Review Article

Theme: Facilitating Oral Product Development and Reducing Regulatory Burden through Novel Approaches to Assess Bioavailability/Bioequivalence
Guest Editors: James Polli, Jack Cook, Barbara Davit, and Paul Dickinson

Challenges and Opportunities in Achieving Bioequivalence for Fixed-Dose Combination Products

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Received 9 February 2012; accepted 24 May 2012; published online 9 June 2012

Abstract. Fixed-dose combination (FDC) products are becoming a popular treatment option because of increased patient compliance and convenience, improved clinical effectiveness, and reduced cost to the patient, among several other reasons. A commonly applied approach for approval of a FDC product is demonstrating bioequivalence between the FDC and co-administration of individual mono-products, provided that there is adequate safety and efficacy data for co-administration of the individual agents. However, achieving bioequivalence between the FDC and individual mono-products can be very challenging, and sometimes not possible since combining multiple active ingredients, especially insoluble molecules, in a single drug product could complicate its biopharmaceutical and pharmacokinetic behavior. In this review, some of the major challenges often encountered while assessing bioequivalence during FDC development will be presented along with discussion of future opportunities to facilitate FDC development and approval.

KEY WORDS: bioequivalence; fixed-dose combination; formulation; pharmacokinetics.

INTRODUCTION

A fixed-dose combination (FDC) is a formulation of two or more active ingredients combined in a single dosage form, available in certain fixed doses. Typically, FDC products are developed to target a single disease such as with antiretroviral FDCs for the treatment of HIV, e.g., Truvada® (tenofovir and emtricitabine) and Atripla® (efavirenz, tenofovir, and emtricitabine). However, FDCs may also target multiple diseases, such as Juvisync™ (sitagliptin and simvastatin) for the treatment of type 2 diabetes and high cholesterol. FDCs are becoming popular treatment options because (a) increased patient compliance and adherence in diseases such as diabetes (1) and hypertension (2), (b) patient convenience and simplification of disease management such as AIDS and cardiovascular diseases, (c) reduced cost to the patient (one co-pay), and finally (d) FDC products provide an excellent opportunity for life cycle management of marketed drug products. These advantages of FDC products along with the possibilities of greater clinical efficacy due to additive or synergistic effect of each active, possibility of reduced dose of each active, and decrease in the occurrence of side effects make combination drug products a very attractive treatment option (3,4). However, careful considerations must be

given to the mechanisms of action of the actives being considered for combination. Since several cellular pathways might operate in disease progression, it is imperative to select molecules that target different pathways to ensure effective treatment and also to reduce the potential for developing drug resistance and clinical relapse. Hence, prudent selection of drugs to be combined will ensure that FDC products are indeed beneficial in disease management and are safe and effective to the patient population. Regulatory agencies have established several guidances for industry regarding the development of FDC products. These are discussed in more detail in the section on “regulatory requirements for bioequivalence of FDC.” A typical strategy for registering oral FDC products is to show that the FDC is bioequivalent to co-administration of the monotherapy agents. However, this strategy is predicated on the fact that there is adequate safety and efficacy data for co-administration of the individual agents. In this review, the challenges in achieving bioequivalence (BE) for FDCs will be discussed along with opportunities for improvement of probability of success of BE studies when comparing FDCs with co-administration.

GENERAL STRATEGIES FOR FDC DEVELOPMENT

There are several ways to assess the equivalency between a FDC and co-administered individual mono-products—(1) cross-over pharmacokinetic (PK) studies comparing FDC and co-administration with the aim to show that 90% confidence interval (CI) of the geometric mean ratio (GMR) is between 80% and 125% for AUC and C_{max} , (2) therapeutic equivalence study with the aim of showing that pharmacodynamic (PD) end-

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point(s) are achieved with the FDC, and (3) a combination of PK and PD studies, where PK study is used to show equivalence for either AUC or $C_{\max}$ and PD study is to ensure either efficacy or safety is not compromised with the FDC. Among the three options, demonstrating BE, if achievable, is the most attractive approach due to potential shorter development timeline and lower development cost. However, as discussed in the subsequent sections, achieving BE between FDC and individual mono-products can be very challenging and sometimes not possible.

A crossover, single-dose PK study is the most common and preferred method to assess bioequivalence, since this is considered to be the most sensitive test to evaluate formulation differences. In this type of study, physiological variables such as gastric emptying, pH, etc. are assumed to contribute less to intersubject variability compared to the variability arising from formulation performance. An example of such a BE study for FDC is Janumet® (sitagliptin and metformin), where Janumet® was shown to be bioequivalent to co-administration of the individual components, sitagliptin and metformin (5). By the virtue of the FDC being bioequivalent to co-administration, Janumet® can be considered therapeutically equivalent and interchangeable to co-administration of the individual mono-products.

A combination of efficacy trial and BE/BA study is often employed in the development of technically complex FDCs. Pivotal efficacy and safety studies using a validated method and end-point can be used to demonstrate therapeutic equivalence in those instances where pharmacokinetic comparison is not straightforward or not possible (e.g., ophthalmic FDC product Cosopt® (timolol and dorzolamide) for treatment of glaucoma (6)). Agency regulations for FDCs generally require demonstration of the contribution of each active in the FDC to the treatment effect. Hence, the primary goal of the efficacy trials is to demonstrate that the FDC has a therapeutic advantage over monotherapy, which justifies the development and marketing of the FDC product (3). For example, in the case of Simcor® (simvastatin and extended-release niacin), the product approval was based on a study in patients with hyperlipidemia and mixed dyslipidemia, where all doses of the FDC after 24 weeks produced greater lowering of LDL-C, significantly greater increases in HDL-C, and greater decreases in triglycerides than simvastatin 20 mg alone (7). To support product approval, the sponsor also conducted relative bioavailability studies to bridge the FDC formulation used in pivotal studies and the individual mono-products per requirements for 505(b) (2) filing. Specifically, BE was demonstrated for niacin (plasma nicotine uric acid $C_{\max}$ and total urinary excretion as surrogates of niacin PK parameters) but not for simvastatin and its active metabolite. It was hypothesized that both drug-drug and formulation interactions are the causes for high values of AUC and $C_{\max}$ of simvastatin and its acid metabolite (8). Nevertheless, long-term safety of Simcor was demonstrated in the phase III study.

Such a hybrid approach was also employed for the development of Vimovo®, a FDC of IR esomeprazole and delayed-release naproxen. Besides the difference in dosing regimen (BID for FDC but QD for Nexium®), another major difference between the FDC and the mono-products is that Nexium® is enteric coated while an immediate-release layer of esomeprazole was incorporated in the FDC tablet. Due to

chemical instability of esomeprazole in the gastric environment, BE was not expected for esomeprazole between Nexium® capsule and the FDC tablet. To support the product labels and approval, the sponsor conducted several phase III studies to demonstrate efficacy and long-term safety of the FDC tablet (9). Even though the sponsor was able to supply FDC tablets that are identical to the formal stability study formulation to cover all pivotal studies, pharmacokinetic studies were conducted to bridge the FDC and the two referenced NDAs to support a 505(B) (2) filing. Specifically, BE was demonstrated for naproxen at both dose strengths while relative bioavailability data were compared for esomeprazole between the FDC and Nexium® (10). The lower exposure of FDC for esomeprazole was deemed not an issue based on the efficacy data from the pivotal studies.

During the development of FDC formulations, biopharmaceutical tools such as *in vitro* biorelevant dissolution and solubility studies, *in silico* absorption modeling, and preclinical *in vivo* studies can be helpful in understanding the critical parameters that affect formulation bioperformance. Dissolution testing, particularly the use of USP I and II apparatus, is a cornerstone in drug product development and has been used routinely to test product performance and for quality control for last few decades (11). However, recently the use of dissolution data has evolved, with emphasis on using it in oral absorption modeling to guide product development. This has necessitated the development of new biorelevant dissolution systems with physiologically relevant conditions and use of biorelevant media (SGF, FaSSIF, and FeSSIF). A recent review on this topic provides a comprehensive overview of several dynamic dissolution methods that have been developed in the last few years (12). Although debate is still ongoing on whether any of these novel dynamic dissolution methods provide a step change rather than an incremental advance in dissolution technology, there is evidence that use of biorelevant dissolution data in absorption models can significantly improve the accuracy of predictions of *in vivo* formulation performance (13,14).

Preclinical animal models particularly dogs are commonly used to assess bioperformance of formulations during product development. However, differences among human and the animal models in GI physiology have been published in the literature including gastric pH, gastric emptying time, intestinal transit time, and bile salt concentrations (15,16). In addition, comparison of fraction absorbed between dogs and human has showed poor correlation (17). Hence, it is important to understand the limitations of current preclinical *in vivo* models and exercise caution when predicting formulation performance in human based on preclinical animal data. A comparison of BE data of several FDC products of lopinavir and ritonavir in dogs and human showed that in some cases, dogs predicted the outcome of human BE study whereas in other cases, the dog model over-predicted the BE outcome, i.e., formulations were bioequivalent in dogs but failed BE in human (18). This again highlights the limitation of a preclinical animal model to accurately predict outcome of a human study. Nevertheless, preclinical animal studies to guide formulation development still remain a useful biopharmaceutical tool (19,20).

Modeling and simulation (oral absorption modeling and IVIVC) has become an important tool in guiding formulation development (21,22). Application of computational modeling in

drug development has several advantages such as integration of all available *in vitro* and *in vivo* data to provide a more holistic view of formulation bioperformance, provides a more mechanistic understanding of *in vitro* formulation performance and bioperformance, and allows exploration of multiple scenarios in a much shorter timeframe and with fewer experiments thus expediting product development. In addition, modeling and simulation methods are now used in regulatory review (23,24). These tools when used in a complementary manner to guide formulation development can increase probability of success of meeting BE end-points.

CHALLENGES IN ACHIEVING BIOEQUIVALENCE FOR FDCS

Many factors can influence the chance for demonstrating bioequivalence. These factors include, but are not limited to, (1) active pharmaceutical ingredient (API) forms used in FDC vs. individual mono-products, (2) formulation composition and process employed for FDC vs. individual mono-products, (3) clinical study designs (e.g., study power, feeding state, choice of references), and (4) complex ADME profiles of APIs. In general, achieving bioequivalence between FDC and individual mono-products is significantly more difficult than demonstrating BE of different formulations of a single API. In addition to the increase in random chance for failure due to multiple PK end-points, there are other challenges in achieving BE that are unique to FDCs. In the following section, some major issues often encountered during FDC development will be discussed.

BE Challenges Originating from Active Pharmaceutical Ingredients

Highly Variable Drugs

Highly variable drugs (HVDs) are classified as drugs or drug products exhibiting intra-subject variability of 30% CV or greater in $C_{\max}$ or AUC (25). Since the outcome of a BE study can be impacted by other factors such as intra-subject variability rather than true differences in $C_{\max}$ and AUC between test and reference, the sample size needed to demonstrate BE increases with greater intra-subject variability. For example, in a two-way crossover design, two products with identical bioavailability may require 40 subjects to demonstrate BE with 90% power if the intra-subject variability is 30% but the number of subjects increases to approximately 140 at intra-subject variability of 60% (26). Similar analysis of BE data by Food and Drug Administration (FDA) for new generic drug applications showed that generally studies of highly variable drugs (root mean square error (RMSE) ≥ 0.3) used more subjects than BE studies of drugs with lower variability (RMSE < 0.3) (27). For drugs that had high variability in $C_{\max}$, the number of study subjects ranged from 18 to 134, with an average of 46 subjects per study. For drugs with lower variability in $C_{\max}$, the number of study subjects ranged from 12 to 113, with an average of 31 subjects per study. For drugs that were highly variable in AUC, the number of study subjects ranged from 24 to 134, with an average of 55 subjects per study, whereas those with lower variability in AUC, the number of study subjects ranged from 12 to 113, with an average of 32 subjects per study.

It is, however, believed that HVDs generally have a wide therapeutic window, such that despite high variability, these products have been demonstrated to be both safe and efficacious in human (28). Hence, applying the conventional BE criteria to these products may unnecessarily expose a large number of healthy subjects to a drug when this large number of subjects is not needed for assurance of BE. Thus, several novel methods to assess BE of HVDs have been published (29), one of them being the scaled average BE approach, where the BE limits are expanded based on the variability of the drug product. FDA has published the outcome of a project to evaluate the impact of scaled average bioequivalence on study power, or percent of studies passing BE, using different intra-subject variability and under different conditions (30). The proposed study design was three-sequence, three-period, reference-replicated crossover BE study with sequences of test/reference/reference (TRR), RTR, and RRT. The reference product was replicated to obtain within subject variability for the reference product. The results suggested that scaled average BE provided a good approach for evaluating the bioequivalence of HVDs and drug products. This approach would effectively decrease sample size, without increasing patient risk. The use of a point estimate constraint addresses concerns that products with large GMR differences may be judged bioequivalent. Thus, a test product which is more variable than the reference is likely to fail BE, despite expansion of the BE limits. The three-way crossover design was selected because it showed a lower probability for a more variable test product demonstrating BE to a superior, less variable reference product and also appeared to provide a more practical and efficient approach for scaling, compared with a full replicate, four-way cross over study design. Hence, while developing FDCs of drugs with known high variability, careful consideration should be given to the BE study design including the number of subjects used in these studies, so as not get a false negative BE result.

Metabolites and Non-linear Pharmacokinetics

The role of metabolites in the determination of BE has been a topic of constant debate (31,32). Usually, BE studies are carried out focusing only on the measurement of the parent drug, which is based on the fact that the concentration-time profile of the parent is more sensitive to detect differences in formulation performance than the metabolite (32). The current FDA and European Medicines Agency (EMA) BE guidances also recommend the use of parent data to assess bioequivalence (33,34), with certain exceptions such as parent drug levels are too low to allow reliable analytical measurement even at higher doses, and metabolite may be formed as a result of gut wall or other presystemic metabolism. The guidances also state that if the metabolite contributes meaningfully to safety and/or efficacy, it is recommended that both the metabolite and the parent drug be measured. This is exemplified in the case of losartan, an angiotensin II receptor antagonist, where its carboxylic acid metabolite, EXP-3174, largely contributes to the efficacy (35). Hence, FDA's guidance on assessing bioequivalence for losartan formulations recommends that both losartan and its carboxylic acid metabolite be quantified (36). Thus, for any FDC containing losartan, the active metabolite would need to be included in the assessment of BE as compared to co-administration.

In cases of non-linear PK, particular considerations should be given to the dose and design of the BE study. In a recent publication, simulations of BE trials based on a semi-physiological model for several molecules in the four BCS classes undergoing first-pass hepatic metabolism under non-linear conditions showed that analysis of the parent drug in single-dose study is generally the most sensitive study design to assess BE between formulations (37). However, an exception to this general rule was noted for low permeability (BCS classes III and IV) and low intrinsic clearance drugs, for which parent drug in steady state showed differences in $C_{\max}$ and also on some occasions in AUC that were not reflected with the same sensitivity in the single-dose scenario. Similarly, when the proposed doses of the FDC are in the range where there is non-linearity in PK for one or more of the active ingredients, then BE studies at two different dose levels might be required. For example, in case of the FDC Janumet® (sitagliptin and metformin), the proposed strengths of the FDC were 50 mg sitagliptin/500 mg metformin, 50 mg sitagliptin/850 mg metformin, and 50 mg sitagliptin/1,000 mg metformin. Since metformin shows less than dose proportional AUC and $C_{\max}$ in this dose range (38), the BE study comparing FDC and co-administration was conducted at two doses—500 and 1,000 mg metformin (5).

Drug–Drug Interaction

It is imperative to understand drug–drug interaction (DDI) between the actives to be combined in a FDC, both from PK and PD perspectives. The main aim of studying pharmacodynamic interactions is to establish that combination of two or more actives leads to additive or synergistic improvement in treatment of the disease state and under no circumstances does the combination result in less effective pharmacological effect than the individual agents. From PK and more importantly patient safety perspectives, it is important to determine that combination of the actives do not significantly affect the plasma concentrations and profiles of each other, prior to embarking on developing a FDC product of the actives. For example, Truvada® is a FDC of emtricitabine and tenofovir disoproxil fumarate for treatment of HIV. Both emtricitabine and tenofovir are primarily excreted renally via glomerular filtration and active tubular secretion. Hence, there is a potential for DDI between the two drugs in the kidneys when co-dosed. To evaluate any potential DDI, a study was conducted in healthy volunteers to compare steady-state PK after co-administration of the drugs with PK of the individual agents (39). The results of the study showed that co-administration of these agents did not affect PK of either drug and supported development of a FDC product. Such proactive studies to clearly understand any potential PK DDI between the actives would minimize the chances of any unexpected BE results during FDC development.

Impact of Food on BE

Food exerts complicated effects on the PK of a drug. For example, food intake triggers physiological changes in the gastric pH, changes in GI motility, etc., which can have profound impact on drug absorption (40). Food can also impact specific transporters that are involved in absorption of a drug. Food may reduce presystemic metabolism thus increasing bioavailability. In certain instances, compounds (e.g., tetracycline) may chelate

with specific components of food, thus leading to reduced bioavailability. In addition, the interplay of physicochemical properties of drugs and food can result in complex profiles in oral absorption and bioavailability. Fleisher *et al.* summarized the general trend of food effect on drug absorption based on biopharmaceutical classification system (BCS) (41). BCS class I compounds are likely to have no food effect on exposure, primarily because absorption of highly soluble and highly permeable drugs is usually pH- and site-independent and thus insensitive to differences in dissolution; BCS class II compounds are likely to have positive food effect (increased absorption); BCS class III compounds are likely to have negative food effect (decreased absorption), and there is no clear trend for BCS class IV compounds. However, even for BCS class I compounds, food can affect $C_{\max}$ and $T_{\max}$ due to delayed gastric emptying as well as for molecules which have high first-pass effect, extensive adsorption, complexation, or instability in the gastrointestinal tract. Since a FDC dosage form often contains two or more APIs of different BCS class, it is important to consider the impact of food on the bioavailability of each API in the FDC and also impact on the BE study design since food can also have an impact on PK variability. In general, as per regulatory guidances, a fed BE study might be required for the FDC depending on the food label for the individual mono-products (34,42). Also, since meals high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product, it is recommended to use high-calorie and high-fat meals during fed BE studies. For instance in the case of FDC of pioglitazone and metformin, the $C_{\max}$ of metformin decreased by 28% when administered with high-fat meal (43). But this decrease in $C_{\max}$ was not deemed to have any clinically significant impact and due to the GI side effects associated with metformin, the label of the FDC product recommends that the product be taken with food (44). However, in certain instances, food can have a more clinically significant impact on the bioperformance of the drug product for, e.g., the antimalarial FDC Coarsucam® (amodiaquine and artesunate) when given with a high-fat meal results in significant increase in the AUC and $C_{\max}$ of amodiaquine and its active metabolite thus raising drug safety concerns (45). Food also results in a decrease in AUC and $C_{\max}$ of artesunate and its metabolite, which might have a negative impact on efficacy of the product (45). Due to these reasons, the FDC product is not recommended to be taken with high-fat meal (46).

In Vivo Interactions Between Components of the FDC Prior to Absorption

Chemical Interactions of API

Loss of bioavailability of one or more components of the FDC due to interaction of the drugs *in vivo* can be a major challenge in developing a viable FDC product. In such cases, it is important to mechanistically understand the interaction and then formulate a FDC to mitigate such interactions. The bioavailability of rifampicin, an anti-tuberculosis drug, has been observed to be significantly reduced when dosed with isoniazide as co-administration or in a FDC (47). This has been ascribed to hydrolysis of rifampicin to an insoluble product in the acidic environment of stomach, and this hydrolysis is accelerated in the presence of isoniazide (48). Furthermore, recent data have

shown that this reaction can also be catalyzed by pyrazinamide and ethambutol, the other two drugs of choice for the treatment of tuberculosis (49). Since frequently these four drugs are combined in FDCs, it is imperative to formulate a product that ensures optimal bioavailability of all four actives. A FDC product (XEED™) of all four drugs has been developed containing isoniazide in the core of the tablet, which is coated with polymers and the outer layer contains rifampicin, pyrazinamide, and ethambutol. Human bioavailability studies comparing XEED™ with another FDC of rifampicin and isoniazide has shown significant enhancement in bioavailability of rifampicin but no meaningful changes in the bioavailability of isoniazide (<http://www.panaceabiotec.com/licensing/XEED.pdf>).

Interactions Between API and Excipients

Excipients, although thought to be inert, can have significant impact on drug absorption and bioavailability (50). There are several examples of excipients having an effect on the disintegration and dissolution process and thus impacting bioavailability. For example, disintegration tests of several generic formulations of praziquantel and the innovator product showed that one of the generic formulations failed to disintegrate in acidic media. Subsequently in a human bioavailability study, this generic product showed a relative bioavailability of ~70% as compared to the innovator product (51). Nifedipine co-ground with polyethylene glycol and hydroxypropylmethyl cellulose showed a higher dissolution rate than the physical mixture. In dogs, the co-ground mixture resulted in a 3-fold increase in AUC and a 10-fold increase in $C_{\max}$ as compared to the physical mixture. The authors hypothesized that the increase in bioavailability for the co-ground mixture was due to hydrophobic interactions between nifedipine and the excipients (52). As previously described, the failed BE for simvastatin and its acid metabolite between Simcor® and co-administration of Niaspan® and Zocor® or Zocor® alone was attributed to both drug–drug (metabolically) and formulation interactions.

Furthermore, excipients have been shown to have an effect on the gastrointestinal physiology in both human and dog and thus impact drug absorption (53). An evaluation of bioequivalence between formulations containing sorbitol or sucrose for ranitidine and metoprolol showed that the $C_{\max}$ and AUC of ranitidine was reduced by approximately 50% and 45%, respectively, for the sorbitol formulation as compared to the sucrose (54). The effect of sorbitol was much less significant in the case of metoprolol, where the reduction in $C_{\max}$ was ~23% and no effect on AUC as compared to sucrose.

These examples suggest that common excipients can have unexpected effect on bioavailability and bioequivalence of drug products, depending on the characteristics of the drug, as well as the type and amount of the excipient present in the formulation. In our experience, one of the common issues in FDC development is the potential effect of basic excipients originally employed in a mono-product on the long-term stability and *in vivo* disproportionation and dissolution of the acidic salt of weakly basic drug in the FDC. Such effects could be reflected in both $C_{\max}$ and AUC, depending on the type of drugs in the FDC. In some cases, physical separation of the interacting components via bilayer tablet turned out to be not effective. Hence, while developing FDC products, it is imperative to have a good understanding of the possible effects of excipients on

FDC bioperformance and impact on BE between FDC and co-administration, especially if there is a significant difference in the type and amount of excipients used between the FDC and the individual mono-products.

Formulation Complexities

Development of FDCs of drugs that have no compatibility issues and require similar release profiles can be relatively simple if identical composition and formulation processes can be employed for both individual mono-products and the FDC. However, in cases where there are possible API–API compatibility issues in the formulation and/or there are requirements of different release profiles, technologies such as bilayer tablets, trilayer tablets (tablets containing an inert layer in between the two active layers), bilayer with immediate-release (IR) and extended-release (XR) layers, and tablets containing a coating of an IR layer on a XR or IR core might have to be used (55). Similarly, combination of insoluble compounds (BCS II and BCS IV) may require development of enabled formulations involving solubilization technologies such as amorphous solid dispersions (56) and nanomilling (57). An example of the use of enabling formulation technology in FDC is that of Kaletra® tablets (lopinavir and ritonavir), which use the hot melt extrusion (HME) process (58). The HME tablet offers several advantages over the capsule formulation such as reduced pill burden for the patients, no need for refrigeration, and the tablets does not need to be taken with food. When developing these complex FDCs, achieving BE to co-administration could be a challenge since the drug release profiles and hence PK for the FDC could potentially be different from that of the individual mono-products. Kombiglyze™ XR is a FDC of IR saxagliptin and XR metformin, where saxagliptin is spray-coated onto metformin XR core (59). The manufacturing process for the FDC is similar to that of saxagliptin individual mono-product, where saxagliptin is spray-coated onto an inert core tablet (60). It was highlighted that the formulation design for the FDC has important implications from a biopharmaceutics perspective, as the *in vivo* behavior of the saxagliptin/metformin XR FDC is essentially identical to the two individual components given together as separate tablets, thus minimizing the differences in characteristics between the FDC and the mono-products (61). The FDC is available in three dose strengths—5 mg saxagliptin/500 mg metformin XR, 5 mg saxagliptin/1,000 mg metformin XR, and 2.5 mg saxagliptin/1,000 mg metformin XR. BE studies were conducted between the FDC and co-administration of saxagliptin and metformin XR (61). However, the 5-mg saxagliptin/1,000-mg metformin XR FDC dose strength presented a unique challenge for the BE study since there is no commercially available metformin XR 1,000 mg product. So the BE study was conducted using two 500-mg metformin XR tablets along with one tablet of 5-mg saxagliptin, as a reference. Bioequivalence between this FDC and co-administration also demonstrated ability for patients taking 5 mg saxagliptin plus two 500 mg metformin XR, to switch to 5 mg saxagliptin/1,000 mg metformin XR FDC. From the *in vitro* dissolution studies, the rate and extent of release of saxagliptin from the saxagliptin/metformin XR 2.5-mg/1,000-mg FDC formulation were shown to be similar to those observed for saxagliptin 5-mg/metformin XR 500- or 1,000-mg FDCs (61).

Drug loading in the FDC is another important consideration, since the effect of drug loading on dissolution and hence bioperformance has been well documented (62,63). If each of the active ingredients requires high doses in the FDC, then due to restrictions on the final size of the FDC tablet, the formulation would have to be developed with high drug loading. It is well-known that high drug loading of insoluble molecules in a formulation might result in dissolution slow down (62). Hence, if the dissolution kinetics of the FDC and the individual mono-products are significantly different, this could lead to failed BE studies when comparing FDC with co-administration. In addition, a thorough understanding of drug loading in a FDC formulation is also important from the perspective of final size of the dosage unit and hence patient acceptability.

In addition to challenges in achieving BE, complex FDCs also give rise to formulation and manufacturing challenges. In general, manufacturing and processing technologies needed to manufacture FDCs can be expected to be more complex than the individual mono-products. Hence, well-designed DOE studies, use of process monitoring tools, and implementation of control strategies are imperative to assure consistent product quality. Draft guidance from FDA provides guidelines on the applicability of current good manufacturing practice provisions to combination products (64). A detailed discussion of this topic is beyond the scope of this review, and interested readers are referred to (55,65,66).

REGULATORY REQUIREMENTS FOR BIOEQUIVALENCE OF FDC

The primary guiding principle for the approval of FDC products is the combination rule as described in FDA's guidance for development of FDC and co-packaged drug products (67) as well as in 21CFR 300.50, which describes FDA's policy on the approval of FDC products for humans. This rule states that "Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug." Similar rule for combination products also exist in the EMA guidelines (68). Thus, for approval of a FDC product, there should be unequivocal evidence that the individual mono-products when used in combination are safe and effective.

Although there are many regulatory guidelines covering various aspects of FDC development and approvals across different regions of the world (69), the focus of the current discussions will be on the bioequivalence between orally administered FDC products and its individual mono-products. In general, the bioequivalence guidelines for FDCs are fundamentally similar to those for products containing a single API. In other words, the rate and extent of absorption of each active from FDC should not be significantly different, respectively, from the rate and extent of each active from individual mono-products. In spite of subtle differences in BE criteria among various agencies (70), the common critical pharmacokinetic parameters are AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} in studies to determine bioequivalence after a single dose. For these parameters, the 90% confidence interval for the ratio of the FDC (test) and individual mono-products

(references) should be contained within the acceptance interval of 80.00–125.00%.

Similar to the requirements for mono-product, bioequivalence studies for FDCs are typically conducted under fasted condition since this is considered to be the most sensitive condition to detect a potential difference between formulations. But if the FDC is to be taken only with food in the product labels, a fed bioequivalence study will likely be required even if one of the active can be administered regardless of feeding status as a mono-product. It should be noted that the formulation technology or process employed in a FDC can be significantly different from those used for each mono-product because of issues such as intellectual properties or formulation compatibility. Therefore, a bioequivalence study under both fasted and fed conditions may be required if the FDC employs a solubilization technology (e.g., microemulsions, solid dispersions) while the individual mono-products may involve simple conventional process (34). The fed BE requirement is also relevant when a FDC combines an immediate release active with a modified release active.

An example of food effect study for a FDC was in the case of ActoPlus Met® and ActoPlus Met® XR, where the former is a FDC of immediate-release pioglitazone and metformin while the latter consists of an extended-release metformin core-coated tablet with an immediate-release pioglitazone-coated layer. In the product labels, it says ActoPlus Met® and ActoPlus Met® XR should be administered with a meal to reduce the gastrointestinal side effects associated with metformin (44). For ActoPlus Met®, it has two strengths of 15/500 and 15/850 mg (pioglitazone/metformin) for once or twice daily with food. For ActoPlus Met® XR, it also has two strengths of 15/1,000 or 30/1,000 mg (pioglitazone/metformin) for once daily with evening meal. The sponsor demonstrated bioequivalence under fasted conditions ($N=47-63$) between ActoPlus Met® and co-administration of Actos® and Glucophage® for both pioglitazone and metformin at both strengths. In addition, the sponsor conducted a food effect study at the higher strength of 15/850 mg and concluded that the observed changes in C_{max} for metformin was clinically insignificant. In contrast, for ActoPlus Met® XR, the sponsor conducted bioequivalence study under the fed conditions ($N=50-60$) between ActoPlus Met® XR and co-administration of Actos® and Fortamet® for both pioglitazone and metformin at both strengths (44).

In the case where an active metabolite is present at a significant level or is exclusively responsible for the pharmacodynamic effect, bioequivalence is still based upon measured concentrations of the parent drug (33,34). However, the determined metabolite pharmacokinetic data are used either as part of bioequivalence metric or as supporting data. The reason for focusing on pharmacokinetic parameters of the parent molecule is that they are usually more sensitive to the differences between formulation performance than the metabolite (32,71). Recently, the request for market authorization was not granted for loratadine Sandoz 10-mg tablets, primarily because of failed bioequivalence for the parent drug (72). While the applicant demonstrated bioequivalence for the active metabolite (desloratadine), it failed to achieve bioequivalence for the parent drug (loratadine) for both AUC and C_{max} . It should be noted that the potentially constrained formulation designing space for a FDC may present additional hurdles in meeting BE criteria for both the parent drug and the active metabolite.

Overall, the unique nature of FDC often presents considerable challenges in meeting various regulatory criteria for bioequivalence to individual mono-products during formulation development. In theory, a FDC can have more strength combinations than the sum of strengths of each individual mono-product. For example, a FDC of drugs A and B could have eight strength combinations if drug A has two strengths and drug B has four strengths. Pending on the ability for justifying biowaivers for intermediate potencies, the large number of FDC strengths can result in the potential need for conducting BE studies at multiple strengths.

Biowaiver or bracketing approach is commonly used for the development of monotherapy products. Biowaiver can be based on BCS classification or establishment of bioequivalence at the strength(s) that are most sensitive to detect a potential difference between products. In the USA, BCS-based biowaiver are applicable to immediate-release FDC products if all actives in the FDC belong to BCS class I. In the EU, the BCS-based biowaiver also includes BCS class III actives and the excipients that fulfill the requirements are outlined in the EMA guideline. When BCS-based biowaiver is not applicable, biowaiver of lower or intermediate strengths are still possible using the bracketing approach if bioequivalence has been demonstrated at the highest and/or lowest strength (often the most sensitive conditions) and additional important requirements (e.g., linear pharmacokinetics, similarity in dissolution profiles) are met. Among the various additional requirements for a biowaiver, demonstrating compositional proportionality across all FDC strengths is often not straightforward. One common scenario is that a FDC contains one active at a constant strength and another active at multiple strengths. Whether the FDC is designed as a single (e.g., monolithic tablet) or multiple-compartment (e.g., bilayer tablet) formulation, the ability to achieve compositional proportionality is not only dictated by the technicality (e.g., drug loading vs. image size) but also the definition of proportionality. In the current EMA guideline, each layer in a bilayer tablet may be considered independently when assessing compositional proportionality. A successful example is Vytorin® where a bioequivalence study in healthy subjects demonstrated that Vytorin® (ezetimibe and simvastatin) 10-/10- and 10-/80-mg combination tablets were bioequivalent to co-administration of corresponding strengths of ezetimibe (Zetia®) and simvastatin (Zocor®) as individual tablets. The bioequivalence for the 10-/20- and 10-/20-mg combination tablets was waived based on the formulation similarity (weight multiples for simvastatin with the constant strength of ezetimibe) and supporting *in vitro* dissolution data (73).

With regard to the selection of reference products for FDC bioequivalence studies, the situation is also complex, since a FDC bioequivalence study typically includes individual mono-products which could be sourced from different markets. In some cases, the potential choices of reference mono-products could include either innovator's products or generic products. The current regulatory guidelines often demand the use of reference mono-products for which a marketing authorization has been granted in the specific region where the FDC is to be filed. Hence, it is common for a sponsor to conduct multiple bioequivalence studies for a FDC development for global markets using reference products from different regions of the world.

While various guidelines for bioequivalence have been implemented and continued updated by different regulatory agencies, some flexibility in FDC approvals has been applied on a case-by-case basis when the bioequivalence study does not meet the desirable outcome. As an example, in the fasted pharmacokinetic study for assessing bioequivalence between Avandaryl® (rosiglitazone and glimepiride) and individual mono-products at 4-/4-mg strength combination, glimepiride did not meet bioequivalence bounds for $C_{\max}$ [90% CI (0.76, 1.01)]. However, bioequivalence was achieved under fed conditions for the FDC. Since the FDC tablet will be administered chronically to patients, the slightly lower $C_{\max}$ of glimepiride observed is not clinically significant. Additionally, the FDC tablet package insert indicates that it should be administered with a meal. Hence, the product was approved in spite of missing the lower bound of the $C_{\max}$ for one of the actives (74).

Another interesting case is for the development of Kaletra® (lopinavir and ritonavir) melt extruded tablets, which were designed to improve the existing soft gelatin capsules (SGC) with regard to pill burden, pharmacokinetic variability, and product stability (75). The Kaletra® SGC (133.3/33.3 mg) requires the dosing of three capsules twice daily while the higher drug loading tablets (200/50 mg) would only need two units twice daily to achieve the same daily dose. In the single-dose bioequivalence study, it was found that the tablet is about 20% more bioavailable than the commercial SGC under non-fasting conditions (under which safety and efficacy data were generated with the SGC). However, the results from a cross-study comparison indicated that the steady-state pharmacokinetics of both actives after administration of the tablet at 400/100 mg BID were similar to that seen in previous multiple-dose studies in healthy subjects using the SGC. Based on the overall evaluations of relative oral bioavailability across studies, Kaletra® tablet was approved with a post-marketing study agreement which requires the sponsor to conduct a phase III clinical study to compare the tablet and SGC in HIV patients.

FUTURE OPPORTUNITIES

In the recent decades, FDC products have made important contributions in improving public health through enhanced patient compliance and lower costs, especially in the areas of infectious and cardiovascular diseases. Significant efforts have been made by various national, international, and supranational regulatory authorities to provide up-to-date guidance documents to streamline the conduct of bioequivalence studies and to facilitate the development of FDC products. As discussed previously, while regulatory authorities put significant emphasis on protecting the public health by assuring the safety and quality of drugs through rigorous reviewing and approval processes, justification for deviation from regulatory criteria has been granted on a case-by-case basis. However, the noticeable differences between the guidelines and practices by the various regulatory authorities have presented significant challenges for the pharmaceutical companies from setting up the FDC development strategy to achieving product approvals. Based on our recent experiences, there are a number of areas that deserve attention for harmonization of regulatory guidelines. For example, the number of strength combinations to be developed can have a profound impact on the technical complexity of formulation development, manufacturing ability,

and product development time and cost. It is not unusual that a sponsor will receive very different responses on the required strength combinations from regulatory authorities of the major markets. In order to accommodate the differences, a sponsor may have to embark a highly complex and expensive development program. In some cases, a sponsor may be forced to consider different dosage form design and/process for different regions.

The choices of strength combinations can also have downstream impact on a sponsor's ability to employ a biowaiver for human bioequivalence studies as a means to reduce the cost of product development. For example, single-compartment or multiple-compartment FDC design may be preferred pending the number of strength combinations, potency range, and other key attributes such as compatibility. In addition, some clear differences have been seen with regard to the definition for compositional proportionality which is one of the key requirements for a biowaiver. For instance, bilayer tablets at multiple strength combinations may be considered weight-multiple by one agency but not for another authority. There are clear differences in the level of acceptance of BCS-based biowaivers among the various regulatory authorities.

Due to the unique nature of FDC, bioequivalence studies for FDC products often involve the use of commercially available mono-products for co-administration as the references. The requirement for a reference mono-product sourced from the specific market often forces the sponsor to conduct multiple bioequivalence studies for the same FDC formulation or between the references. Besides, the difference in regulatory requirement for a fed bioequivalence study further complicates the FDC development process.

To improve the development process for FDC products, it is important to establish a clear strategy for both formulation development and clinical evaluations within the pharmaceutical companies. As has been described in this article, there can be a high risk associated with showing bioequivalence between FDC formulations and co-administered mono-products. Hence, establishing bioequivalence *vs.* therapeutic equivalence strategy early on in the development will allow the sponsor to fully align the development paradigm and plan for scenario where the FDC does not meet the bioequivalence criteria. For example, in the case of Micardis® HCT (telmisartan and hydrochlorothiazide), bioequivalence studies comparing the FDC to co-administration showed that the FDC was not equivalent to co-administration in terms telmisartan $C_{\max}$ (76). However, a clinical efficacy study comparing the FDC to telmisartan alone in patients with mild-to-moderate hypertension showed that the FDC was more effective in reducing blood pressure than telmisartan. In addition, the safety profile of the FDC was similar to the individual agents. Based on these efficacy and safety data, the FDC was approved and the failed $C_{\max}$ bioequivalence was deemed not clinically relevant (76).

While physiologically based absorption and pharmacokinetic modeling and simulations have become a common tool for general formulation development, its application to FDC development has great potential as well. In addition to guiding formulation designs, biorelevant *in vitro* dissolution testing coupled with pharmacokinetic modeling and simulations can provide quantitative assessment on probability of success for bioequivalence (77,78). Similar to developing monotherapy products, established IVIVC for individual mono-product(s)

can significantly facilitate FDC development and approval, especially if one of the actives is delivered via modified release.

CONCLUSION

The current impetus on FDC products is driven by several advantages they provide to the patients, providers, and pharmaceutical industry. However, FDC development also presents several challenges such as achieving bioequivalence to co-administration of the individual mono-products, formulation complexities, and manufacturing challenges. In this review, the challenges in achieving bioequivalence for FDCs were discussed. From that perspective, it is imperative to carefully review the physicochemical and biopharmaceutical properties of the compounds to be combined and understand their impact on pharmacokinetics. In addition to PK and API variables, formulation variables can further complicate BE study design. In the current environment of timeline and cost pressures, the combination of inadequately powered study and attempting to assess too many variables in a probe clinical PK study can result in less robust data. This could mislead formulation development and be counter-productive. Hence, particular attention should be given to the clinical study design. Finally, a clear strategy (*i.e.*, BE study only *vs.* combination of BE and therapeutic equivalence study *vs.* therapeutic equivalence study only) for approval of a FDC, based on the comprehensive review of technical data for drug substance and drug product, is critical.

ACKNOWLEDGMENTS

The authors would like to thank Drs. Ron Smith, Greg Szpunar, Gary Herman, and Paul Fackler for their insightful comments in this review paper.

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