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PERSPECTIVE

Pharmaceutical Equivalence by Design for Generic Drugs: Modified-Release Products

André Sirota Raw • Robert Lionberger • Lawrence X. Yu

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ABSTRACT The Office of Generic Drugs has ensured the high quality of generic products based upon two requirements: pharmaceutical equivalence and bioequivalence to the reference listed drug (RLD). This paradigm has been used with success toward ensuring quality generic drug products that provide the same therapeutic benefit as the RLD. Drug products have increased in design complexity; as a result, approaches to ensure therapeutic equivalence must evolve to provide assurance of quality generic drug products. The Food and Drug Administration quality by design initiative (QbD) provides an enhanced evaluation approach by introducing the concept of a quality target product profile (QTPP). The QTPP introduces, within the context of the current regulatory framework, the quality concept of "pharmaceutical equivalence by design." This article illustrates through several examples how this QbD element in the evaluation of modified-release drug products enhances the current framework to ensure generic drug product equivalence. It achieves this by complementing the traditional paradigm, "equivalence by testing," where product equivalence is based upon inferences from a limited bioequivalence study, to one that also considers whether the drug product was developed to be an equivalent to the RLD, using appropriate quality surrogates that target "pharmaceutical equivalence by design."

KEY WORDS generic drugs · modified release · pharmaceutical equivalence · quality by design (QbD) · quality target product profile (QTPP) · therapeutic equivalence

The views presented in this article do not necessarily reflect those of the Food and Drug Administration.

A. S. Raw (✉) · R. Lionberger · L. X. Yu
Food and Drug Administration, Office of Generic Drugs
7519 Standish Place
Rockville, Maryland 20855, USA
e-mail: andre.raw@fda.hhs.gov

INTRODUCTION

The Food and Drug Administration (FDA) Pharmaceutical Good Manufacturing Practices (GMPs) for the 21st Century and Quality by Design (QbD) initiatives are meant to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. In line with these FDA initiatives, the Office of Generic Drugs (OGD) has developed a Question-Based Review (QbR) for its Chemistry, Manufacturing, and Controls (CMC) evaluation of Abbreviated New Drug Applications (ANDAs) (1).

In order to understand the basis for these initiatives, it becomes critical to have an understanding of the meaning of pharmaceutical quality, particularly in the context of generic drugs. In a paper by Janet Woodcock (Director for the Center of Drug Evaluation and Research), *pharmaceutical quality* is defined as a drug product that is free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer (2). For a generic drug product, by virtue of being therapeutically interchangeable and equivalent to the brand name product or reference listed drug (RLD), there is the expectation that it should provide the same therapeutic benefit as promised by the label.

Historically, the Office of Generic Drugs (OGD) ensured the high quality of generic drug products based upon a combination of two fundamental requirements: 1) pharmaceutical equivalence and 2) bioequivalence. Pharmaceutical equivalence requires, among other things, that the generic drug product contain the same active ingredient(s), are of the same dosage form and route of administration, and are identical in strength or concentration. Pharmaceutical equivalence also requires that the generic drug product meet compendial or other applicable standards including strength, quality, and purity. Bioequivalence refers to the

absence of a statistically significant difference in the rate and extent to which the active ingredient in pharmaceutically equivalent products becomes available at the site of action, when administered to subjects at the same molar dose under similar conditions. By establishing both pharmaceutical equivalence and bioequivalence, the generic drug product is considered to be a therapeutic equivalent, meaning that the generic product will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling, and may be substituted for each other without adjustment in dose or other additional monitoring (3).

This traditional review paradigm has been used with great success in bringing to approval high quality generic drug products that provide the same therapeutic benefit as the RLD. While this approach has been successful, it must also be noted that the vast majority of generic drug products approved under this paradigm were solution and immediate release oral products, which are inherently simple in design. Drug products, however, have increased in design complexity to encompass modified (oral) release products, transdermal delivery systems, and other complex dosage forms. As these drug products have increased in complexity, it has become apparent that the review paradigm to ensure the quality of generic products must likewise evolve in order to continue to provide assurance of high quality generic drug products.

For this reason, enhancement of the historical approaches to ensure generic drug product quality may be useful, particularly in the context of these more complex drug products. FDA's QbD initiative provides an enhanced approach to ensure generic drug product quality. In line with this QbD framework, the International Conference on Harmonization ICH Q8 (4) introduces the concept of a quality target product profile (QTPP). As indicated, pharmaceutical equivalence requires, among other things, that a generic drug product have suitable quality. The QTPP introduces within the context of the regulatory framework of pharmaceutical equivalence, the quality concept of drug product "pharmaceutical equivalence by design." We illustrate how the QTPP would serve as a key element to ensure the quality of these increasingly complex generic products, not solely based upon the traditional requirement that the drug products have the same active ingredient and dosage form and demonstrate bioequivalence to the RLD, but also based upon an assessment of drug product design. We show that the use of a QTPP that considers the clinical use of the RLD, identifies its critical quality attributes, and employs measurable surrogates for them in pharmaceutical development is "pharmaceutical equivalence by design."

TRADITIONAL APPROACH USED TO ESTABLISH EQUIVALENCE OF GENERIC DRUG PRODUCTS TO THE REFERENCE LISTED DRUG

ANDAs are approved based upon the underlying presumption that the generic drug product will be a therapeutic equivalent to the RLD, provided the generic drug product has the same active ingredient strength and dosage form; includes the same route of administration; and demonstrates bioequivalence to the RLD. While this is true in the vast majority of cases, particularly for simple dosage forms, in the case of complex dosage forms, there are certain instances where additional information based upon an assessment of generic drug product design may be useful to provide assurance of therapeutic equivalence. The examples cited below, although not a comprehensive list, illustrate the critical importance of comparing the generic drug product design to that RLD, particularly for complex dosage forms.

Modified-Release Drug Products: Impact of the Active Ingredient that Modifies Absorption Characteristics

The first example cites the importance of considering generic drug product design, particularly for modified-release drug products where the pharmacodynamic effect of the active ingredient may alter or modify the absorption characteristics of the drug. This is particularly important, as often these effects may not be captured in the single-dose bioequivalence studies in healthy subjects typically used to support approval of the generic drug product. Although not a comprehensive list, one drug product class that falls within this class includes the proton pump inhibitors (PPIs) such as omeprazole. A common property of these PPIs is that they are acid labile and are often formulated in a drug product design having an enteric coat to avert acid degradation of the active ingredient in the stomach (5). PPIs raise the gastric environment from an acidic pH of approximately 1 to levels in the range of pH 2–7, which in turn may affect the bioavailability of the drug (6). Thus, given the acid lability of PPIs and their pharmacodynamic effect on gastric pH, these effects may interact and impact the rate and extent of the absorption during repeated therapeutic use, which is not captured in a single dose bioequivalence testing study.

Consider, for example, if the generic product is formulated with an enteric coating designed to protect the active ingredient against degradation through pH 3, and the RLD is formulated with an enteric coating to guard against degradation through pH 5–6. In this case, it may be

anticipated that the two products may be shown to be bioequivalent in a single dose study, where the gastric environment is near pH 1. However, following multiple dosing, as a result of the drug pharmacodynamic effect, where the gastric pH will rise to 2–7, it is quite conceivable that in those subjects having a gastric pH of 3–5, a generic product with an enteric coating designed to protect the active ingredient through pH 3 may prematurely release the PPI into the stomach, resulting in acid degradation and lower bioavailability, as compared to the RLD with an enteric coat designed to protect the active through a pH of 5–6 (7). In fact, this was reported when comparing some enteric-coated formulations of omeprazole marketed outside the United States. While the Losec reference formulation contained an enteric coat designed to protect the PPI through pH 5, the corresponding Omepradex formulation contained a hydroxypropyl methylcellulose (HMPC) acetate succinate enteric coat that is protective only through pH 3. In a comparative single dose bioequivalence study at day 1, the two formulations exhibited a geometric mean point estimate ratio of 0.85 (Omepradex/Losec) for both C_{max} and AUC parameters. However, as a result of these differences in the enteric coating, following multiple dosing through 5 days, the corresponding geometric mean point estimate for C_{max} and AUC changed to 0.73 and 0.71, respectively, outside the bioequivalence acceptance limits of 0.80–1.25 (Fig. 1) (7).

This illustrates the important concept that although a generic drug product may have the same active ingredient and dosage form as the RLD and demonstrate bioequivalence to the RLD via a typical single dose study in healthy subjects, in order to ensure therapeutic equivalence during chronic use, in some instances it may be critical to ensure the generic product shows similarity to the RLD with respect to the design of critical formulation attributes. As will be discussed in the next section, for PPIs, this would entail similarity in design characteristics of the enteric coating used to guard the active ingredient against acid degradation.

Interestingly, in contrast to the omeprazole products marketed outside the US which may differ in their enteric coating design characteristics, the omeprazole products approved in the US are similarly designed to the RLD to provide comparable protection against acid degradation through pH 5–5.5 (8). It appears, in this instance, that although this was not considered as a precondition for ANDA approval, the US generic manufactures may have been aware of the critical importance of having within their product design, an enteric coating that provides similar protection as the RLD to ensure therapeutic equivalence.

Modified-Release Drug Products with Multiphasic Drug Release Components

A second example illustrates some current limitations in the evaluation of modified-release drug product formulations that incorporate multiphasic drug release components to achieve a drug plasma profile critical to clinical performance. Under the traditional review paradigm for establishing bioequivalence for generic drug products, the vast majority of immediate release products may be shown to have a comparable drug plasma profile to the RLD based upon a consideration of the bioequivalence parameters AUC and C_{max}. However, for more complicated modified-release drug products, such as those that incorporate multiphasic drug release components, it is possible that a generic drug product designed to provide for monophasic release, despite meeting traditional bioequivalence parameters, may have a very different drug plasma concentration profile to the RLD. These differences in the drug plasma concentration profiles may have important implications to the clinical properties of the drug product.

For example, there are several formulations of methylphenidate that are designed to provide for both immediate release for onset of action, followed by extended release to maintain efficacy. Each of these designs provides for a characteristic drug blood plasma profile important to the clinical characteristics of the drug. For example, in one of these modified-release products, the capsule formulation (20 mg) achieves biphasic release of the active based upon a design with 30% of the dose contained in immediate release beads with the remaining 70% of the dose contained in extended release beads (9). In another modified-release product, the tablet formulation (18 mg) achieves biphasic release based upon having 22% of the active ingredient in a tablet overcoat for immediate release, with the remaining 78% of the active ingredient contained in an osmotic pump designed to provide for zero-order release independent of pH and hydrodynamic conditions (10). As might be anticipated, due to these differing drug product designs, these products give rise to dissimilar drug plasma profiles (Fig. 2) (11), and a comparative study between these products indicates that they have differing clinical effects (12). However, if one were to calculate both dose-unnormalized and dose-normalized ratios using the traditional bioequivalence parameters for both AUC and C_{max}, the 90% confidence interval would fall within 0.80–1.25 bioequivalence limits (Table I).

An important regulatory caveat to the above example is that because these two drug products contain different doses of drug (20 mg *versus* 18 mg) in different dosage forms (capsule *versus* tablet), these are not pharmaceutical equiv-

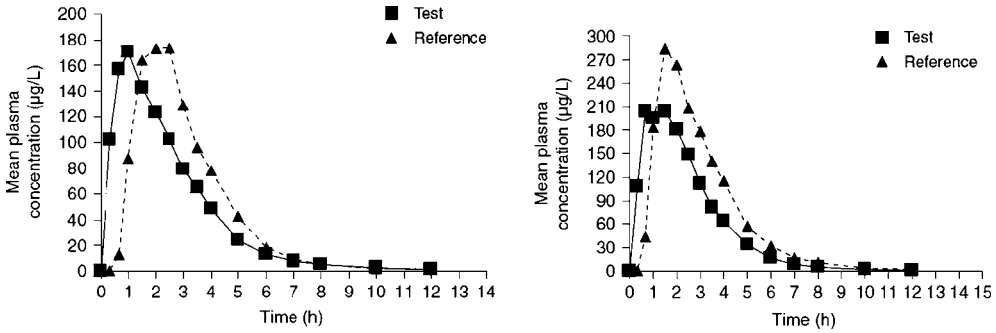

Fig. 1 Mean plasma concentration of test (Omepradex) and reference (Losec) omeprazole formulations following single-dose fasted administration (*left*) and multiple-dose fasted administration (*right*) (7). Reproduced with permission from Adis International Limited.

alents, and therefore would not be considered as possible therapeutic equivalents. Nonetheless, despite this regulatory caveat, the analysis based upon unnormalized and normalized dose demonstrates some of the underlying limitations of relying upon the historical bioequivalence parameters of AUC and C_{max} to ensure equivalence of drug plasma profiles, particularly for modified-release drug products designed to provide for multiphasic release. As discussed under the next section, based upon the underlying principles of "pharmaceutical equivalence-by-design," the QbD approach provides an opportunity to enhance the evaluation of these complex modified-release products.

Dose-Dumping Considerations in Design of Modified-Release Products

A third example demonstrates the importance of evaluating the generic drug product design for modified-release products in the context of whether or not it has been designed appropriately to mitigate the risk for dose dumping. In general, for modified-release products, this potential risk of dose dumping has been well recognized. For example, it has been known for more than two decades that although a product may perform acceptably under fasting conditions, typically used to assess bioequivalence, dose dumping may occur for poorly designed products when administered with food (13). This is one of the underlying reasons for requiring that a food-effect bioequivalence study be performed on modified-release drug products (14). However, apart from these considerations, the evaluation of the potential risk for dose dumping in the context of formulation design has received renewed attention. This is due to the awareness that as both generic and innovator applicants develop increasingly complex modified-release formulations, it is essential that these be designed to be sufficiently robust to mitigate underlying risks of dose dumping under conditions of use, not captured by the traditional bioavailability and bioequivalence studies used to approve these products.

For example, as a consequence of not considering and/or mitigating these dose dumping risks, Palladone (hydromorphone hydrochloride extended-release capsules), was designed with rate-controlling excipients soluble in alcohol aqueous solutions. During its broader use, it was discovered that a percentage of the population was prone to ingesting this drug in conjunction with alcoholic beverages, resulting in a potentially lethal dose dumping. A pharmacokinetic study revealed that co-ingestion of this product with 40% (80 proof) alcohol compared with water raised the hydromorphone peak plasma levels approximately six-fold. These studies indicated that even the equivalent of a two-thirds serving of beer may lead to a two-fold increase in some subjects. This ultimately resulted in FDA's health alert and request that Purdue Pharma voluntarily suspend the sale of Pallodone due to the potentially lethal effects of alcohol-induced dose dumping (15).

Likewise, for transdermal delivery systems, dose dumping must be considered in the context of drug product design, particularly for highly potent drugs. For example, while both the reservoir and matrix transdermal delivery systems may provide for comparable plasma profiles of the active ingredient, these delivery systems may have quite different risks with respect to dose dumping. In the reservoir system, because the entire load of the active ingredient is in a liquid reservoir, the product design and manufacturing process must be sufficiently robust and the quality control strategy highly stringent in order to ensure that there is no compromise of the reservoir seal, which may result in potential drug overexposure. In fact, this leakage with risk of lethal drug overexposure was attributed to a manufacturing defect and resulted in recalls of both brand name and generic products using this reservoir system (16,17). FDA, however, has approved a fentanyl transdermal patch using a matrix system for which there have not been any recalls attributable to leakage and dose dumping. In this design, the drug is incorporated directly into the adhesive or polymeric layer, thereby mitigating this safety risk.

These examples illustrate the important concept that when considering a generic version for a modified-release product, although it may have the same active ingredient and dosage form and be shown to be bioequivalent to the RLD, this narrow evaluation by the traditional review paradigm does not assess the design of the rate-controlling

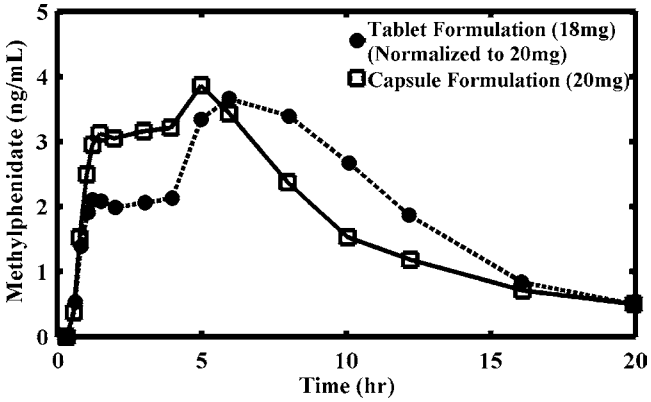

Fig. 2 Mean plasma concentration of two extended release formulations of methylphenidate. (Adapted from 11).

mechanism with respect to the potential risks associated with dose dumping. Therefore, for these modified-release products, there must be an evaluation of the rate-controlling mechanism used in the generic drug product to ensure that it is sufficiently robust with respect to its potential for dose dumping and that it poses no greater safety risk than the corresponding RLD.

QUALITY BY DESIGN: A BASIS FOR GENERIC "PHARMACEUTICAL EQUIVALENCE BY DESIGN"

As discussed in the previous section, in addition to the traditional approaches used successfully to ensure equivalence of simple generic products, as drug products have increased in design complexity, there are instances where an evaluation of generic product design may be useful to assess equivalence to the RLD. Many of these concepts are embodied by QbD principles, which focus, among other things, on the target design goals during drug product development.

First we begin with the premise that a generic product must be a therapeutic equivalent and should have, for the most part, the same label as the RLD. Given this target goal, the pharmaceutical scientist must decide how to design the drug product in order to ensure that it will have equivalent clinical characteristics to the RLD. In order to achieve these goals, prior to starting any development program, the applicant must define a quality target product profile (QTPP). The QTPP is the key element under QbD (18,19) that advances a pharmaceutical equivalence quality concept not previously invoked under the traditional review paradigm for evaluation of ANDAs. The QTPP defines the critical product attributes and the qualitative and/or quantitative surrogates used by pharmaceutical scientists, as they target the design of the generic product to ensure therapeutic equivalence.

QTPP: Modified-Release Products with Active Ingredient that Modifies Absorption Characteristics

To best illustrate the QTPP, consider the case scenario for PPI delayed release products. Due to the drug pharmacodynamic effect on gastrointestinal pH, differences in formulation design resulted in products that were not therapeutic equivalents to the RLD on chronic dosing, despite the fact the generic product was shown to be bioequivalent in a single dose study. This limitation of the traditional review paradigm is reconciled under the QbD paradigm by invoking the QTPP element of "pharmaceutical equivalence by design." To illustrate this point, consider a hypothetical QTPP surrogate target, based upon drug product attributes that a pharmaceutical scientist would use to target formulation development of a generic product equivalent to a PPI delayed release product (Table II). First, the QTPP of the generic product must include attributes of the RLD that are essential for demonstrating the traditional regulatory requirements of pharmaceutical equivalence. This includes the requirement that the generic drug products contain the "same" active ingredient, as well as be in the same dosage form and strength as the RLD. The dosage form must also have attributes such as appearance and size acceptable to the consumer. These design target goals are already typically evaluated in the Chemistry, Manufacturing, and Control (CMC) review of ANDAs.

However, apart from the traditional design targets, such as equivalent dosage form, the QTPP provides for a quality surrogate guiding the rationale design of a generic drug product bioequivalent to the RLD. In this context, based upon an understanding of the RLD and its *in-vivo* delivery profile (iDDP) (20), the QTPP serves as an element to

Table I Methylphenidate Pharmacokinetic Parameters Comparing the Modified-Release Capsule (20 mg) with the Modified-Release Tablet (18 mg) (11)

	Unadjusted Mean Ratio[a]	90% Confidence Interval	Dose-Normalized Mean Ratio[a]	90% Confidence Interval
$AUC_{0\text{-}t}$	0.97	0.93–1.01	1.08	1.03–1.12
$AUC_{0-\infty}$	0.93	0.90–0.97	1.04	1.00–1.08
C_{max}	0.89	0.84–0.95	0.99	0.94–1.05

[a] Mean ratios calculated based on the capsule formulation as reference

Table II QTTP for a Hypothetical Proposed Generic Product PPI Inhibitor

Profile Component	QTPP Target	Rationale
Active Ingredient	Same as RLD	Pharmaceutical equivalence requirement, same active ingredient
Dosage Design	Capsule	Pharmaceutical equivalence requirement, same dosage form
Strength	Dose: 50 mg	Pharmaceutical equivalence requirement, same strength
Appearance	Capsule conforming to description, shape and size	Needed for patient acceptability
In-Vitro Release	NMT 10% at pH 1.0 and 4.5 after 30 min	PPI is acid labile (20% degradation in 15 min at pH 3), RLD enteric coat is designed to protect API through pH 4.5
	NLT >80% at pH 5.5 at 30 min	RLD enteric coat is designed to release the active ingredient at pH 5.0–5.5 where there is <2% degradation after 30 min
		Immediate release of the drug following transit through the stomach and at site of absorption, similar to the RLD, will enhance the likelihood the drug product design will meet AUC and C_{max} bioequivalence requirements

facilitate the understanding of critical targeted formulation attributes that may be needed to successfully design a drug product bioequivalent to the RLD. First, by taking into consideration that the PPI is acid labile through pH 3–4 and given the *in-vitro* release profile for the RLD is indicative of an enteric coating designed to protect the active ingredient from degradation up through pH 4.5, a plausible QTPP target would guide the design of generic product prototypes with an enteric coat having similar integrity and providing a similar degree of protection against acid degradation as the RLD. Further, in order to ensure that the formulation prototype will provide similar drug systemic exposure following its transit through the stomach, the QTPP will likewise target the design of products having enteric coatings that maintain their integrity only up to a pH range of 5.0–5.5. This will ensure, like the RLD, for release of the active ingredient in the intestine for comparable drug absorption.

One of the facets of implementing QbD in the evaluation of generic drug products is to compare the formulation between generic and RLD products. However, this formulation comparison is not primarily based upon composition of excipients, but rather upon a comparison of overall performance characteristics. Thus, differences in formulation composition between a generic drug product and the RLD are acceptable, provided a suitable QTPP is invoked to target equivalent performance. For example, given that there are several enteric coating polymers, such as hydroxypropyl methylcellulose phthalate and methacrylic acid co-polymer, that protect the active ingredient against acid degradation through pH 4.5–5.0, differences in the composition between generic and RLD enteric coatings using these excipients would pose little concern with respect to the determination of generic product equivalence.

The main advantage of having ANDA sponsors provide their QTPP surrogates that guide product design is that now FDA reviewers of these complex drug products will be able to ensure drug product equivalence to the RLD, not solely upon inferences derived from "bioequivalence by testing" under limited conditions of use, but also based on a consideration as to whether the

Table III QTTP for a Hypothetical Proposed Generic Zolpidem CR

Profile Component	QTPP Target	Rationale
Active Ingredient	Same as RLD	Pharmaceutical equivalence requirement, same active ingredient
Dosage Design	Tablet	Pharmaceutical equivalence requirement, same dosage form
Strength	Dose: 12.5 mg	Pharmaceutical equivalence requirement, same strength
Appearance	Tablet conforming to description, shape and size	Needed for patient acceptability
Drug Release	Biphasic *in-vitro* release of drug similar (but not necessarily identical) to the RLD, with initial rapid release followed by sustained release ER of dose	Need to provide for initial plasma concentrations through the first 1.5 h ($AUC_{0\text{-}1.5}$) to provide for a clinically relevant drug exposure for rapid sleep onset and sustained release phase designed to maintain plasma concentrations for maintenance of a sleep ($AUC_{1.5\text{-}t}$)

drug product was developed upon considerations of "pharmaceutical equivalence by design." While such a flawed product with an enteric coating at pH 3 would not be rejected in the context of the traditional ANDA review, under the QbD paradigm, product design would be a paramount consideration, and reviewers may question the suitability of the generic drug product based upon these design differences. For example, because for PPIs the limitations of a single dose *in vivo* bioequivalence study are clear, an applicant with a QTPP target that did not focus on "pharmaceutical equivalence by design" will have to provide justification as to why these differences in product design would not raise uncertainties in relation to therapeutic equivalence during chronic dosing or in other patient subpopulations having altered gastric pH. While a QTPP targeting a drug product design fundamentally different from the RLD may still be permissible, applicants in this instance would be expected to provide justification for such differences in design, beyond simply relying upon a passing bioequivalence study submitted under the traditional paradigm. In such a case, these differences in product design should be supported by further information to ensure therapeutic equivalence under chronic conditions of use or in other patient populations having altered gastric pH. This may come from a mechanistic understanding of drug absorption, pilot studies performed with other formulation designs, pilot studies in other subpopulations having a different gastric pH, or studies following multiple dosing to justify that these design differences would not result in any underlying uncertainties regarding product therapeutic equivalence.

QTPP: QbD Assessment for Drug Products with Multiphasic Release Components

A potential limitation of the traditional approach for establishing drug product bioequivalence is evident for modified-release products incorporating multiphasic drug release components. For these complex product designs, the historical parameters of AUC and C_{max} may fail to ensure equivalence of drug plasma profiles, critical to the clinical performance characteristics of the product. For example, although the RLD may incorporate biphasic drug release with both an immediate release component for onset of action and an extended release component to maintain drug plasma levels throughout the day, it is quite conceivable that a generic drug product may be designed to provide for only monophasic release. In this case, the generic product may still meet the traditional bioequivalence parameters of AUC and C_{max}, despite a differing design and drug plasma concentration profile from the RLD. Such differences in drug plasma profiles have been shown in the case of methylphenidate to be clinically relevant and result in different clinical properties.

Again, incorporating the QTPP in the evaluation of these modified-release products may serve as an invaluable tool in resolving underlying uncertainties regarding potential differences in drug plasma profiles between generic and RLD not captured by the traditional "bioequivalence-by-testing approach" using AUC and C_{max}. For example, if the ANDA applicant develops their generic product based upon "pharmaceutical equivalence by design," they will focus on a design target having a QTTP surrogate that provides for biphasic release of the active ingredient similar to the RLD, as opposed to monolithic drug release. Therefore, although there may be some underlying uncertainties with regard to a conclusion of therapeutic equivalence for these products based solely upon relying on "bioequivalence by testing using AUC and C_{max}," many of these uncertainties would be resolved if the generic sponsor targets their formulation development based upon a "pharmaceutical equivalence by design" to provide for similar biphasic release as the RLD. The acceptability of the formulation design would be confirmed through *in vivo* studies that demonstrated similar pharmacokinetic profiles between test and reference products.

As noted in the preceding section, although equivalence in design of both immediate and extended release components to achieve similar biphasic release characteristics as the RLD would constitute a QTPP that focuses on "pharmaceutical equivalence by design," there may be alternative QTPPs that use *in vivo* performance surrogates to implement "pharmaceutical equivalence by design." Rather than targeting a similar biphasic design as the RLD, an applicant may target equivalence of early drug exposure from the immediate release component using the partial $AUC_{0\text{-}x}$ parameter and equivalence of the extended exposure from the extended release component using the AUC_{x-t} parameter. For example, Ambien (zolpidem tartrate) CR is designed to provide for biphasic release of the active ingredient for immediate onset of action and maintenance of dose in the plasma. In such a case, there may be inherent limitations of the traditional bioequivalence of AUC and C_{max} toward ensuring generic product therapeutic equivalence. However, based upon the clinical profile of this drug and a mechanistic basis of drug absorption, an appropriate "pharmaceutical equivalence by design" surrogate could be based upon a design that provides for equivalence of early drug exposure for sleep onset using the partial $AUC_{0\text{-}1.5}$ parameter and equivalence of extended release exposure for maintenance of sleep using the $AUC_{1.5-t}$ parameter (21,22). Thus, there is not only a single unique QTPP that must be invoked to target "pharmaceutical equivalence by design." Rather, several approaches are possible depending on the surrogate used

by the applicant. Nevertheless, although the two differing QTPPs may target product design based upon two viewpoints, one from the *in-vitro* release perspective and one from a mechanistic understanding of drug absorption, they both achieve the same goals based upon "pharmaceutical equivalence by design" principles. In this instance, a QTPP that targets equivalence of both the partial $AUC_{0\text{-}x}$ parameter for immediate exposure and the partial AUC_{x-t} parameter for extended release exposure will, based on this target, constrain the ranges of putative formulations to a narrow range having similar *in-vitro* release rates to the RLD, similar to the QTPP that invokes *in-vitro* release to target the product development (Table III).

Finally, under this QbD paradigm, if the RLD incorporates multiphasic drug release components in its product design, and the applicant chooses to develop a generic drug product design by invoking a QTPP not focusing on "pharmaceutical equivalence by design" (e.g. the QTPP would target a vastly dissimilar *in-vitro* release profile) and rely solely upon "testing to bioequivalence" using AUC and C_{max} parameters, then in such instances justification should be provided to ensure that these design target differences and resultant dissimilar drug plasma profiles would not present concerns with respect to therapeutic equivalence. For instance, this justification may be based upon the clinical characteristics of the drug under its labeled conditions of use, where the clinical effect is dependent upon the drug at steady-state values due to drug accumulation on multiple dosing to levels at the plateau of the dose-response curve across the patient population.

QTPP: QbD Assessment Tool for Dose-Dumping in Modified-Release Products

Apart from defining target goals based upon "pharmaceutical equivalence by design" principles, the sponsor must take into consideration the potential risk of dose dumping when designing a modified-release drug product. Dose dumping is an important safety consideration, and it is crucial that these products are sufficiently robust to mitigate this risk. For example, in the case of Palladone (hydromorphone hydrochloride-extended release), the risk of inadvertent alcohol-induced dose dumping was not considered during product design, and this led to the product's recall and suspension of sale. For this reason, sponsors should consider within their QTPP an appropriate surrogate to guide design of formulation prototypes that provide for similar or better resistance of release of the active with respect to alcohol-induced dose dumping. In fact, this QTPP target goal is reflected in FDA's bioequivalence recommendations for generic versions of several modified-release products which require data showing comparable or lower drug release compared to the RLD in %5 (*v*/*v*), %20 (*v*/*v*), and %40 (*v*/*v*) aqueous alcohol media (23). By meeting these design goals, generic modified-release products should have similar or lower propensity as the RLD to result in alcohol-induced dose dumping.

Likewise, using a similar conceptual framework in order to address the lethal safety risk associated with fentanyl transdermal patch drug leakage, a QTPP target should guide the design of transdermal product prototypes that mitigate this risk of dose dumping. This concept is also embodied in the recent Guidance for Industry for Residual Drug in Transdermal and Related Drug Delivery Systems (24). The guidance discusses that as a result of sub-optimal product design transdermal, transmucosal, and topical delivery devices have been approved which retained as much as 95% of the initial total amount of drug even after the intended duration of use. As a consequence, this resulted in unintended safety issues to patients, family members, caregivers, children and pets. In order to mitigate these potential safety risks, sponsors are expected, based upon QbD principles, to develop systems that deliver the optimum amount of drug while at the same time minimizing excess residual drug. Such general principles raise the expectation that as generic sponsors develop generic delivery systems they establish QTPP target goals which not only ensure bioequivalence, but also product designs which minimize excess residual drug not exceeding that of RLD (24).

SUMMARY

Historically, OGD ensured the high quality of generic drug products based upon two fundamental requirements: 1) pharmaceutical equivalence and 2) bioequivalence to the RLD. This traditional review paradigm has been used with great success in bringing to the consumer high quality generic drug products that provide the same therapeutic benefit as the RLD. Drug products, however, have increased in their design complexity, and as such it has become apparent that the traditional review paradigm used to ensure therapeutic equivalence must likewise evolve to consider drug product design.

FDA's QbD initiative provides such an enhanced evaluation approach. In line with this QbD framework, ICH Q8 introduces the quality target product profile (QTPP). The QTPP introduces in the context of the current regulatory framework of pharmaceutical equivalence, the quality concept of "pharmaceutical equivalence by design." Invoking this key QbD element in the evaluation of increasingly complex modified-release products provides an opportunity to enhance the current regulatory framework used to establish generic drug product therapeutic equivalence. It achieves this by

complementing the traditional paradigm where generic product equivalence is based primarily upon limited inferences from a "bioequivalence by testing" study to one that considers whether the generic drug product was developed to be an equivalent to the RLD, based upon appropriate quality surrogates targeting "pharmaceutical equivalence by design."

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