Pharmaceutical Research, Vol. 25, No. 12, December 2008 (© 2008)
DOI: 10.1007/s11095-008-9743-8

Commentary

Equivalence-by-Design: Targeting *In Vivo* Drug Delivery Profile

Mei-Ling Chen[1,3] and Vincent H.L. Lee[2]

Received August 28, 2008; accepted October 2, 2008; published online October 28, 2008

Abstract. In the United States (U.S.), drug products are considered therapeutically equivalent if they meet regulatory criteria of pharmaceutical equivalence and bioequivalence. These requirements can be traced back to 1977 when the U.S. Food and Drug Administration (FDA) published the regulations on bioavailability and bioequivalence. Over the years, to keep up with the advancement in science and technology, the FDA has been constantly updating the regulatory approaches to assessing and ensuring equivalence. In view of the recent growth in novel pharmaceutical dosage forms and delivery systems, this paper examines the current framework for documentation of therapeutic equivalence and explores the opportunities of further advancing equivalence methods for complex drug products. It is proposed that equivalence may be established by matching the *in vivo* drug delivery profile (iDDP) between drug products in comparison. This can be achieved by characterizing the iDDP of the reference formulation with application of an equivalence-by-design approach for pharmaceutical development. Critical variables can be identified to serve as *in vitro* markers or biomarkers for mapping the desired drug delivery profile *in vivo*. A multidisciplinary approach may be necessary to develop these markers for characterization of iDDPs.

KEY WORDS: bioequivalence; *in vivo* drug delivery profile; pharmaceutical equivalence; quality by design; therapeutic equivalence.

INTRODUCTION

The 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) deems drug products *therapeutic equivalents* if they are pharmaceutical equivalents and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling (1). In this setting, a major premise underlying the law is that evidence of pharmaceutical equivalence (PE) and bioequivalence (BE) provides the assurance of therapeutic equivalence (TE), hence interchangeability. Implicit in the inclusion of PE as part of the definition of TE has been the regulatory objective of achieving 'sameness' to the greatest extent possible between a generic and innovator product, thereby avoiding unnecessary *in vivo* human testing (2).

How much evidence is necessary for establishing TE may depend on the prevailing science and technology at the time of evaluation. In retrospect, the regulatory requirement of *in vivo* BE studies for drug applications originated from a 1974 report issued by the U.S. Congressional Office of Technology Assessment (3). Based on the recommendations in this report, many regulations were published in 1977 focusing on the information needed for establishment of BE (4). Over the years, the U.S. Food and Drug Administration (FDA) has been vigilant in maintaining the quality and equivalence of generic drug products, as evidenced by a multitude of initiatives and programs geared to advance regulatory approaches to assessing and ensuring equivalence (5–9). Despite all of the FDA's efforts, however, skepticism about generic substitution continues with sporadic reports from patients or healthcare professionals regarding the possible therapeutic failure of certain generic drug products (10–21). Scientific investigations have revealed that some of these issues could potentially be explained or avoided by obtaining a better understanding of the unique characteristics of the product during development. In addition to the necessity of upholding public confidence in generic substitution, there is a further need for enhancing regulatory approaches to keep up with the rapid development in pharmaceutical science and technology (22). A recent example relates to establishing equivalence of some advanced pharmaceutical dosage forms, given the complexity of these delivery systems (23–25).

The objectives of this commentary are to (a) examine current regulatory framework for determination of PE and BE, (b) identify opportunities to advance methodology for demonstrating equivalence, and (c) further explore a novel approach to achieving and assessing equivalence, particularly for advanced or complex dosage forms. Equivalence evaluation of macromolecules in biological products is much more complex, requiring a separate commentary.

The opinions expressed in this article do not necessarily represent the views or policies of the U.S. Food and Drug Administration

[1] Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993-0002, USA.
[2] School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR.
[3] To whom correspondence should be addressed. (e-mail: meiling.chen@fda.hhs.gov)

PHARMACEUTICAL EQUIVALENCE

In the U.S., drug products are considered pharmaceutical equivalents if they are in identical dosage forms that contain identical amounts of the identical active drug ingredient, and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates (26). Pharmaceutically equivalent drug products do not necessarily contain the same inactive ingredients (26) and they may differ in their characteristics such as release mechanisms and excipients (1).

Determination of PE has been made by a qualitative (Q1) and quantitative (Q2) comparison of composition between formulations for simple dosage forms or drug products. This approach, however, may need to be refined for complicated dosage forms or drug delivery systems. For example, some differences in the physicochemical properties of lipid-based formulations have been shown to result in varying bioavailability when mixed with different vehicles for administration (27,28). Particle size distribution and viscosity are important variables for maintenance of suspension homogeneity over the product shelf life. Similarly, rheology is germane to the performance of semisolid dosage forms such as creams and ointments. Recognizing the importance of having additional measures for certain complex dosage forms and drug products, the FDA has recommended a higher level of comparison (Q3) that examines the arrangement of matter (or microstructure) of drug products to supplement the traditional approach for PE evaluation (29).

BIOEQUIVALENCE

As defined in the U.S. regulation (26), bioequivalence means "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 study". Based on this definition, BE determination can be made through the measurement of drug concentrations in an accessible biological fluid that reflect the drug availability at the site of action (30).

The implementing regulations recommend that drug sponsors conduct BE testing using the most accurate, sensitive, and reproducible approach available for the drug product under examination (31). The FDA has further listed the following methods, in descending order of preference, for establishment of BE: (1) pharmacokinetic studies, (2) pharmacodynamic studies, (3) clinical trials, and (4) *in vitro* studies (32). As such, pharmacokinetic studies with drug concentration measurement in blood/plasma have mostly been used for BE demonstration whereas pharmacodynamic studies or clinical trials are employed only when appropriate methods are unavailable for measurement of a drug or its metabolite(s) in accessible biological fluids (32). The *in vitro* tests alone are seldom utilized except for the instances where the tests have been shown to be correlated with and predictive of *in vivo* bioavailability (32). Nonetheless, it should be noted that with the recent introduction of the Biopharmaceutics Classification System (BCS), comparative *in vitro* dissolution studies can be used as part of the criteria for determining whether *in vivo* BE studies may be waived for a BCS Class I drug product (33).

Pharmacokinetic studies cannot be used for BE demonstration of many locally acting or targeted delivery drug products. This is partly due to the fact that drug concentrations in blood/plasma following the administration of these products may not reflect drug availability at the site of action. As a result, the regulatory methods recommended for BE evaluation of these products have often been tailored to individual dosage forms or drug products, using a variety of different approaches (9). For example, to establish BE of inhalation products, the FDA requires a battery of *in vitro* testing for device performance, pharmacodynamic studies for local delivery between products, and a pharmacokinetic study to ensure minimal systemic exposure to the drug (9). On the other hand, clinical equivalence trials are recommended for BE demonstration of most dermatological products with the exception of topical solutions and corticosteroids (9). BE is considered self-evident for topically applied dermatological solutions if the components are qualitatively and quantitatively the same (34) whereas pharmacodynamic studies have been used for BE determination of topical corticosteroids (35).

An ongoing concern regarding the current BE approach has been its heavy reliance on the conduct of healthy volunteer studies (11,12,15,17). The question is the extent to which the results from these studies can be extrapolated to the target patient populations. This question, in fact, has been addressed by the crossover design of most BE studies using pharmacokinetic measures where each subject serves as his/her own control. In this way, the conclusion of the study with respect to BE determination is unbiased, regardless of the populations used. Nevertheless, with the advent of modern science and technology, there are distinct challenges in developing methods for equivalence evaluation of complex dosage forms or novel drug delivery systems, as to be illustrated below.

FUNDAMENTAL CHALLENGES IN ADVANCING EQUIVALENCE METHODS

Unique Features of Modified Release Dosage Forms

U.S. regulation does not require pharmaceutically equivalent products to have the same release mechanisms for the same drug substance in the same dosage form (1). Depending on the formulation and design, they may thus exhibit similar or different bioavailability. Interestingly, some case reports of suspected therapeutic inequivalence involve modified-release dosage forms (17).

Several modified-release dosage forms currently available release drug by unique release mechanisms. For example, Procardia XL (nifedipine extended-release tablets) is fabricated as a gastrointestinal therapeutic system (GITS) to provide the drug delivery rate independent of pH or motility of the GI tract (36). Yet, Adalat CC tablets (another nifedipine extended-release product) consist of an external coat and an internal core, with the coat as a slow release formulation and the core a fast release formulation (37). While most oral controlled-release dosage forms are based on

reservoir- or matrix-type systems with constant or variable rates of drug release, the pulsatile drug delivery system gives rise to a release profile that may be characterized by a well-defined lag time with the subsequent release of the drug (38).

From the formulation point of view, many product designs are possible for an extended-release dosage form to attain the expected peak drug concentration (Cmax) and area under the concentration *versus* time curve (AUC) in the blood or plasma. This can be achieved by altering polymer type, drug/polymer ratio, excipients, compression pressure and/or temperature (39). The resulting formulations, however, may yield a set of concentration-time profiles that vary widely in the peak time (Tmax) and/or shape of the profile. The question is, to what extent does a discrepancy in the blood/plasma profiles translate into a difference in clinical outcomes. Clinical experiences with knowledge of pharmacology, pharmacokinetics and pharmacodynamics may be helpful to address such questions. However, circumstances can arise where it is difficult to determine if the difference in these blood/plasma profiles will lead to a significant difference in clinical efficacy or safety.

Likewise, for delayed-release dosage forms such as enteric-coated drug products, use of enteric coating is intended for protection of an acid-labile drug from degradation by the acidic medium present in the upper part of the GI tract. However, there are several types of enteric coating in the marketplace that may possess comparable protective function with different onset times for coating breakdown and drug release. Indeed, it was speculated that variation in the quality of enteric coatings might account, in part, for the observed difference in clinical effectiveness between formulations (40,41).

Complexity of Novel Dosage Forms and Delivery Systems

With the recent advancement in science and technology, there is increasing growth in novel pharmaceutical dosage form and delivery systems, such as liposomes, drug-eluting stents, and nanotechnology-derived pharmaceutical products. In view of the complexity of these dosage forms, the need for identifying innovative ways to assess equivalence is imminent. For example, in the case of liposome drug products, a lack of thorough understanding of the drug delivery pathway *in vivo* can present a significant challenge in the establishment of regulatory approaches for demonstrating PE and BE of these products (23–25,42). The same problem may occur with modern targeted delivery systems including the emerging pharmaceuticals derived from nanotechnology. Similarly, drug-device combination products such as drug-eluting stents may require novel regulatory pathways that not only address risk and benefit of each component, but also effectiveness and safety as a whole unit (43). The time is ripe to consider how to achieve equivalence of complex dosage forms while ensuring the quality and performance of these products.

NEED FOR ALTERNATIVE METHODS TO ASSESS EQUIVALENCE

Over the decades, the field of biopharmaceutics has evolved from empirical science that investigates the bioavailability and pharmacokinetics of different formulations to more sophisticated mechanism-based art that delineates the relationship between drug kinetics and various formulation or administration factors at the molecular level. The evolution in science and technology may provide opportunities for optimization of scientific approaches for assessing equivalence. The application of the BCS serves as a good example of how the biopharmaceutic attributes (i.e., aqueous solubility and intestinal permeability) can be utilized for prediction of BE in certain circumstances. With a better understanding of physicochemical properties of drug substances and formulation characteristics of drug products, more *in vitro* studies should be developed and validated to support BE. A case in point is cholestyramine resin, for which the FDA has recommended the use of *in vitro* equilibrium and kinetic binding studies of bile acid salts for BE determination (44). The application of *in vitro* assays takes advantage of the mechanism of action from the resin to assess the binding behavior between a generic and the innovator formulation of cholestyramine. This is an excellent model where an *in vitro* mechanistic-based approach, in lieu of *in vivo* human studies, serves as an efficient marker for evaluation of BE. Similarly, a careful examination of pharmaceutical attributes as well as characterization of *in vivo* drug delivery and absorption processes may help achieve equivalence between formulations.

THEORETICAL BASIS FOR THE NEW APPROACH

In the BE arena, it has been well recognized that with identical drug substance and route of administration, the characteristics of a formulation will determine drug bioavailability. Furthermore, clinical experiences reveal that the clearance of a drug within each individual is generally unchanged across different formulations. As such, a disparity between formulations can be best distinguished by differences in their absorption patterns rather than in the post-absorptive processes, such as distribution, metabolism or excretion of the drug (30,45,46). Since the absorption pattern of a drug is mainly controlled by when, where, and how the drug is released from the formulation, the *in vivo* drug delivery pathway of the formulation becomes a key determinant for BE consideration. To achieve BE, therefore, it is imperative to understand the fate of a formulation in the body, before the drug is absorbed or reaches the site of action. There may be exceptions to the premise of constant clearance in equivalence assessment, which can be exemplified by the inclusion of cholesterol in a liposomal formulation that is handled by the intrinsic lipid pathway (47). These cases, albeit rare, should be considered separately.

Schematically, based on the movement of a formulation (with associated drug), an *in vivo* drug delivery profile (iDDP) may be divided into the following key stages: a) deposition, b) transit, c) retention, d) release, and e) transport, from formulation entry into the body until the drug reaches systemic circulation or the site of action (48). In this setting, equivalent rate and extent of absorption may be reflected by the similarity in one or more of the key stages of iDDP as characterized for the reference formulation. It is surmised that *in vitro* markers or biomarkers can be developed to characterize each stage of the iDDP. A viable way to achieve BE is thus to first determine which stage(s) of iDDP is critical to drug absorption from the reference

product, and then use this information as the target profile for development of the test product. As iDDP can be influenced by a number of variables (discussed later in this paper), it is essential to investigate *a priori* the potential factors that may affect the *in vivo* delivery path of the drug under examination when designing the test formulation. This can be done through the use of *in vitro*, *in silico* or *in vivo* techniques. Hence, an equivalent product can be rationally developed with informed knowledge of the target iDDP and all the potential factors that may impact the product performance through their influences on iDDP.

IN VIVO DRUG DELIVERY PROFILE (IDDP)

Depending on the dosage form, drug product, route of administration and intended clinical indication, there can be different needs for the site of drug deposition, length of transit time, retention potential, retention time, drug release profile, and transport process. In the case of inhaled dosage forms, where the drug is deposited in the respiratory tract is an important question, hence the need to control particle size distribution and flow rate for these products. In contrast, for an orally administered modified-release dosage form, GI transit time is a critical variable that can be maneuvered by proper selection of excipients and formulation designs. While an acid-labile drug must be formulated in an enteric-coated dosage form to bypass the stomach, a floating delivery system is built in some oral solid dosage forms to enhance the gastric retention of drugs (49). Accordingly, for a floating delivery system, it is pertinent to consider how much and how long the drug will be retained in the stomach. On the contrary, for an enteric-coated dosage form, the questions may be focused on (a) what percentage of the drug will be released in the intestine, and (b) where in the intestine most drug molecules will be released.

Drug release *in vivo* is well recognized as one of the important factors governing drug absorption. As such, *in vitro* dissolution or release testing has been widely employed for multiple purposes during the drug development and regulatory approval processes (30). The key issue is whether the *in vitro* release or dissolution testing adequately emulates critical *in vivo* release or dissolution processes. In fact, a major problem with many of the current *in vitro* dissolution or release testing methods lies in the lack of correlation between *in vitro* and *in vivo* data.

As for the *in vivo* transport process, endogenous uptake (absorptive) and efflux transporters may play a significant role in drug absorption via their interactions with the drug or excipients present in a formulation (50–74). The importance of transporter–excipient interactions is exemplified by P-glycoprotein (P-gp) transport, which can complicate the absorption of hydrophobic drugs formulated in lipid-based delivery systems (74). For a liposomal product, the importance of *in vivo* transport process for the drug encapsulated in liposomes cannot be overemphasized. To ensure targeted delivery, one must know (a) whether the liposome-encapsulated drug (or other targeted delivery systems) is transported to the expected site of action, but not other tissues, before drug release, and (b) whether the encapsulated drug may be released in a premature manner before it reaches the target tissue.

POTENTIAL FACTORS INFLUENCING IDDP

From the standpoint of drug development, several pharmaceutical factors are known to influence the course of drug delivery and release *in vivo*. These factors may range from excipients and formulation to product design and manufacturing processes. Additionally, often neglected by pharmaceutical scientists are some of the intrinsic (e.g., genetic) and extrinsic (e.g., environmental) factors that may interact with the underlying pharmaceutical attributes, thereby affecting the *in vivo* performance of a product. Discussion of all the pharmaceutical and biopharmaceutical factors is beyond the scope of this paper. However, for illustration purposes, this commentary will highlight some of the relevant factors that may have been underestimated in their potential to influence the iDDP of a formulation.

Pharmaceutical and Biopharmaceutical Considerations

Common excipients used in pharmaceutical formulations, for the most part, are believed to exert little or no effects on BE. However, some of these excipients have been found to alter drug absorption *in vivo* or *in vitro* (59–76). In addition to the potential influence on drug solubility and/or intestinal permeability, plausible mechanisms for these excipient effects may include change in the GI transit time or pH, inhibition or induction of metabolizing enzymes and/or transporters in the GI membrane, alteration of *in vivo* dissolution rate, complexation and/or degradation in GI lumen (59–76). The effects of some excipients, e.g., sorbitol and polysorbate 80, on drug absorption have been shown to depend on the amount of these excipients present in the formulation (75,76). Therefore, it would be beneficial to identify such 'active' excipients and determine their threshold levels to influence bioavailability and BE during pharmaceutical development.

The use of lipid excipients for formulations is complicated, and has presented several challenges to both pharmaceutical industry and regulatory scientists (28). Lipid excipients are able to solubilize hydrophobic drugs within the dosage form matrix. However, as with dietary lipids, these excipients can also be digested and dispersed *in vivo*. Therefore, different types of lipid excipients can have a significant impact on the transport process and clearance kinetics of liposome drug products. It has been observed that cholesterol-poor liposomes were cleared more readily than cholesterol-rich liposomes (47). While cholesterol-poor vesicles were predominantly localized in the liver, incorporation of cholesterol in the latter increased liposomal uptake by both spleen and bone marrow (47,77–78). A question that has been raised is the due regulatory oversight on the safety of an excipient. It should be noted that for a drug or biological product subject to pre-marketing approval, the FDA has routinely evaluated the submitted data and information on the excipients as they are considered 'components' of the product in the application.

Dosage form and product design are important determinants for formulation delivery and drug kinetics *in vivo.* Hence, special attention should be given to the key characteristics in chemistry, manufacturing and controls that are relevant to the final performance of the dosage form under

consideration. Using extended release dosage forms as an example, there are at least two principles that should be kept in mind when designing a test product intended to be equivalent to the innovator's product. First, to meet the product claim, it is imperative to maintain the prolonged release of the drug. If the test product has a different release mechanism from the reference product, additional investigation may have to be carried out to assess whether there is any impact on the onset and extent of drug release, and possibly, clinical consequences. Secondly, in view of the special features of an extended release dosage form, it is equally important to guard against dose dumping from the product. Modified-release products with different release mechanisms may have disparate drug release patterns when subject to external environments. This is illustrated by recent experiences with some extended-release formulations of hydromorphone that were found to dose-dump when co-administered with alcohol (79). Inadequate control of drug release from such extended-release products may thus result in reduced efficacy or increased toxicity.

Intrinsic and Extrinsic Factors

Pre-absorption drug delivery pathways may be influenced by the presence of various preexisting intrinsic and extrinsic factors. Important intrinsic factors may include genetic, physiological and pathological conditions of the patient (80). Relevant extrinsic factors may be related to environment (e.g., climate, sunlight and pollution), food intake (e.g., diet and beverage), lifestyle (e.g., smoking and exercise), and concomitant medications (including over-the-counter drugs, dietary supplements and herbal products) (80). With different formulations, product designs and manufacturing processes, these intrinsic and extrinsic factors may directly or indirectly affect the route of drug delivery and drug release profile *in vivo* before it is absorbed or carried to the site of action.

An example of internal factors may be drawn from the case of a calcium channel blocker where BE of two extended-release formulations was evaluated (81). In both single-dose and multiple-dose studies, the mean ratios of AUC and Cmax measures for Formulation A over Formulation B were significantly different between male and female subjects, suggesting the presence of a gender-by-formulation interaction. This interaction was attributable to the differential pH-dependent drug release profiles, as well as the sex-related differences in GI transit time between the two formulations (81). Another internal factor that may need consideration in some cases is the pathophysiological conditions of a patient. For instance, lipid-based formulations such as liposome drug products can be transported by serum lipoproteins, and the levels of these proteins can be influenced by the disease state of a patient (82,83). As for external factors, a good example is illustrated by the heat on medicated patches (84,85). Drugs delivered through the skin via medicated patches can present safety hazards when subjected to heat by exercise, soaking in a hot tub, or even in the presence of a high fever, all of which may cause increased rate and extent of drug permeation from the patches to the skin (84,85).

Overall, the potential interplay between pharmaceutical attributes and intrinsic/extrinsic factors may be investigated during the course of drug development. These interactions may be proactively explored through *in vitro, in silico or in vivo* methods that allow for the study of drug delivery profiles before drug absorption.

CHARACTERIZING IDDP WITH *IN VITRO* MARKERS OR BIOMARKERS

Currently, the *in vivo* drug delivery pathways prior to the absorption of the drug are not well documented. This is probably due, in part, to the lack of methodology for study in this area. The conventional drug concentration-time curve in the blood/plasma only depicts the kinetic profile after the drug has been absorbed and reached the systemic circulation. Therefore, questions remain as to where the drug or formulation was deposited, how much time it took for the drug or formulation to transit in the GI tract, how long the drug or formulation was retained at the various sites during transit, when and where the drug was released, how the drug or formulation was transported to the site of action, and how extensive the interaction between drug/excipient and transporters occurred prior to the absorption of the drug. Conduct of mechanistic studies may be necessary to address these questions.

Mechanistic studies have sometimes been performed during the new drug development. For example, gamma scintigraphy or other methods were used to study drug deposition, transit time or tissue distribution from an inhaled dosage form or an orally administered modified release product (86–92). It can be envisioned that the study of pre-absorption kinetics may require a multidisciplinary approach including various fields such as biopharmaceutics, biochemistry, biophysics and/or other relevant areas. Through the integration of knowledge and tools from these different disciplines, *in vitro* markers or biomarkers may be identified to assess the dynamic processes during drug delivery *in vivo*.

EQUIVALENCE-BY-DESIGN

Conventional drug development has mostly relied on empirical and/or iterative processes. With the modernization of pharmaceutical science and technology, however, use of a more systematic approach may be possible. In this context, the approach of quality-by-design (QbD) has recently been recommended by several regulatory authorities for pharmaceutical development and manufacturing (93). This approach begins with predefined objectives, and emphasizes a greater understanding of pharmaceutical product, manufacturing process and process control, based on sound science and quality risk management (93). Indeed, the QbD approach promises to build quality into a final product by prospectively designing formulations and processes to meet the product quality attributes that may have impact on the clinical outcome (94,95).

Similarly, in the equivalence arena, a more systematic approach can be applied to the development of a pharmaceutical product intended to be equivalent to a reference product. This may be referred to as the concept of *equivalence-by-design,* a natural extension of the QbD principle. As illustrated in the International Conference on Harmonization (ICH) Annex to Q8 guideline, application of the QbD

approach requires the determination of a target product profile as it relates to quality, safety and efficacy (93). Likewise, to use the *equivalence-by-design* approach, it is essential for the manufacturer to predefine a target reference profile, which may be characterized by the critical stages of the iDDP for the reference product. The continuous innovation in pharmaceutical industry may facilitate the development of novel tools as *in vitro* markers or biomarkers to assess iDDPs for the test and reference products. Ultimately, successful design of an equivalent test product can be accomplished with a better understanding of all the relevant factors that may have potential impact on the iDDP's for the products in comparison.

CONCLUSION

Extraordinary progress has been made in pharmaceutical science and technology since the enactment of 1977 BE regulations in U.S. The contemporary knowledge and methodologies may provide an opportunity to enhance the approaches for equivalence demonstration, particularly for advanced or complex dosage forms and delivery systems. Theoretical considerations prescribe that equivalence can be better established by matching the *in vivo* drug delivery profile (iDDP) of a reference formulation of interest. This may be achieved by characterizing the iDDP of the formulation with application of an equivalence-by-design approach for pharmaceutical development. In addition to pharmaceutical and biopharmaceutical considerations, more attention should be given to the intrinsic and extrinsic factors that may have a profound influence on the iDDP of complex dosage forms or delivery systems. To accomplish equivalence, critical variables or parameters can be identified to serve as *in vitro* markers or biomarkers for mapping the drug delivery *in vivo*. A multidisciplinary approach is necessary to develop such markers or biomarkers.

ACKNOWLEDGEMENT

The authors would like to thank Helen Winkle, Keith Webber, Nakissa Sadrieh and Barbara Davit for their valuable suggestions during the preparation of this paper.

REFERENCES

1. Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Office of Generic Drugs. Current through February 2008. http://www.fda.gov/cder/ob/default.htm
2. U.S. Food and Drug Administration, Title 21 Code of Federal Regulations (CFR) Part 320.25(a), Office of Federal Register, National Archives and Records Administration (2007).
3. Drug Bioequivalence Study Panel. Drug bioequivalence. Office of Technology Assessment, Superintendent of Documents, U.S. Government Printing Office, Washington DC 20402 (1974).
4. U.S. Food and Drug Administration, Title 21 Code of Federal Regulations (CFR) Part 320, Office of Federal Register, National Archives and Records Administration (2006).
5. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance Documents, accessed on March 3, 2008. http://www.fda.gov/cder/guidance/index.htm
6. Pharmaceutical Manufacturers Association, A presentation to the U.S. Food and Drug Administration Hearing on Bioequivalence of Solid Oral Dosage Forms, September 29–October 1, 1986.
7. U.S. Department of Health and Human Services, Food and Drug Administration, Establishment of the Therapeutic Inequivalence Action Coordinating Committee; Availability of committee reports, 53 Federal Register 35562, September 14, 1988.
8. M.-L. Chen, R. Patnaik, W.W. Hauck, D.J. Schuirmann, T. Hyslop, R.L. Williams, and FDA Population/Individual Bioequivalence Working Group. An individual bioequivalence criterion: Regulatory considerations. *Stat. Med.* **19**:2821–2842 (2000).
9. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Office of Generic Drugs. *Critical Path Opportunities for Generic Drugs.* May 1, 2007. http://www.fda.gov/oc/initiatives/criticalpath/reports/generic.html
10. S. Sabatini, R.M. Ferguson, J.H. Helderman *et al.* Drug substitution in transplantation: A National Kidney Foundation white paper. *Am. J. Kidney Dis.* **33**:389–397 (1999).
11. F.M.C. Besag. Is generic prescribing acceptable in epilepsy? *Drug Safety.* **23**:173–182 (2000).
12. J.A. Reiffel. Issues in the use of generic antiarrhythmic drugs. *Curr. Opin. Cardiol.* **16**:23–29 (2001).
13. L.S. Welage, D.M. Kirking, F.J. Ascione, and C.A. Gaither. Understanding the scientific issues embedded in the generic drug approval process. *J. Am. Pharm. Assoc.* **41**:856–867 (2001).
14. Y.W.F. Lam, L. Ereshefsky, G.B. Toney, and C. Gonzales. Branded *versus* generic clozapine: bioavailability comparison and interchangeability issues. *J. Clin. Psychiatry.* **62**(suppl 5):18–22 (2001).
15. L. Wartofsky. Levothyroxine: Therapeutic use and regulatory issues related to bioequivalence. *Exp. Opin. Pharmacother.* **3**:727–732 (2002).
16. G. Borgherini. The bioequivalence and therapeutic efficacy of generic *versus* brand-name psychoactive drugs. *Clin. Ther.* **25**:1578–1592 (2003).
17. P. Meredith. Bioequivalence and other unresolved issues in generic drug substitution. *Clin. Ther.* **25**:2875–2890 (2003).
18. R.A. Bongiorno, and E.A. Nutescu. Generic warfarin: Implications for clinical practice and perceptions of anticoagulation providers. *Semin. Thromb. Hemost.* **30**:619–626 (2004).
19. V. Blakesley, W. Awni, C. Locke, T. Ludden, G.R. Granneman, and L.E. Braverman. Are bioequivalence studies of levothyroxine sodium formulations in euthyroid volunteers reliable? *Thyroid.* **14**:191–200 (2004).
20. T.E. Welty. Pharmacy and generic substitution of antiepileptic drugs: Missing in action? *Ann. Pharmacother.* **41**:1065–1068 (2007).
21. M. Healy. FDA standards for generics are questioned. Los Angeles Times, March 17, 2008.
22. U.S. Department of Health and Human Services, Food and Drug Administration, *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products.* March 2004. http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html
23. D.J. Burgess, A.S. Hussain, T.S. Ingallinera, and M.-L. Chen. Assuring quality and performance of sustained and controlled release parenterals: Workshop report. *Pharm. Res.* **19**:1761–1768 (2002).
24. D.J. Burgess, D.J.A. Crommelin, A.S. Hussain, and M.-L. Chen. Assuring quality and performance of sustained and controlled release parenterals: EUFEPS workshop report. *Eur. J. Pharm. Sci.* **21**:769–790 (2004).
25. K. Kumi. Complex drug substances—liposome drug products: Bioavailability and bioequivalence (biopharmaceutics issues). U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Advisory Committee for Pharmaceutical Science Meeting, May 3–4, 2005. http://www.fda.gov/ohrms/dockets/ac/01/slides/3763s2.htm
26. U.S. Food and Drug Administration, Title 21 Code of Federal Regulations (CFR) Part 320.1, Office of Federal Register, National Archives and Records Administration (2006).

27. J.E. Henney. Nationwide recall of SangCya oral solution. *JAMA.* **284**:1234 (2000).
28. M.-L. Chen. Lipid excipients and delivery systems for pharmaceutical development. *Adv. Drug Deliv. Rev.* **60**:768–777 (2008).
29. R. Lionberger, Topical bioequivalence update. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Advisory Committee for Pharmaceutical Science Meeting, May 3–4, 2005. http://www.fda.gov/ohrms/dockets/9ac/05/briefing/2005-4137b1_Index.htm
30. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations.* Division of Drug Information, HFD-240, Rockville, Maryland 20857, March 2003. http://www.fda.gov/cder/guidance/5356fnl.doc
31. U.S. Food and Drug Administration, Title 21 Code of Federal Regulations (CFR) Part 320.24(a), Office of Federal Register, National Archives and Records Administration (2006).
32. U.S. Food and Drug Administration, Title 21 Code of Federal Regulations (CFR) Part 320.24(b), Office of Federal Register, National Archives and Records Administration (2006).
33. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. *Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.* Office of Training and Communication, Division of Communications Management, Drug Information Branch, HFD-210, Rockville, Maryland 20857, August 2000. http://www.fda.gov/cder/guidance/3618fnl.htm
34. U.S. Food and Drug Administration, Title 21 Code of Federal Regulations (CFR) Part 320.22, Office of Federal Register, National Archives and Records Administration (2006).
35. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. *Guidance for Industry: Corticosteroids, Dermatologic (topical) In Vivo.* Office of Training and Communication, Division of Communications Management, Drug Information Branch, HFD-210, Rockville, Maryland 20857, June 1995. http://www.fda.gov/cder/guidance/old098fn.pdf
36. P.D.R. Thomson. *Physicians' Desk Reference (PDR)*. 57th Ed., Montvale, NJ, 2003.
37. P.D.R. Thomson. *Physicians' Desk Reference (PDR)*. 59th Ed., Montvale, NJ, 2005.
38. T. Bussemer, I. Otto, and R. Bodmeier. Pulsatile drug-delivery systems. *Crit. Rev. Ther. Drug Carrier Syst.* **18**:433–58 (2001).
39. D.J. Brayden. Controlled release technologies for drug delivery. *Drug Discovery Today.* **8**:976–978 (2003).
40. A. Farinha, A. Bica, J.P. Pais, M.C. Toscano, and P. Tavares. Bioequivalence evaluation of two omeprazole enteric-coated formulations in humans. *Eur. J. Pharm. Sci.* **7**:311–315 (1999).
41. Z. Elkoshi, D. Behr, A. Mirimsky, I. Tsvetkov, and A. Danon. Multiple-dose studies can be a more sensitive assessment for bioequivalence than single-dose studies—The case with omeprazole. *Clin. Drug Invest.* **22**:585–592 (2002).
42. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. *Draft Guidance for Industry: Liposome Drug Products—Chemistry, Manufacturing and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation.* Office of Training and Communications, Division of Drug Information, HFD-240, Rockville, MD. http://www.fda.gov/cder/guidance/2191dft.pdf
43. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health (CDRH), Center for Drug Evaluation and Research. *Draft Guidance for Industry: Coronary Drug-Eluting Stents—Nonclinical and Clinical Studies.* Office of Training and Communications, Division of Communications Management, HFD-210, Rockville, MD. http://www.fda.gov/cdrh/ode/guidance/6255.html
44. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drugs, Division of Bioequivalence. *Interim Guidance: Cholestyramine Powder—In Vitro Bioequivalence.* July 1993. http://www.fda.gov/cder/guidance/cholesty.pdf
45. M.-L. Chen, and A.J. Jackson. The role of metabolites in bioequivalency assessment. I. Linear pharmacokinetics without first-pass effect. *Pharm. Res.* **8**:25–32 (1991).
46. M.-L. Chen, and A.J. Jackson. The role of metabolites in bioequivalency assessment. II. Drugs with linear pharmacokinetics and first-pass effect. *Pharm. Res.* **12**:700–708 (1995).
47. F.H. Roerdink, J. Regts, T. Handel, S.M. Sullivan, J.D. Baldeschwieler, and G.L. Scherphof. Effect of cholesterol on the uptake and intracellular degradation of liposomes by liver and spleen; a combined biochemical and γ-ray perturbed angular correlation study. *Biochim. Biophys. Acta.* **980**:234–240 (1989).
48. M.-L. Chen. Novel approaches to establishing equivalence of advanced dosage forms. American Association for Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition, San Diego, November 11–15, 2007.
49. S. Arora, J. Ali, A. Ahuja, R.K. Khar, and S. Baboota. Floating drug delivery systems: A review. *AAPS Pharm. Sci. Tech.* **6**(03): E372–E390 (2005).
50. P.D. Dobson, and D.B. Kell. Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule? *Nat. Rev.—Drug Discov.* **7**:205–220 (2008).
51. T.M. Sissung, E.R. Gardner, R. Gao, and W.D. Figg. Pharmacogenetics of membrane transporters: A review of current approaches. *Methods Mol. Biol.* **448**:41–62 (2008).
52. M. Takano, R. Yumoto, and T. Murakami. Expression and function of efflux drug transporters in the intestine. *Pharmacol. Ther.* **109**:137–161 (2006).
53. Y. Su, and P.J. Sinko. Drug delivery across the blood-brain barrier: Why is it difficult? How to measure and improve it? *Expert Opin. Drug Deliv.* **3**:419–435 (2006).
54. U. Hoffmann, and H.K. Kroemer. The ABCC transporters MDR1 and MRP2: multiple functions in disposition of xenobiotics and drug resistance. *Drug Metab. Rev.* **36**:669–701 (2004).
55. L.Z. Benet, C.L. Cummins, and C.Y. Wu. Unmasking the dynamic interplay between efflux transporters and metabolic enzymes. *Int. J. Pharm.* **11**:3–9 (2004).
56. B. Steffansen, C.U. Nielsen, B. Brodin, A.H. Eriksson, R. Andersen, and S. Frokjaer. Intestinal solute carriers: An overview of trends and strategies for improving oral drug absorption. *Eur. J. Pharm. Sci.* **21**:3–16 (2004).
57. N. Mizuno, T. Niwa, Y. Yotsumoto, and Y. Sugiyama. Impact of drug transporter studies on drug discovery and development. *Pharmacol. Rev.* **55**:425–461 (2003).
58. R.B. Kim. Drugs as P-glycoprotein substrates, inhibitors, and inducers. *Drug Metab. Rev.* **34**:47–54 (2002).
59. K.M. Koch, A.F. Parr, J.J. Tomlinson, E.P. Sandefer, G.A. Digenis, K.H. Donn, and J.R. Powell. Effect of sodium acid pyrophosphate on ranitidine bioavailability and gastrointestinal transit time. *Pharm. Res.* **10**:1027–1030 (1993).
60. D.A. Adkin, S.S. Davis, R.A. Sparrow, P.D. Huckle, A.J. Philips, and I.R. Wilding. The effects of pharmaceutical excipients on small intestinal transit. *Br. J. Clin. Pharmac.* **39**:381–387 (1995).
61. D.A. Adkin, S.S. Davis, R.A. Sparrow, P.D. Huckle, and I.R. Wilding. The effect of mannitol on the oral bioavailability of cimetidine. *J. Pharm. Sci.* **84**:1405–1409 (1995).
62. M.M. Nerurkar, P.S. Burton, and R.T. Borchardt. The use of surfactants to enhance the permeability of peptides through Caco-2 cells by inhibition of an apically polarized efflux system. *Pharm. Res.* **13**:528–534 (1996).
63. L. Yu, A. Bridgers, J. Polli, A. Vickers, S. Long, A. Roy, R. Winnike, and M. Coffin. Vitamin E-TPGS increases absorption flux of an HIV protease inhibitor by enhancing its solubility and permeability. *Pharm. Res.* **16**:1812–1817 (1999).
64. B. J. Aungst. Intestinal permeation enhancers. *J. Pharm. Sci.* **89**:429–442 (2000).
65. A. Bernkop-Schnurch. Chitosan and its derivatives: potential excipients for peroral peptide delivery systems. *Int. J. Pharm.* **194**:1–13 (2000).
66. B.D. Rege, L.X. Yu, A.S. Hussain, and J.E. Polli. Effect of common excipients on Caco-2 transport of low-permeability drugs. *J. Pharm. Sci.* **90**:1776–1786 (2001).
67. A.W. Basit, F. Podczeck, J.M. Newton, W.A. Waddington, P.J. Ell, and L.F. Lacey. Influence of polyethylene glycol 400 on the gastrointestinal absorption of ranitidine. *Pharm. Res.* **19**:1368–1374 (2002).

68. B.D. Rege, J.P.Y. Kao, and J.E. Polli. Effect of nonionic surfactants on membrane transporters in Caco-2 cell monolayers. *Eur. J. Pharm. Sci.* **16**:237–246 (2002).
69. E.D. Hugger, B.L. Novak, P.S. Burton, K.L. Audus, and R.T. Borchardt. A comparison of commonly used polyethoxylated pharmaceutical excipients on their ability to inhibit P-glycoprotein activity *in vitro*. *J. Pharm. Sci.* **91**:1991–2002 (2002).
70. J.D.R. Schulze, W.A. Waddington, P.J. Ell, G.E. Parsons, M.D. Coffin, and A.W. Basit. Concentration-dependent effects of polyethylene glycol 400 on gastrointestinal transit and drug absorption. *Pharm. Res.* **20**:1984–1988 (2003).
71. T. Nozawa, H. Toyobuku, D. Kobayashi, K. Kuruma, A. Tsuji, and I. Tamai. Enhanced intestinal absorption of drugs by activation of peptide transporter PEPT1 using proton-releasing polymer. *J. Pharm. Sci.* **92**:2208–2216 (2003).
72. Y. Tayrouz, R. Ding, J. Burhenne, K.D. Riedel, J. Weiss, T. Hoppe-Tichy, W.E. Haefeli, and G. Mikus. Pharmacokinetic and pharmaceutic interaction between digoxin and Cremophor RH40. *Clin. Pharmacol. Ther.* **73**:397–405 (2003).
73. K. Bogman, Y. Zysset, L. Degen, G. Hopfgartner, H. Gutmann, J. Alsenz, and J. Drewe. P-glycoprotein and surfactants: Effect on intestinal talinolol absorption. *Clin. Pharmacol. Ther.* **77**:24–32 (2005).
74. P.P. Constantinides, and K.M. Wasan. Lipid formulation strategies for enhancing intestinal transport and absorption of P-glycoprotein (P-gp) substrate drugs: *In vitro/in vivo* case studies. *J. Pharm. Sci.* **96**:235–248 (2007).
75. M.-L. Chen, A.B. Straughn, N. Sadrieh, M. Meyer, P.J. Faustino, A.B. Ciavarella, B. Meibohm, C.R. Yates, and A.S. Hussain. A modern view of excipient effects on bioequivalence: Case study of sorbitol. *Pharm. Res.* **24**:73–80 (2007).
76. J.M. Odeberg, A. Lignell, A. Pettersson, and P. Hoglund. Oral bioavailability of the antioxidant astaxanthin in humans is enhanced by incorporation of lipid based formulations. *Eur. J. Pharm. Sci.* **19**:299–304 (2003).
77. J. Senior, J.C.W. Crawley, and G. Gregoriadis. Tissue distribution of liposomes exhibiting long half-lives in the circulation after intravenous injection. *Biochim. Biophys. Acta.* **839**:1–8 (1985).
78. S.M. Morghimi, and H.M. Patel. Serum-mediated recognition of liposomes by phagocytic cells of the reticuloendothelial system—The concept of tissue specificity. *Adv. Drug Deliv. Rev.* **32**:45–60 (1998).
79. R. Meyer. Clinical relevance of alcohol-induced dose dumping. FDA Advisory Committee for Pharmaceutical Science Meeting, Rockville, Maryland. Oct. 25–26, 2005. http://www.fda.gov/ohrms/dockets/ac/acmenu.htm
80. The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, ICH E5 Guideline, August 1998; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. *Guidance for Industry: Ethnic Factors in the Acceptability of Foreign Clinical Data*. Federal Register **63**:31790–6 (1998).
81. M.-L. Chen. Confounding factors for sex differences in pharmacokinetics and pharmacodynamics: Focus on dosing regimen, dosage form, and formulation. *Clin. Pharmacol. Ther.* **78**:322–329 (2005).
82. K.M. Wasan, and S.M. Cassidy. Role of plasma lipoproteins in modifying the biological activity of hydrophobic drugs. *J. Pharm. Sci.* **87**:411–424 (1998).
83. K.M. Wasan, M. Ramaswamy, M. Kwong, K.D. Boulanger. Role of plasma lipoproteins in modifying the toxic effects of water-insoluble drugs: Studies with cyclosporine A. AAPS PharmSci. 4: Article 30 (2002).
84. D. Fallik. Experts: Patches + Heat = Danger, *Philadelphia Inquirer*, Mar. 5, 2006. http://www.yourlawyer.com/articles/read/11446
85. M.A. Ashburn, L.L. Ogden, J. Zhang, G. Love, and S.V. Basta. The pharmacokinetics of transdermal fentanyl delivered with and without controlled heat. *J. Pain.* **4**:291–297 (2003).
86. E. Lundin, W. Graf, U. Garske, S. Nisson, E. Maripuu, and U. Karlbom. Segmental colonic transit studies: comparison of a radiological and a scintigraphic method. *Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland.* **9**(4):344–351 (2007).
87. B.J. Cook, E. Lim, D. Cook, J. Hughes, C.W. Chow, M.P. Stanton, S.S. Bidarkar, B.R. Southwell, and J.M. Hutson. Radionuclear transit to assess sites of delay in large bowel transit in children with chronic idiopathic constipation. *J. Pediatr. Surg.* **40**:478–483 (2005).
88. A. Perkins, and M. Frier. Nuclear medicine imaging and drug delivery. *Nuclear Medicine Communications.* **21**:415–416 (2000).
89. S.P. Newman, and I.R. Wilding. Imaging techniques for assessing drug delivery in man. *PSTT.* **2**(5):181–189 (1999).
90. P.H. Layer, H. Goebell, J. Keller, A. Dignass, and U. Klotz. Delivery and fate of oral mesalamine microgranules within the human small intestine. *Gastroenterology.* **108**:1427–1433 (1995).
91. G. Meseguer, R. Gurny, and P. Buri. *In vivo* evaluation of dosage forms: Application of gamma scintigraphy to non-enteral routes of administration. *J. Drug Target.* **2**:269–288 (1994).
92. S.S. Davis, J.G. Hardy, S.P. Newman, and I.R. Wilding. Gamma scintigraphy in the evaluation of pharmaceutical dosage forms. *J. Nucl. Med.* **19**(11):971–986 (1992).
93. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Draft Consensus Guideline on Pharmaceutical Development: Annex to Q8. November 1, 2007. http://www.ich.org/LOB/media/MEDIA4349.pdf
94. J. Woodcock. The concept of pharmaceutical quality. *Am. Pharm. Rev.* **3**:1–3 (2004).
95. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Advisory Committee for Pharmaceutical Science Meeting, Oct. 5–6, 2006. http://www.fda.gov/ohrms/dockets/ac/cder06.html#PharmScience