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Review Article

The Importance of Pharmacokinetic and Pharmacodynamic Models in Sustained Release Formulation

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ABSTRACT

The main role of preclinical pharmacokinetics and pharmacodynamics in drug discovery and development is to optimize candidate selection for the target therapeutic area, taking into consideration the type of agent required, and to predict the dose and dosing regimen for initial clinical trials with due concern to the requirements for effective treatment in the target therapeutic area. In order for this approach to be successful, a clear understanding is required for both the pharmacological target and drug disposition (absorption, clearance and distribution) of new chemical entities. A fundamental tenet in linking the pharmacokinetic and pharmacodynamic phases is that free drug in the systemic circulation is in equilibrium with the receptors. In the pharmacokinetic phase, only free drug can be cleared and drug is reversibly bound to tissues and blood. The pharmacodynamic phase is further subdivided into the interaction with the drug receptor triggering post-receptor events, eventually leading to actual drug effect. In this phase, only free drug can exert pharmacological effect and the free concentration of drug in plasma is in direct equilibrium with the interstitial fluid bathing most cells, since the capillary wall contains sufficient aqueous pores to allow the rapid passage of relatively small molecules, regardless of physicochemistry. Most receptor targets are accessed extracellularly. Therefore, one can expect that all drugs regardless of physicochemistry will be in direct equilibrium, at these targets, with free drug in plasma.

Key words: Bioavailability, Drug discovery, Formulations, PK-PD models, Sustained release dosage form.

INTRODUCTION

The cost of bringing a new drug to market is estimated to be between $800 million and $1 billion. Currently, there is a huge gap between the number of candidate drug compounds in testing and the ones that actually get approved. Less than 10% of drugs in phase I clinical trials make it to the approval phase. Two key reasons the drugs fail at late stages are a lack of understanding of the relationship between dose-concentration response and unanticipated safety events. Given this scenario, it is critical to have enabling tools that help predict how a drug will perform *in vivo* and assist in the success of a clinical therapeutic candidate. Pharmacokinetics (PK) characterizes the absorption, distribution, metabolism, and elimination properties of a drug. Pharmacodynamics (PD) defines the physiological and biological response to the administered drug.

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Pharmacokinetic-pharmacodynamic (PK-PD) modeling

PK-PD modeling is a scientific tool to help developers for selecting a rational dosage regimen for confirmatory clinical testing. PK/PD modeling can be executed using various approaches, such as direct versus indirect response models and parametric versus non-parametric models. PK/PD concepts can be applied to individual dose optimization. The limits of PK/PD approaches include the development of appropriate models, the validity of surrogate endpoints, and the acceptance of these models in a regulatory environment. When a PK/PD model is employed, both the time course and variability in the effect versus time relationship can be predicted for different dosage-regimen scenarios. In this way, the PK/PD models help developers to select a rational dosage regimen for confirmatory clinical testing. Failure to determine a safe and effective dosage regimen for use in pivotal clinical trials has been acknowledged as a frequent flaw encountered during the development of many drugs for humans. It establishes a mathematical and theoretical link between these two processes and helps better predict drug action. Integrated PK/PD modeling and computer assisted trial design via simulation are being incorporated into many drug development programs and are having a growing impact. PK/PD testing is typically performed at every stage of the drug

development process. Because development is becoming increasingly complex, time consuming, and cost intensive, companies are looking to make better use of PK/PD data to eliminate flawed candidates at the beginning and identify those with the best chance of clinical success. A major factor in the drug development process is time. Predictive modeling tools can provide invaluable information to better streamline the drug development process. Pharmaceutical companies traditionally perform sequential testing of drug candidates by screening and selecting the best performers at every phase of the clinical drug-development cycle. This can take as long as six to 10 years and cost several hundred million dollars. Hence, it is imperative for companies to adopt technologies that improve the quality of the drug development process and improve speed to market.

Traditional PK/PD modeling in drug development defines parameters such as drug dose concentration, drug exposure effects, drug half-life, drug concentrations against time, and drug effects against time. "When used more broadly, quantitative techniques such as drug modeling, disease modeling, trial modeling, and market modeling can support the entire development process, which results in better decisions through explicit consideration of risk and better utilization of knowledge,". However, implementing a PK/PD modeling approach can be challenging. "One has to invest time and resources up front in the drug development process. From a modeling standpoint, one needs to identify and build into the trial design frequent measures of clinical efficacy and/or toxicity as well as representative biomarkers for effective modeling".

To date, methodologies available for PK-PD analysis barely suppose the use of powerful computing resources. Some of these algorithms are able to generate individual estimates of parameters based on population analysis and Bayesian forecasting. Notwithstanding, attention must be paid to avoid over interpreted data from mathematical models, so that reliability and clinical significance of estimated parameters will be valuable when underlying physiologic processes (disease, age, gender, etc.) are considered. PK-PD modeling is the mathematical description of the relationships between PK and PD. PK-PD modeling allows the estimation of PK-PD parameters and the prediction of these derived, clinically relevant parameters as well. PK-PD simulations allow the assessment of the descriptive parameters as functions of dose and dose rate. These simulations can provide the dose–response curve for onset, magnitude, and duration of effect. This information can be valuable in optimizing dose and dosing regimens.[1] Currently, there is growing recognition of the importance of PK-PD studies in all phases of drug development.[2–5] In preclinical studies, PK-PD is used to interpret toxicokinetics data and via physiological modeling and allometric scaling, it is also used to extrapolate results from animals to humans.[6,7] During early clinical testing, PK-PD is used to aid in the interpretation of dose–response and escalation studies. In addition, there are several instances in which PK-PD modeling has been used by regulatory agencies to recommend a dose and/or regimen not originally studied as part of the clinical program.[8] As in the case of pharmacokinetics, methods to measure pharmacologic effects and bio-mathematical models had to be developed to characterize and evaluate pharmacodynamic processes.

Mathematical models can be considered as simplifications of a phenomenon described in terms of an algebraic or differential equation. In the case of PK-PD modeling, it is expected to not only describe, but also predict distinct situations, such as scaling between preclinical to clinical trials, multiple dosing schemes, or different routes of administration.[9] To choose the most appropriate PK-PD model, it is essential to identify the significance of the biological processes involved in eliciting a drug-induced response. Eventually, PK processes, biophase distribution, drug–receptor interaction, signal transduction, and secondary postreceptor events are factors altering the PD behavior of a drug. If that information is available—although only partially—it is possible to link PK and PD with actual physiologic support instead of only abstract numbers. Then, the model-building process involves fitting the available data and the consideration of possible biological differences that usually are translated into inter and intra variability. In the case of PD variability, it becomes important to identify the useful predictor (covariates) of PD individuality to facilitate individually optimized pharmacotherapy. It is necessary, therefore, to establish very comprehensive patient profiles during the development of studies. Moreover, the study populations must be representative of the target patient population with respect to age, gender, race, and environmental and pathophysiological characteristics. If these requirements are absent, the relevance and usefulness of covariates may be questionable.[10,11]

Because of the multiple factors intervening in a PK-PD study, it then appears adequate to divide the modeling project into the following two basic blocks such as concerning the clinical or experimental design by itself and the data analysis. Diverse models have been suggested to describe the PK-PD relationship depending upon the nature of drug administration scheme (single doses, multiple doses, long-term infusions, etc.) and the time dependency of PD parameters. Thus, when the system is kinetically at steady state, the concentrations of the active moiety at the active site are constant (after long-term infusions or multiple doses), relatively simple models are needed to characterize the PK-PD relationship. Otherwise, after single doses (nonsteady-state condition) and when time variant PD parameters are present, more complex models are needed to account for phenomena involved in the PK-PD relationship. Approaches such as disequilibrium between biophase and plasma compartment,[12] appearance of active metabolites,[13,14] indirect mechanisms of action,[15,16] sensitization, and tolerance,[17–19] have been proposed to explain the apparent dissociation between time courses of concentration and effect. Recently, the combination of powerful nonlinear, mixed effect regression models, statistically robust software tools, and the integration of pharmacokinetic-pharmacodynamic knowledge has permitted optimization of the decision process in therapeutic management. By incorporation of previous information into these systems, Bayesian forecasting certainly promises the more adequate individualized therapy for a particular patient.

Sustained release dosage form

The sustained release (SR) mode of drug administration has certain features that have an important impact on the magnitude of the pharmacologic response: (a) it minimizes fluctuation in blood drug concentrations (i.e. between peak and trough). However, due to the pronounced non-linear relationship between drug concentration and pharmacologic effect (i.e. pharmacodynamics) the impact of this property differs considerably as a function of the shape of the pharmacodynamic profile and the position of the specific range of concentrations on the curve of this profile; (b) it produces a slow input rate which tends to minimize the body's counteraction to the drug's intervening effect on regulated physiological processes; and (c) it provides a continuous mode of drug administration. This important pharmacodynamic characteristic may produce, in certain cases, an opposite clinical effect than that attained by an intermittent (pulsatile) mode of administration of the same drug. For many drugs with non-concentration-dependent pharmacodynamics, the exposure time, rather than the AUC, is the relevant parameter and it can therefore be optimized by SR preparations. The slow input function may minimize hysteresis in cases where the site of action is not in a rapid equilibrium with the blood circulation. The pharmacodynamics of the desired effect(s) and/or adverse effect(s) may also be influenced by the site of administration, especially in cases where the drug is delivered directly to its site of action. These factors demonstrate the important influence of the mode of administration on the pharmacological and clinical outcomes. In addition, they highlight the need to include these pharmacodynamic considerations in all stages from drug development to the optimization of their clinical use.

TIME RELEASE TECHNOLOGY

It is also known as sustained-release (SR), sustained-action (SA), extended-release (ER, XR, or XL), time-release or timed-release, controlled-release (CR), modified release (MR), or continuous-release (CR) is a mechanism used in pill tablets or capsules to dissolve slowly

and release a drug over time. The advantages of sustained-release tablets or capsules are that they can often be taken less frequently than instant-release formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream.[20]

Today, most time-release drugs are formulated so that the active ingredient is embedded in a matrix of insoluble substance(s) (various: some acrylics, even chitin; these substances are often patented) such that the dissolving drug must find its way out through the holes in the matrix. Some drugs are enclosed in polymer-based tablets with a laser-drilled hole on one side and a porous membrane on the other side. Stomach acids push through the porous membrane, thereby pushing the drug out through the laser-drilled hole. In time, the entire drug dose releases into the system while the polymer container remains intact, to be later excreted through normal digestion.

In some SR formulations, the drug dissolves into the matrix, and the matrix physically swells to form a gel, allowing the drug to exit through the gel's outer surface.

Micro-encapsulation is also regarded as a more complete technology to produce complex dissolution profiles. Through coating an active pharmaceutical ingredient around an inert core, and layering it with insoluble substances to form a microsphere you are able to obtain more consistent and replicable dissolution rates in a convenient format you can mix and match with other instant release pharmaceutical ingredients in to any two piece gelatin capsule.

There are certain considerations for the formation of sustained-release formulation

If the active compound has a long half-life (over 6 hours), it is sustained on its own.

If the pharmacological activity of the active compound is not related to its blood levels, time releasing has no purpose.

If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.

Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unwarranted and another mode of administration would be recommended.

Bioavailability Consideration for Immediate Release Tablets and sustained release Tablets

For product quality[21] BA and BE studies, we recommend that where the focus is on release of the drug substance from the drug product into the systemic circulation, a single-dose, fasting study be performed. We also recommend that *in vivo* BE studies be accompanied by *in vitro* dissolution profiles on all strengths of each product. For ANDAs, we also recommend that the BE study be conducted between the test product and reference listed drug using the strength(s) specified in Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). 2. Waivers of *In vivo* BE Studies (Biowaivers)

a. INDs, NDAs, and ANDAs: Preapproval When the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to the strength on which BA or BE testing has been conducted, an *in vivo* BE demonstration of one or more lower strengths can be waived based on dissolution tests and an *in vivo* study on the highest strength. For an NDA, biowaivers of a higher strength will be determined to be appropriate based on (1) clinical safety and/or efficacy studies including data on the dose and the desirability of the higher strength, (2) linear elimination kinetics over the therapeutic dose range, (3) the higher strength being proportionally similar to the lower strength, and (4) the same dissolution procedures being used for both strengths and similar dissolution results obtained. We recommend that a dissolution profile be generated for all strengths. If an appropriate dissolution method has been established (see section III.D.), and the dissolution results indicate that the dissolution characteristics of the product are not dependent on the product strength, then dissolution profiles in one

medium are usually sufficient to support waivers of *in vivo* testing. Otherwise, dissolution data in three media (pH 1.2, 4.5, and 6.8) are recommended. We recommend that the f2 test be used to compare profiles from the different strengths of the product. An f2 value > 50 indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not needed. For an f2 value < 50, further discussions with CDER review staff may help to determine whether an *in vivo* study is appropriate (21 CFR 320.22(d)(2)(ii)). The f2 approach is not suitable for rapidly dissolving drug products (e.g., > 85% dissolved in 15 minutes or less). For an ANDA, conducting an *in vivo* study on a strength that is not the highest may be appropriate for reasons of safety, subject to approval by the Division of Bioequivalence, Office of Generic Drugs, and provided that the following conditions are met

- Linear elimination kinetics has been shown over the therapeutic dose range.
- The higher strengths of the test and reference products are proportionally similar to their corresponding lower strength.
- Comparative dissolution testing on the higher strength of the test and reference products is submitted and found to be appropriate.

b. NDAs and ANDAs: Postapproval

Information on the types of *in vitro* dissolution and *in vivo* BE studies for immediate-release drug products approved as either NDAs or ANDAs in the presence of specified postapproval changes are provided in an FDA guidance for industry entitled SUPAC-IR: Immediate Release Solid Oral Dosage Forms:

Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, *In vitro* Dissolution Testing, and *In vivo* Bioequivalence Documentation. For post approval changes, we recommend that the *in vitro* comparison be made between the prechange and post change products. In instances where dissolution profile comparisons are suggested, we also recommend an f2 test be used. An f2 value of > 50 suggests a sufficiently similar dissolution profile and no further *in vivo* studies are needed. When *in vivo* BE studies are called for, we recommend that the comparison be made for NDAs between the prechange and post change products, and for ANDAs between the post change and reference listed drug products.

D. Modified-Release Products

Modified-release products include delayed-release products and extended- (controlled) release products. As defined in the USP, delayed-release drug products are dosage forms that release the drugs at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are intended to delay the release of medication until the dosage form has passed through the acidic medium of the stomach. *In vivo* tests for delayed-release drug products are similar to those for extended release drug products. We recommend that *in vitro* dissolution tests for these products document that they are stable under acidic conditions and that they release the drug only in a neutral medium (e.g., pH 6.8). Extended-release drug products are dosage forms that allow a reduction in dosing frequency as compared to when the drug is present in an immediate-release dosage form. These drug products can be developed to reduce fluctuations in plasma concentrations. Extended-release products can be capsules, tablets, granules, pellets, and suspensions. If any part of a drug product includes an extended-release component, the following recommendations apply.

NDAs: BA and BE Studies

An NDA can be submitted for a previously unapproved new molecular entity, new salt, new ester, prodrug, or other noncovalent derivative of a previously approved new molecular entity formulated as a modified-release drug product. We recommend that the first modified-release drug product for a previously approved immediate-release drug product be submitted as an NDA. We also recommend

that subsequent modified-release products that are pharmaceutically equivalent and bioequivalent to the listed drug product

be submitted as ANDAs. BA requirements for the NDA of an extended-release product are listed in § 320.25(f). The purpose of an *in vivo* BA study for which a controlled release claim is made is to determine if all of the following conditions are met:

- The drug product meets the controlled-release claims made for it.
- The BA profile established for the drug product rules out the occurrence of any dose dumping.
- The drug product's steady-state performance is equivalent to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units. As noted in § 320.25(f)(2), "the reference material(s) for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the controlled release claims made for the drug product," such as: A solution or suspension of the active drug ingredient or therapeutic moiety
- A currently marketed non controlled-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling
- A currently marketed controlled-release drug product subject to an approved full NDA containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling This guidance recommends that the following BA studies be conducted for an extended release drug product submitted as an NDA:
- A single-dose, fasting study on all strengths of tablets and capsules and highest
- strength of beaded capsules
- A single-dose, food-effect study on the highest strength
- A steady-state study on the highest strength BE studies are recommended when substantial changes in the components or composition and/or method of manufacture for an extended-release drug product occur between the marketed NDA dosage form and the clinical trial material.

ANDAs: BE Studies

For modified-release products submitted as ANDAs, the following studies are recommended: (1) a single-dose, nonreplicate, fasting study comparing the highest strength of the test and reference listed drug product and (2) a food-effect, nonreplicate study comparing the highest strength of the test and reference product (see section VI.A).

Because single-dose studies are considered more sensitive in addressing the primary question of BE (i.e., release of the drug substance from the drug product into the systemic circulation), multiple-dose studies are generally not recommended, even in instances where nonlinear kinetics are present.

Waivers of *In vivo* BE Studies (Biowaivers): NDAs and ANDAs

a. Beaded Capsules — Lower Strength

We recommend that for modified-release beaded capsules where the strength differs only in the number of beads containing the active moiety, a single-dose, fasting BE study be carried out only on the highest strength, with waiver of *in vivo* studies for lower strengths based on dissolution profiles. A dissolution profile can be generated for each strength using the recommended dissolution method. The f2 test can be used to compare profiles from the different strengths of the product. An f2 value of > 50 can be used to confirm that further *in vivo* studies are not needed.

b. Tablets — Lower Strength

For modified-release tablets, when the drug product is in the same dosage form but in a different strength, when it is proportionally similar in its active and inactive ingredients and when it has the same drug release mechanism, an *in vivo* BE determination of one or more lower strengths can be waived based on dissolution profile comparisons, with an *in vivo* study only on the highest strength. We recommend that the drug products exhibit similar dissolution profiles between the highest strength and the lower strengths based on the f2 test in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8). We recommend that the dissolution profile be generated on the test and reference products of all strengths.

4. Postapproval Changes

Information on the types of *in vitro* dissolution and *in vivo* BE studies for extended release drug products approved as either NDAs or ANDAs in the presence of specified post approval changes are provided in an FDA guidance for industry entitled SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, *In vitro* Dissolution Testing, and *In vivo* Bioequivalence Documentation. We recommend that for post approval changes, the *in vitro* comparison be made between the prechange and post change products. In instances where dissolution profile comparisons are recommended, an f2 test can be used. An f2 value of > 50 suggests a similar dissolution profile. A failure to demonstrate similar dissolution profiles may indicate an *in vivo* BE study be performed. When *in vivo* BE studies are conducted, we recommend that the comparison be made for NDAs between the prechange and post change products, and for ANDAs between the post change product and reference listed drug.

CONCLUSION

PK-PD modeling has emerged as a major tool in clinical pharmacology to optimize drug use by designing rational dosage forms and dosage regimes. Quantitative representation of the dose–concentration–response relationship should provide information for prediction of the level of response to a certain level of drug dose. Several mathematical approaches can be used to describe such relationships, depending on the single dose or the steady-state measurements carried out. The development of a correlation is based on the scientific principles associated with mathematical modeling, statistical evaluation, and numerical deconvolution. The development and validation of a PK/PD is based on the ability of fraction of the drug absorbed versus fraction of the drug-dissolved relationship of various formulations.

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