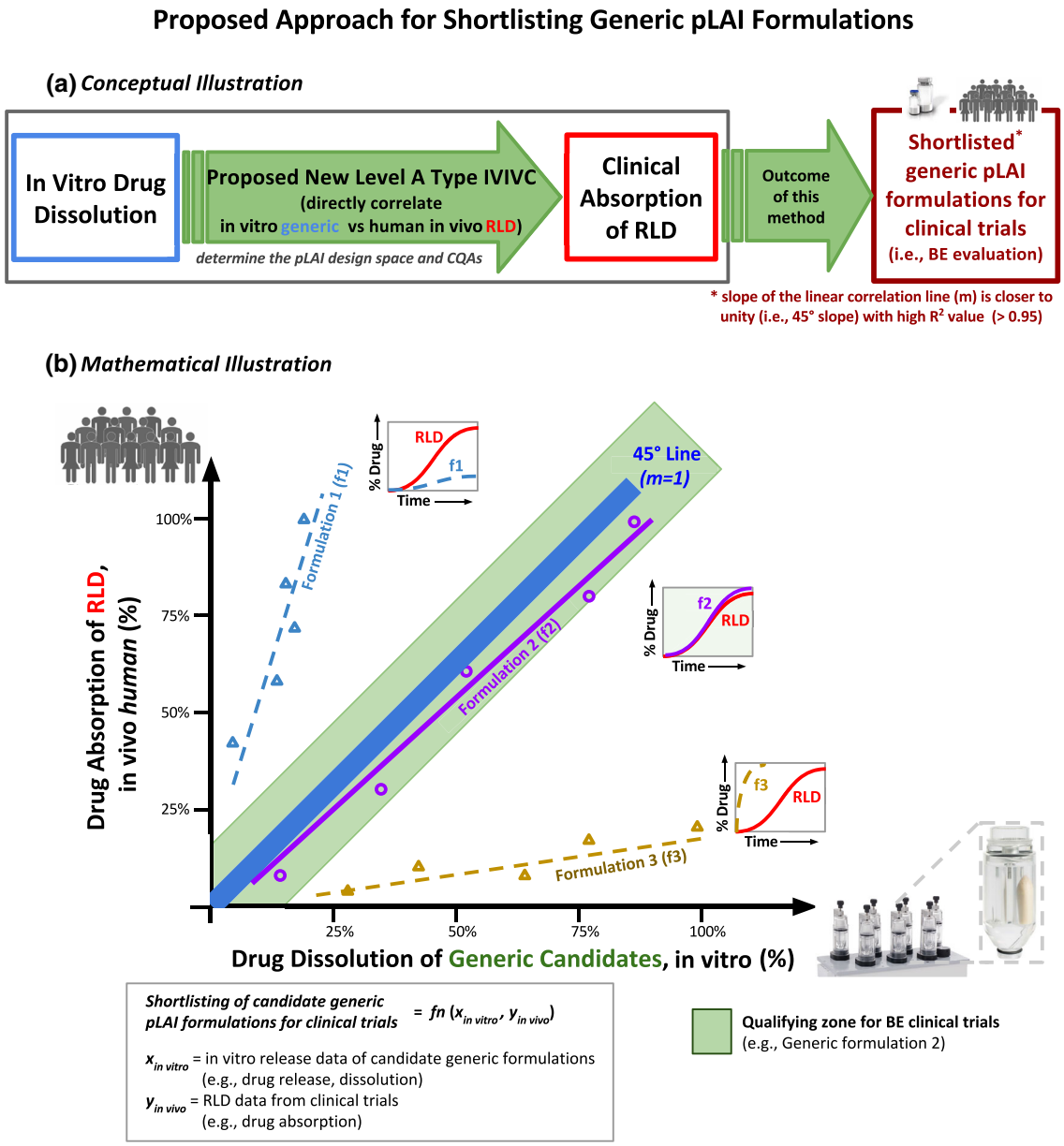

Fig. 5 **a** Overview of the proposed new Level A Type in vitro to in vivo correlation (IVIVC) for the rational design of clinical trials. By directly correlating the in vitro outcomes of candidate generic formulations with the clinical absorption characteristics of the reference listed drug (RLD), we conjecture that our method can rationally shortlist and identify specific drug formulations for which the clinical absorption is likely to be similar to that of the RLD. Consequent clinical bioequivalence (BE) studies are required to validate the proposed approach. **b** Mathematical illustration of the proposed new Level A Type IVIVC for shortlisting candidate pLAI generic formulations (f1: formulation 1; f2: formulation 2; f3: formulation 3) for BE clinical trials when the pharmacokinetic data of a RLD are available to the new generic drug developers. Based on this method, the formulation(s) for which the slope of the linear correlation line (m) is closer to unity (i.e., 45° slope) with a high R^2 value (>0.95) during IVIVC are likely to be bioequivalent with the RLD and thus qualify for further clinical testing

affect prospective generic drug developers. We conjecture that the proposed method will help shortlist the specific generic pLAI formulations requiring clinical trials (i.e., the rational design of clinical trials), thereby reducing the development time required for BE evaluation and approval. Furthermore, the method can serve as a tool to assist drug developers and regulatory bodies, such as OGD and Center for Drug Evaluation and Research (CDER), in establishing the BE criteria for modified-release products, including pLAIs.

For the successful application of this method, the clinical data for the RLD must be made available to developers of new generic pLAIs without compromising the market exclusivity of the brand LAI drug. Currently, such data may either be available in open literature, given in Table 2

Table 2 Selected list of pLAI-based RLDs identified in the open literature. Such data can be used to demonstrate the proposed Level A IVIVC for evaluating generic formulations in vitro and shortlisting candidates for further clinical BE evaluation

Name of the RLD	Year of FDA Approval	API [average microsphere size]	Administration route [dosage; interval]	References
Risperdal® Consta™ (Janssen)	2003	Risperidone [17–25 μm]	IM [12.5–50 mg; 2 weeks]	[57, 58, 66]
Lupron Depot® (AbbVie)	1995	Leuprolide acetate [100–500 μm]	IM/SC [3.75–30 mg; 1–6 months]	[59, 60]
Bydureon™ (AstraZeneca)	2012	Exenatide [60 μm]	SC [2 mg; 1 week]	[61]
Sandostatin LAR® (Novartis)	1998	Octreotide acetate [50 μm]	IM/SC [20 mg; 1 month]	[62, 63]
Trelstar™ LA (Actavis)	2000	Triptorelin pamoate	IM [3.75–22.5 mg; 1–6 months]	[64, 65]

API active pharmaceutical ingredient, *FDA* Food and Drug Administration, *IM* intramuscular, *pLAI* polymeric long acting injectable, *RLD* reference listed drug, *SC* subcutaneous

[57–65], or through specific documents submitted to the FDA, such as the Citizen Petition [66]. We anticipate that if the FDA approves the proposed new Level A Type IVIVC for the regulatory evaluation of generic pLAI formulations, it will facilitate the availability of critical in vivo drug absorption data (of RLD) for prospective generic drug developers before the market exclusivity of the brand drug expires. Such a measure will enable generic developers to test and finalize the candidate formulations for the rapid launch of the LAI product into the market following the expiration of the RLD patent.

6 Future Directions

Drug safety post-approval is an important topic because the likelihood of unintended drug actions in the general population during actual therapy cannot be completely ruled out. In other words, although many safety concerns can be identified during clinical testing, the anomalous behavior of an approved drug that was not detected in clinical trials, remains a possibility when used by a larger population (i.e., post-approval). Therefore, the FDA as a regulatory body has set in place safety oversight programs such as post-marketing surveillance to continuously monitor such adverse effects via reporting from manufacturers, hospitals, and the public [67, 68]. These reports are analyzed by the FDA to establish the relevant remarks for the product, such as black box warnings for re-labeling the product. For example, consider Risperdal Consta (risperidone), an antipsychotic pLAI approved for the treatment of schizophrenia and bipolar disorder by the FDA in 2003 [57]. After market launch and based on actual use, it was determined that the drug could increase the risk of cardiovascular or infectious-related deaths in patients with dementia-related psychosis. As a result, the FDA issued a black box warning for Risperdal Consta that precluded its use for this patient population [69]. Another relevant example is Zyprexa Relprevv (olanzapine pamoate), a suspension-based LAI developed by Eli Lilly and a known antipsychotic drug for the treatment of schizophrenia [70]. Although no adverse events were observed during clinical trials, severe reactions were later seen in 0.03 % of patients due to dose dumping, which resulted in drug plasma spikes [71]. This anomalous drug action led to the FDA approving this drug with a black box warning in 2010 that resulted in restricted access to patients [69]. Additionally, adverse event reporting may trigger the need for additional clinical trials to re-evaluate the safety and effectiveness and to occasionally recall a therapeutic product [69, 72, 73].

6.1 Inherent Physiological Risks of LAIs

In addition to the safety concerns mentioned above, we acknowledge the inherent risks of pLAIs because of their complexity in formulation; the drug-release kinetics; the longer residence times in the body, particularly in the vicinity of the injection sites (IM, SC spaces); and the unexpected toxicity due to dose dumping, which result in concentration spikes in the plasma. Such risks have led to the incorporation of Patient Care Programs that enable healthcare professionals to increase the monitoring of patients after the administration of LAIs (e.g., Zyprexa Relprevv Patient Care Program) [74].

6.2 Extension of the Proposed Approach to Include Drug Safety Issues

At the outset, the proposed Level A Type IVIVC is intended for shortlisting the specific generic pLAI formulations that qualify for clinical BE evaluation and not necessarily to analyze the drug safety and effectiveness either during clinical trials or post-approval, as discussed above. Because the RLD and its generic equivalents share the same API, and with the PK setting the initial conditions for PD and toxicodynamics (TD), it is conceivable that a mere alignment of the PK profiles of the candidate generic pLAI formulations and the RLD could also provide insights into the PD and TD aspects of the generics. However such an observation would not consider the anomalous behavior

of the RLD. To address this problem, we posit that improvements to the proposed method could also help in deducing the PD and TD of the shortlisted generic formulations when the safety and effectiveness data of the RLD are available (e.g., from clinical testing and adverse events). This idea is mathematically illustrated in the equation below. In addition, we think that the improved method can be adapted to identify the CQAs that can cause anomalous drug behavior. However, this technical hypothesis should be verified and validated with actual clinical data. For example, in the case of Zyprexa Relprevv, it would be interesting to identify the CQAs that caused the dose dumping and improve the formulation and biomanufacturing of this drug using tight QbD. In summary, we envision that shortlisting the candidate generic pLAI formulations using this improved IVIVC method would refine and strengthen the qualification criteria for BE evaluation, i.e., further reduce the number of generic formulations that qualify for clinical testing, thereby accelerating the development and approval of generic pLAIs.

Improvements to the proposed method:

$$\text{Shortlisting of candidate generic pLAI formulations for clinical trials} = fn\left(x_{\text{in vitro}},\, y_{\text{in vivo}},\, z_{\text{PD/TD}}\right)$$

$x_{\text{in vitro}}$ = in vitro release data of candidate generic formulations (e.g., drug dissolution)

$y_{\text{in vivo}}$ = RLD data from clinical trials (e.g., drug absorption)

$z_{\text{PD/TD}}$ = pharmacodynamics and toxicodynamics (e.g., drug safety, black box warning, plasma spikes/dose-dumping effects, toxicity, adverse event reporting, etc.)

Author contributions MRS conceived the ideas and the presentation. MRS and DD wrote the manuscript. AJP reviewed the final manuscript.

Compliances with Ethical Standards

Conflict of interest MRS, DD and AJP report no conflicts of interest. There was no financial support for this work, and there are no relations with any organizations.

References

1. National Institutes of Health (NIH). The numbers count: mental disorders in America. In: NIMH health and education statistics; 2013. Available from: http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america/index.shtml. Accessed 4 Mar 2016.
2. Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin. 2007;23:2305–12.
3. Kaplan G, Casoy J, Zummo J. Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. Patient Prefer Adherence. 2013;7:1171–80.
4. Lieberman JA. Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. Biol Psychiatry. 1999;46:729–39.
5. Punke H. 2.5 k hospitals penalized by CMS for high readmissions: 10 things to know. In: Becker's infection control and clinical quality; 2015. Available from: http://www.beckershospitalreview.com/quality/2-5k-hospitals-penalized-by-cms-for-high-readmissions-10-things-to-know.html. Accessed 4 Mar 2016.
6. Burgess DJ, Wright JC. An introduction to long acting injections and implants. In: Wright JC, Burgess DJ, editors. long acting injections and implants. Berlin: Springer Verlag; 2012. p. 1–9.
7. Kennedy WK. When and how to use long-acting injectable antipsychotics. Curr Psychiatry. 2012;11:40.
8. Remenar JF. Making the leap from daily oral dosing to long-acting injectables: lessons from the antipsychotics. Mol Pharm. 2014;11:1739–49.
9. Makadia HK, Siegel SJ. Poly lactic-*co*-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers. 2011;3:1377–97.
10. Lü JM, Wang X, Marin-Muller C, Wang H, Lin PH, Yao Q, Chen C. Current advances in research and clinical applications of PLGA-based nanotechnology. Expert Rev Mol Diagn. 2009;9:325–41.
11. Das D, Zhang Z, Winkler T, Mour M, Günter C, Morlock M, Machens HG, Schilling AF. Bioresorption and degradation of biomaterials. In: Kasper C, Witte F, Pörtner R, editors. Tissue engineering III: cell-surface interactions for tissue culture. Berlin: Springer Verlag; 2012. p. 317–33.
12. Mour M, Das D, Winkler T, Hoenig E, Mielke G, Morlock MM, Schilling AF. Advances in porous biomaterials for dental and orthopaedic applications. Materials. 2010;3:2947–74.
13. D'Souza S, Faraj JA, Giovagnoli S, DeLuca PP. Development of risperidone PLGA microspheres. J Drug Deliv. 2014;2014:620464. doi:10.1155/2014/620464.
14. Chue P. Long-acting risperidone injection: efficacy, safety, and cost-effectiveness of the first long-acting atypical antipsychotic. Neuropsychiatr Dis Treat. 2007;3:13–39.
15. Burgess DJ, Crommelin DJA, Hussain AS, Chen M. Assuring quality and performance of sustained and controlled release parenterals: EUFEPS workshop report. AAPS Pharmsci. 2004;6:100–11.
16. Almeida AJ, Souto E. Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Adv Drug Deliv Rev. 2007;59:478–90.
17. Zhang L, Pornpattananangku D, Hu CM, Huang CM. Development of nanoparticles for antimicrobial drug delivery. Curr Med Chem. 2010;17:585–94.
18. Wischke C, Schwendeman SP. Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles. Int J Pharm. 2008;364:298–327.
19. Zhang X, Zheng N, Lionberger RA, Yu LX. Innovative approaches for demonstration of bioequivalence: the US FDA perspective. Ther Deliv. 2013;4:725–40.
20. U.S. Food and Drug Administration (FDA). Guidance for industry, bioavailability and bioequivalence studies for orally administered drug products-general considerations; 2003. Available from: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3995B1_07_GFI-BioAvail-BioEquiv.pdf. Accessed 4 Mar 2016.
21. Schwendeman S. Importance of regulatory research funding for long acting release (LAR) drug products. In: FDA Public Forum; 2014. Available from URL: http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM399483.pdf. Accessed 4 Mar 2016.

22. D'Souza S, Faraj JA, Giovagnoli S, DeLuca PP. IVIVC from long acting olanzapine microspheres. Int J Biomater. 2014;2014:407065.
23. Martinez M, Rathbone M, Burgess D, Huynh M. In vitro and in vivo considerations associated with parenteral sustained release products: a review based upon information presented and points expressed at the 2007 Controlled Release Society Annual Meeting. J Control Release. 2008;129:79–87.
24. Raw AS, Lionberger R, Yu LX. Pharmaceutical equivalence by design for generic drugs: modified-release products. Pharm Res. 2011;28:1445–53.
25. U.S. Food and Drug Administration (FDA). Pharmacometric modeling and simulation for long acting injectable products. Funding opportunity announcement number RFA-FD-15-008; 2015. Available from: http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-15-008.html. Accessed 4 Mar 2016.
26. U.S. Food and Drug Administration (FDA). Categories of in vitro/in vivo correlation. In: Guidance for industry extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations; 1997. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070239.pdf. Accessed 4 Mar 2016.
27. Banakar UV. Factors that influence dissolution testing. In: Banakar UV, editor. Pharmaceutical dissolution testing. New York: Marcel Dekker; 1991. p. 133–87.
28. Dunne A, Devane J, O'Hara T. The relationship between in vitro drug dissolution and in vivo absorption. J R Stat Soc D. 1999;48:125–33.
29. Lionberger RA. FDA critical path initiatives: opportunities for generic drug development. AAPS J. 2008;10:103–9.
30. Larsen C, Larsen SW, Jensen H, Yaghmur A, Østergaard J. Role of in vitro release models in formulation development and quality control of parenteral depots. Expert Opin Drug Deliv. 2009;6:1283–95.
31. Kumar R, Nagarwal RC, Dhanawat M, Pandit JK. In-vitro and in-vivo study of indomethacin loaded gelatin nanoparticles. J Biomed Nanotechnol. 2011;7:325–33.
32. Cao X, Deng WW, Fu M, Wang L, Tong SS, Wei YW, Xu Y, Su WY, Xu XM, Yu JN. In vitro release and in vitro-in vivo correlation for silybin meglumine incorporated into hollow-type mesoporous silica nanoparticles. Int J Nanomed. 2012;7:753–62.
33. Tiwari R, Pathak K. Nanostructured lipid carrier versus solid lipid nanoparticles of simvastatin: comparative analysis of characteristics, pharmacokinetics and tissue uptake. Int J Pharm. 2011;415:232–43.
34. Dunne A. Approaches to developing in vitro–in vivo correlation models. In: Chilukuri DM, Sunkara G, Young D, editors. Pharmaceutical product development. New York: Informa Healthcare; 2007. p. 47–70.
35. Lu Y, Kim S, Park K. In vitro–in vivo correlation: perspectives on model development. Int J Pharm. 2011;418:142–8.
36. Levy G, Hollister LE. Dissolution rate limited absorption in man. Factors influencing drug absorption from prolonged-release dosage form. J Pharm Sci. 1965;54:1121–5.
37. Wagner JG, Nelson E. Per cent absorbed time plots derived from blood level and/or urinary excretion data. J Pharm Sci. 1963;52:610–1.
38. Sirisuth N, Eddington ND. Systemic methods for the development and validation of an IVIVC metoprolol and naproxen drug examples. Int J Generic Drugs. 2002;3:250–8.
39. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. AAPS J. 2014;16:771–83.
40. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Annex to pharmaceutical development. In: Draft consensus guideline: pharmaceutical development annex to Q8 (R2); 2009. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf. Accessed 4 Mar 2016.
41. Lionberger RA, Lee SL, Lee L, Raw A, Yu LX. Quality by design: concepts for ANDAs. AAPS J. 2008;10:268–76.
42. Fotaki N, Gray V, Kesisoglou F, Mayock S, Mirza T, Salt A, Selen A. Survey results for in vitro-in vivo correlations (IVIVC): critical variables for success. Dissolution Technol. 2013;20:48–51.
43. Nasr MN. Implementation of quality by design (QbD): status, challenges, and next steps. FDA Advisory Committee of Committee for Pharmaceutical Science; 2006. Available from: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4241s1_6.ppt. Accessed 4 Mar 2016.
44. Varu RK, Khanna A. Opportunities and challenges to implementing quality by design approach in generic drug development. J Generic Med. 2010;7:60–73.
45. Rosencrance S. QbD status update generic drugs. In: GPhA Fall Technical Conference; 2011. Available from: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm292666.pdf. Accessed 4 Mar 2016.
46. Sharp SS. Establishing clinically relevant drug product specifications: FDA perspective. AAPS Annual Meeting and Exposition Chicago, IL, USA. October. 2012;16. Available from: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM341185.pdf. Accessed 4 Mar 2016.
47. Cetin M, Atila A, Kadioglu Y. Formulation and in vitro characterization of Eudragit® L100 and Eudragit® L100-PLGA nanoparticles containing diclofenac sodium. AAPS PharmSciTech. 2010;2010(11):1250–6.
48. Zolnik BS, Burgess DJ. Evaluation of in vivo–in vitro release of dexamethasone from PLGA microspheres. J Control Release. 2008;127:137–45.
49. Pedersen BT, Østergaard J, Larsen SW, Larsen C. Characterization of the rotating dialysis cell as an in vitro model potentially useful for simulation of the pharmacokinetic fate of intra-articularly administered drugs. Eur J Pharm Sci. 2005;25:73–9.
50. Kobayashi D, Tsubuku S, Yamanaka H, Asano M, Miyajima M, Yoshida M. In vivo characteristics of injectable poly (DL-lactic acid) microspheres for long-acting drug delivery. Drug Dev Ind Pharm. 1998;24:819–25.
51. Yin DF, Wu C, Lu Y, Zhu Y. Zhong YQ [Long-acting injectable microspheres of glucagon-like peptide-1]. Yao Xue Xue Bao. 2006;41:603–7.
52. Kostanski JW, DeLuca PP. A novel in vitro release technique for peptide-containing biodegradable microspheres. AAPS PharmSciTech. 2000;1:30–40.
53. Kramer JA, Sagartz JE, Morris DL. The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates. Nat Rev Drug Discov. 2007;6:636–49.
54. Olson H, Betton G, Robinson D, Thomas K, Monro A, Kolaja G, Lilly P, Sanders J, Sipes G, Bracken W, Dorato M, Van Deun K, Smith P, Berger B, Heller A. Concordance of the toxicity of pharmaceuticals in humans and in animals. Regul Toxicol Pharmacol. 2000;32:56–67.
55. International Transporter Consortium, Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, Dahlin A, Evers R, Fischer V, Hillgren KM, Hoffmaster KA, Ishikawa T, Keppler D, Kim RB, Lee CA, Niemi M, Polli JW, Sugiyama Y, Swaan PW. Membrane transporters in drug development. Nat Rev Drug Discov. 2010;9:215–36.
56. Hodgson J. ADMET-turning chemicals into drugs. Nat Biotechnol. 2001;19:722–6.

57. Janssen Pharmaceuticals. Risperdal® Consta® indication and important safety information; 2015. Available from: http://www.risperdalconsta.com/sites/default/files/RisperdalConstaPI.pdf. Accessed 4 Mar 2016.
58. Mannaert E, Vermeulen A, Remmerie B, Bouhours P, Levron JC. Pharmacokinetic profile of long-acting injectable risperidone at steady-state: comparison with oral administration. Encéphale. 2005;31:609–15.
59. Periti P, Mazzei T, Mini E. Clinical pharmacokinetics of depot leuprorelin. Clin Pharmacokinet. 2002;41:485–504.
60. Makino K. Drug delivery system. In: Ohshima H, editor. Electrical phenomena at interfaces and biointerfaces: fundamentals and applications in nano-, bio-, and environmental sciences. Hoboken: Wiley; 2012. p. 709–23.
61. Kolterman OG, Kim DD, Shen L, Ruggles JA, Nielsen LL, Fineman MS, Baron AD. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. Am J Health Syst Pharm. 2005;62:173–81.
62. Petersen H, Bizec JC, Schuetz H, Delporte ML. Pharmacokinetic and technical comparison of Sandostatin® LAR® and other formulations of long-acting octreotide. BMC Res Notes. 2011;4:344.
63. Astruc B, Marbach P, Bouterfa H, Denot C, Astruc B, Marbach P, Bouterfa H, Denot C, Safari M, Vitaliti A, Sheppard M. Long-acting octreotide and prolonged-release lanreotide formulations have different pharmacokinetic profiles. J Clin Pharmacol. 2005;45:836–44.
64. U.S. Food and Drug Administration (FDA). Trelstar (triptorelin pamoate for injectable suspension); 2010. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022437_trelstar_toc.cfm. Accessed 4 Mar 2016.
65. Watson Pharma. Inc. Trelstar™ patient brochure (triptorelin pamoate for injectable suspension); 2015. Available from: http://www.actavis.ca/NR/rdonlyres/04A40336-25D0-4F39-AD04-1E9E4DADD32A/0/Trelstar_PMendmsen_26Feb2015_clean.pdf. Accessed 4 Mar 2016.
66. Herald DL. Statement of grounds. In: Citizen Petition of J&JPRD requesting adoption of certain parameters to govern the review of bioequivalence of proposed follow-on versions of Risperdal® Consta®. Available from: https://www.pharmamedtechbi.com/~/media/Images/Publications/Archive/The%20Pink%20Sheet%20Daily/2011/3/1/14110301005/risperidone_petition.pdf. Accessed 04 Mar 2016.
67. Somayaji MR. Perspectives on development and regulation of therapeutic products for CED-based therapy of neurodegenerative diseases. Curr Pharm Biotechnol. 2016;17:495–512.
68. U.S. Food and Drug Administration (FDA). Postmarketing surveillance programs; 2014. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm090385.htm. Accessed 4 Mar 2016.
69. McDonagh M, Peterson K, Carson S, Fu R, Thakurta S. Drug class review: atypical antipsychotic drugs: final update 3 report [internet]. Portland: Oregon Health & Science University; 2010.
70. Lindenmayer JP. Long-acting injectable antipsychotics: focus on olanzapine pamoate. Neuropsychiatr Dis Treat. 2010;6:261–7.
71. U.S. Food and Drug Administration (FDA). FDA drug safety communication: FDA review of study sheds light on two deaths associated with the injectable schizophrenia drug Zyprexa Relprevv; 2015. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm439147.htm. Accessed 04 Mar 2016.
72. U.S. Food and Drug Administration. Guidance for industry. Warnings and precautions, contraindications, and boxed warning sections of labeling for human prescription drug and biological products-content and format; 2011. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf. Accessed 4 Mar 2016.
73. Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander GC. Impact of FDA black box advisory on antipsychotic medication use. Arch Intern Med. 2010;170:96–103.
74. Wehring HJ, Thedford S, Koola M, Kelly DL. Patient and health care provider perspectives on long acting injectable antipsychotics in schizophrenia and the introduction of olanzapine long-acting injection. J Cent Nerv Syst Dis. 2011;3:107.
75. Emami J. In vitro–in vivo correlation: from theory to applications. J Pharm Pharm Sci. 2006;9:169–89.
76. United States Pharmacopoeia. Correlation levels. In: In vitro and in vivo evaluations of dosage forms; 2004. Available from: http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1088.html. Accessed 4 Mar 2016.
77. Schliecker G, Schmidt C, Fuchs S, Ehinger A, Sandow J, Kissel T. In vitro and in vivo correlation of buserelin release from biodegradable implants using statistical moment analysis. J Control Release. 2004;94:25–37.
78. Charoo NA, Shamsher AA, Zidan AS, Rahman Z. Quality by design approach for formulation development: a case study of dispersible tablets. Int J Pharm. 2012;423:167–78.