EXPERT OPINION

Bioequivalence challenges in development of fixed-dose combination products: looking beyond reformulation

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Introduction: Bioequivalence study is a critical step in the development of novel fixed-dose combination products (FDCPs). While bioequivalence of prototype FDCP to the approved monocomponent products facilitates speedier development and approval, lack of bioequivalence often leads to development delays due to reformulation.

Areas covered: Pharmacokinetic (PK) interaction is one of those issues that often have the potential to completely derail the product development process. The objective of the present article is to highlight PK challenges along with strategies to resolve them.

Expert opinion: A rationale development approach that integrates formulation and clinical insight, so as to understand the clinical significance of non-bioequivalence, would help to minimize the development timeline. While bioequivalence should always be the initial goal in the formulation development, failure to meet it should not immediately lead to reformulation. Instead, evaluating the PK of actives in FDCPs in approved market products, and their consequent clinical implications, would help to make rationale and pragmatic decisions. Such an approach will facilitate the initiation of clinical studies, without increasing the risk of failing to meet safety and efficacy end points, and in turn will significantly improve the productivity.

Keywords: bioequivalence, clinical significance, fixed-dose combination, pharmacokinetic interaction, reformulation

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1. Introduction

Fixed-dose combination products (FDCPs) contain more than one active ingredient. While there are drug products that combine as much as four active ingredients (e.g., various acetaminophen combination products), combination of two or three active ingredients are more common. The rationales for FDCPs are:

A. Improve safety and/or efficacy. For example, combination of bisoprolol fumarate with hydrochlorothiazide (Ziac®) shows synergistic antihypertensive effect [1]. The enhanced antihypertensive effect allows the use of a lower strength of hydrochlorothiazide (6.25 mg) than the lowest approved strength of monocomponent product of hydrochlorothiazide (Microzide®). Another example is the combination of proton pump inhibitors with non-steroid anti-inflammatory drugs (e.g., Vimovov tablets containing esomeprazole and naproxen) to control harmful gastrointestinal effect of the latter.

B. Reduce the pill burden in chronic therapy, especially in geriatric patient population which often has multiple co-morbidities and needs to take multiple pills. This

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improves adherence to the prescribed dosage regimen and thus enhances the probability of therapeutic benefit.

While improved safety, efficacy or compliance offers a technical justification for development of FDCPs, another, and probably more important, reason leading to increasing development of such products is their complementary role in strengthening new product pipeline with discovery of new drugs increasingly getting difficult. As evident from the **Figure 1**, in recent years the proportion of new FDCPs approvals of overall new drug products approved is same or even more than new molecular entities approved.

In terms of development complexity, FDCP falls in between new drug development and generic product development. Active ingredients in FDCP are usually preapproved as monocomponent products, thus doing away the requirement of extensive preclinical research on FDCP to establish safety and efficacy of individual actives. However, there is always a possibility of altered pharmacokinetics (PK), that is, absorption, distribution, metabolism and elimination, or pharmacodynamics (PD) of actives when administered together. Such interaction may range from being totally absent to very high. While the lack of PK interaction indicates that the actives when administered together will not have any higher safety issues than that of individual actives, presence of PK interaction calls for a closer look on the possible impact of such interaction on safety and efficacy, and taking appropriate measures to ensure that the final product has an acceptable risk–benefit profile.

The typical development program of new FDCPs using actives of approved monocomponent products involves preclinical evaluation, formulation development and clinical evaluation. While each of these activities is challenging, they can be executed as per the standard procedures. There are strategies and guidelines [2,3] to handle adverse results, if any, which usually may not pose a threat to a development team with adequate development experience. For example, the selected actives may interact chemically when combined, generating new impurities. Such a product will not be approvable unless new impurities are qualified to be safe in accordance with the ICH guideline (Q3A) which outlines necessary procedures to conclude safety of new impurities. This is highlighted by the recent FDA's refusal to approve Truvada, an FDCP containing tenofovir and emtricitabine, developed by Gilead.

However, there are some development aspects that need a logical and pragmatic approach to timely resolve critical issue and ensure speedy delivery of lifesaving products to needy patients. PK interaction is one of those issues that often have potential to completely derail the product development. The objective of the present article is to highlight PK challenges and strategies to resolve them.

2. PK interaction in FDCPs

Let us understand why PK interactions are important in development program of a new FDCP. PK of drug molecules is defined in terms of absorption, distribution, metabolism and elimination of drug product after its administration. The interplay of these four processes decides the pattern of patients' systemic exposure to the drug and its metabolite. Based on the exposure pattern, physiological processes in patients' body undergo changes, addressing the cause of disease. The systemic drug exposure pattern is represented in terms of C_{max} (i.e., rate of drug absorption and peak exposure), $AUC_{0\text{-}t}$ (extent of absorption and total exposure), t_{max} (time to achieve peak drug exposure), $t_{1/2}$ (elimination half-life) and K_{el} (elimination rate constant).

Each approved product has a specific PK profile characterized in terms of above parameters. Any change in the profile would be a potential source of influencing the body's physiological process in a different manner. The consequence of such altered exposure pattern may be multifold ranging from no effect to life-threatening events. For example, let us assume that an approved formulation 'A' of a drug has PK profile as shown in **Figure 2**. Another formulation 'B' of the same drug at same dose has a different PK profile also shown in **Figure 2**. Such an alteration may be due to diverse reasons like tempering with the product (e.g., crushing tablet prior to administration), administration in a manner different than prescribed in product label (e.g., with or without food, alcohol, etc.), interaction with co-administered drug or due to patient's systemic reasons (e.g., low drug metabolism and clearance due to abnormal liver functioning). While such events in case of drugs with wide therapeutic window may not be life threatening (though it may lead to higher non-serious adverse events), a similar event in case of diabetic or cardiovascular drugs which have narrow therapeutic window (e.g., insulin, clonidine, digoxin) may be life threatening. No surprise then that any change in the PK profile of actives in FDCPs as compared with that of their market products can trigger the need of conducting time-consuming costly studies to find the root cause of such changes, and understand their implication on safety and efficacy of product.

In a conventional FDCP development program, the PK end point is to achieve bioequivalence of PK profile for each active in the FDCP (i.e., test product) and approved monocomponent market formulations of each actives (i.e., reference products). The bioequivalence is achieved if the confidence interval (CI) of ratio (test product:reference product) of geometric mean of C_{max} as well as AUC for each active in FDC and the respective reference product are within a range of ± 20% (i.e., 80 – 125%). Once the actives in FDCP are demonstrated to be bioequivalent to the respective monocomponent reference products, the FDCP can be subjected to clinical evaluation of their safety and efficacy in human volunteers. However, not in every case bioequivalence is achieved for each active in FDCP.

3. Non-bioequivalent fixed-dose combination products

Non-bioequivalent products introduce significant complexity in the development process. The bioequivalence issues can

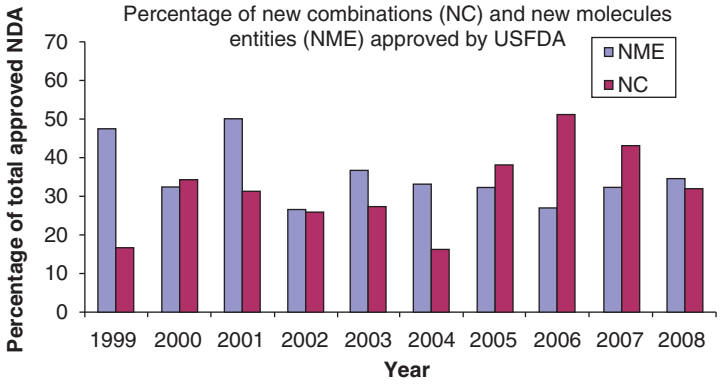

Figure 1. Percentage pf new fixed dose combination products and new molecular entities launched of total new drug product lanches between 1999 to 2008.

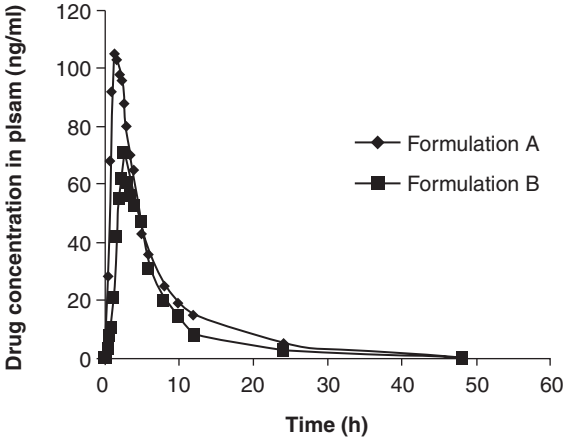

Figure 2. Pharmacokinetic profile of one active in two formulations A and B containing same active and same dose.

have multiple reasons which need diverse approaches to resolve. Working on misdiagnosed root cause can not only cause significant cost and time overrun, but more seriously the issue may remain unaddressed resulting into a potential non-approvability of such product during regulatory scrutiny. Hence, it is very important that such issues are addressed in a logical fashion to ensure accurate estimation of root cause and implementing the best solution.

Achieving bioequivalence for an FDCP is often challenging. Consider a case of two actives, both BCS (Biopharmaceutics Classification System) class II (i.e., drugs having low solubility and high permeability). The reference product of one active is a fast release tablet (> 85% drug released in 15 min) while the reference product of second product is relatively slow release tablet (< 30% drug released in 15 min). Another scenario can be where reference product for one active is a tablet while for second product is a capsule containing micronized drug. For such actives, formulating a matrix formulation that results into differential releases of different actives so as to match their release profile with that of their respective reference products and thus improving the probability of achieving bioequivalence needs innovative formulation design.

Notwithstanding, a well-devised formulation strategy that provides the *in vitro* drug release of actives closely resembling that of respective reference products, bioequivalence failure is not rare in new FDCP development. What is more critical is how such adverse results are interpreted and used to define the future course of development. Generally, failure of one bioequivalence study prompts the development team to investigate the probable root cause of failure and fix it. The root cause finding exercise is invariably related to a critical evaluation of the drug release patterns from test and reference products by generating additional drug release profile in different media at different stirring rates, and their correlation to the *in vivo* behavior. Once a pattern between *in vitro* release and *in vivo* absorption is found, the formulation is tweaked to alter the *in vitro* drug release that would result into the desired

in vivo release and absorption pattern for each active similar to the respective of reference products. While this is the standard approach of addressing non-bioequivalence issues in FDCP development, it is often frustrating making it worthwhile to understand other aspects that can facilitate smooth progression of FDCP development.

The basic assumption that achieving bioequivalence is an absolute necessity is itself misplaced. This notion of achieving bioequivalence leads to prolonged development cycle, especially in case of products containing BCS class III and IV drugs, which is often scientifically unjustified. The development team needs to understand why regulatory bodies insist on demonstrating bioequivalence, and should be able to relate such requirement with the intended label indication of the FDCP. While a bioequivalence significantly simplifies the development program, backup strategies should be available just in case proving bioequivalence turns out tricky. These strategies would be addressed specifically in the subsequent sections.

4. Label indication for a new fixed-dose combination product

A new FDCP can be approved with a label that may have any one of the two possible indications: i) substitution indication and ii) efficacy indication. A product with substitution indication label qualifies to replace the concomitantly administered monocomponent product of each active present in FDCP. Label of such a product cannot claim to treat disease condition, even those mentioned on the label of approved monocomponent products used as reference products in bioequivalence studies. For example, the label of a generic FDCP of enalapril maleate (20 mg) and hydrochlorothiazide (12.5 mg) tablets (Teva), additionally approved for a substitution indication, reads as, '…This fixed dose may also replace the combination of 20 mg enalapril maleate and 12.5 mg hydrochlorothiazide in patients who have been stabilized on the individual active substances given in the same proportions as separate medications' (PAR, 2007). While, development of an FDCP merely for the substitution indication may not be commercially viable due to possible low market penetration, it can be used as a strategy for an early market entry while the product undergoes clinical evaluation intended to extend the label indication to first-line or second-line treatment of respective disease condition and widen the market share after subsequent approval and launch.

On other hand, an FDCP with efficacy indication specifies the disease condition in which the product can be used. The indication is based on a clinical evidence of the claimed efficacy from randomized, controlled clinical trials where the FDCP has been compared with placebo or individual monocomponent products in parallel design to demonstrate its superior or non-inferior efficacy and safety. Based on the results of these trials and consequent risk: benefit ratio, the product can be indicated for first-line or second-line treatment.

Thus, while the bioequivalence is necessary to get a substitution indication, it is desirable but not necessary when the product is intended to be taken through clinical development route to get specific treatment-related indication.

5. Bioequivalence: why are they required for a new product?

It is a paradox that for a new product that contains actives which are already available in multiple doses as approved monocomponent products in market, and are in use for multiple years, compulsorily need to be subjected to bioequivalence rather than a comparative bioavailability study-based estimation of any major safety issues followed by a clinical study plan that would ultimately establish the safety and efficacy of the product. Yet, the demonstration of bioequivalence helps to:

A. Demonstrate the absence of PK interaction between the actives, indicating that the safety and efficacy of individual actives can be expected similar to the monocomponent products.
B. Based on above assumption, get the product approved with a substitution indication without conducting any further clinical trial, unless there is any change in the regimen (e.g., changes in the administration timings).
C. Faster regulatory approvals, either marketing approval under substitution indication label, or a clinical trial to study safety and efficacy, or final marketing approval with sufficient clinical evidence on safety and efficacy. The bioequivalence mitigates risk of any regulatory query on the formulation or PK interaction and a possible need to establish the reason and consequences of such interaction.

While demonstration of bioequivalence indicates lack of formulation and PK interaction, it does not entirely rule out a PD interaction, an equally important aspect of FDC development program which is evaluated through clinical studies.

6. Non-bioequivalence: implications and rescue strategies

Figure 3 and **Table 1** show hypothetical results of a bioequivalence study for one active ingredient in three new prototype FDCPs ('B', 'C' and 'D'), all containing same active ingredients, and its monocomponent reference product ('A'). Assume that other actives show bioequivalence to the respective reference products. Based on the results, following can be concluded:

A. FDC product 'D' is bioequivalent to product 'A'. The bioequivalence implies that actives present in the FDC product 'D' do not have any PK interaction. Hence, it

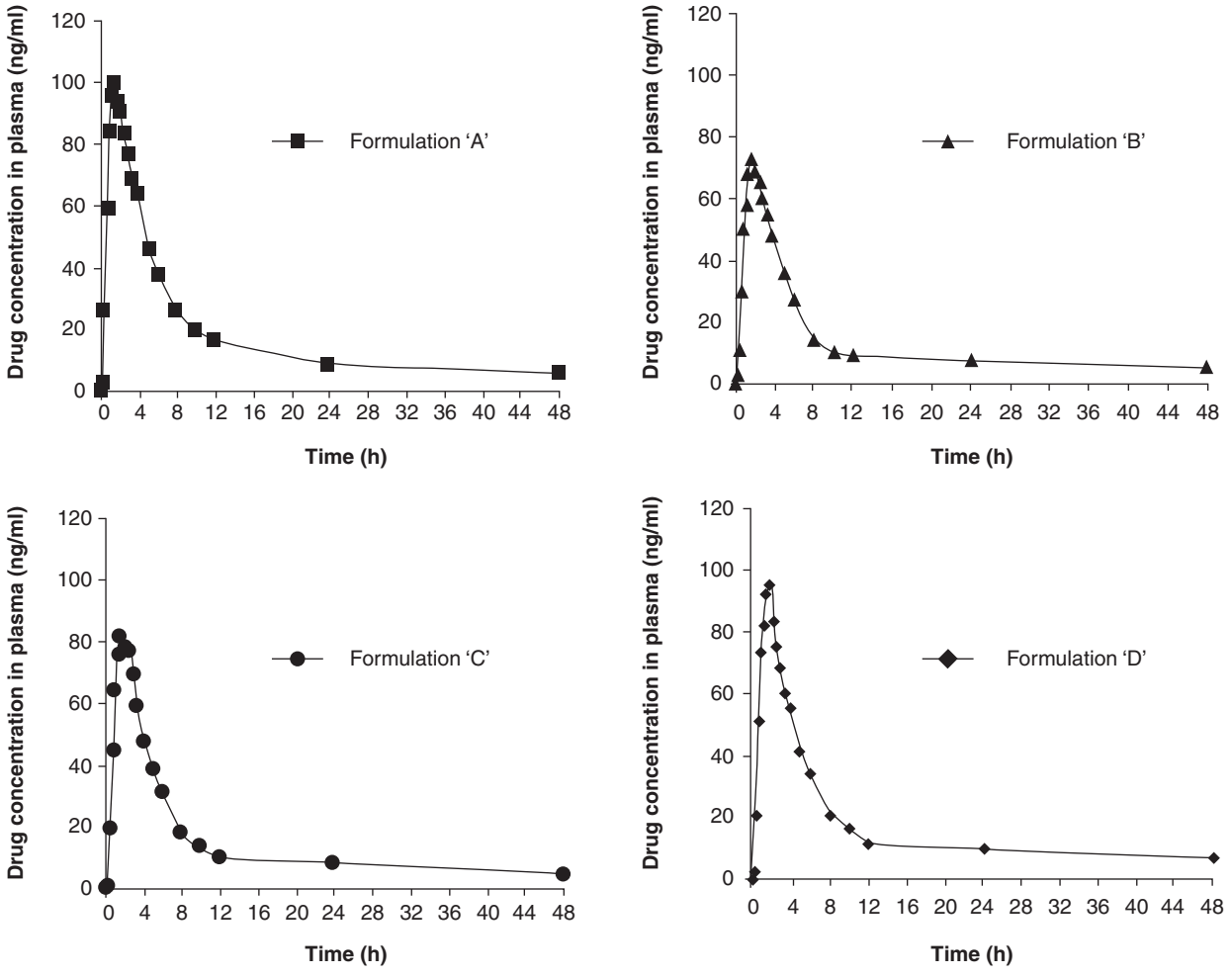

Figure 3. Pharmacokinetic profile of an active from an approved monocomponent product (formulation 'A', used as reference) and three prototype fixed dose combination products (formulation 'B', 'C' and 'D').

Table 1. Bioequivalence study outcome for an active in three FDC formulations ('B', C', and 'D') as compared to an approved monocomponent product 'A' used as reference product.

PK parameters	Bioequivalence study outcome		
	Formulation 'B'	Formulation 'C'	Formulation 'D'
T_{max} (hr)	2	1.67	1.67
C_{max} ratio (test/reference)	73.71	81.96	96.15
90% Confidence interval for C_{max} ratio (test/reference)*	63.21 – 89.22	74.97 – 89.61	88.05 – 104.97
$AUC_{0\text{-last}}$ ratio (test/reference)	72.68	86.72	92.77
90% Confidence interval for $AUC_{0\text{-last}}$ ratio (test/reference)*	62.88 – 92.61	79.39 – 94.74	87.06 – 98.85

*The acceptable limit of 90% confidence interval for test/reference ratio of C_{max} as well as $AUC_{0\text{-last}}$ is 80 - 125%.

can be inferred that this FDC product would not have any significantly higher adverse event profile associated with the active ingredient than the monocomponent product 'A', unless these actives have any PD interaction. The FDC product 'D' can be dosed to human subjects to assess clinical efficacy and safety.

B. FDC product 'B' and 'C' are non-bioequivalent to product 'A' indicating different PK of the active at the same dose in the test and reference products. The products 'B' and 'C' fail in the bioequivalence test on both the criteria, $AUC_{0\text{-last}}$ as well as C_{max}. It implies that the absorption rate as well as extent of absorption of the

active from the FDCPs, and consequently the peak and total exposure, would be significantly different than that from reference product. Lower C_{max} and $AUC_{0\text{-last}}$ may decrease therapeutic efficacy. On other hand, higher C_{max} and $AUC_{0\text{-last}}$ would indicate a possibility of higher adverse event.

With standard development approach, product 'D' would qualify for clinical evaluation, while product 'B' and 'C' would be subjected to reformulation. The reformulation may or may not result in achieving bioequivalence depending on whether or not it addresses the actual reason of different PK profile of the active in FDCP. The non-bioequivalence may be due to two reasons:

A. Drug–drug interaction: A drug can influence various physiological components that would alter one or more of the PK processes. For example, one active can down-regulate metabolic enzymes resulting into decreased metabolism of active moiety which would eventually lead to higher C_{max} or $AUC_{0\text{-last}}$ or both.
B. Formulation interaction: The absorption of drug also depends on its release pattern from the formulation. For example, a formulation may release the drug slower or faster than that from reference product. This would lead to a different absorption profile, especially for BCS class I or class II drug which undergo rapid absorption. Another example is that the matrix component (i.e., excipients) may lead to drug degradation in *in vivo* condition.

Formulation interaction-led effect can be addressed in many cases, if not all, by innovative formulation design. For example, if different actives need to be released at different rates, a multilayered tablet, or coating of one or more actives followed by tabletting can be plausible strategies. However, there may still be cases where drug release or absorption of an active is highly susceptible to formulation components. In such cases, it may be worthwhile to look beyond the formulation as discussed later.

There are very few formulation strategies which can be evaluated to control drug–drug interaction. For example, formulations that release two actives at different rates or at different regions in gastrointestinal tract may minimize the interaction. However, in most of the cases, a drug–drug interaction becomes difficult to address. In fact, it is always desirable that the actives in FDCPs should not have any interaction, PK or PD, barring cases where such interactions are consciously used to improve safety and/or efficacy.

In addition to the limited formulation options available to achieve bioequivalence, the other tool which mostly is not heeded to is to examine the implications of difference in PK on safety and efficacy of the active. While bioequivalence assures that the actives can be expected to retain their safety profiles as in the approved products, it does not guarantee that the new FDCP would necessarily meet the safety and/or efficacy end points mainly because the PK equivalence does not indicate PD equivalence. It is this logic that necessitates clinical study in order to get approval of safety and efficacy indications on the label claim. Similarly, it can be argued that PK non-equivalence, within a limit, does not necessarily indicate a PD non-equivalence, the main argument that makes PK non-equivalence unacceptable in FDCP development.

Consider the case of formulation 'B' and 'C' in **Figure 3** and **Table 1**. The CI for C_{max} as well as $AUC_{0\text{-last}}$ for formulation 'C' is out of the acceptable limit (i.e., 80 – 125%) making it non-bioequivalent to the reference product 'A'. While, with similar results, it can be unacceptable to approve a generic product, or a new FDCP intended to have a substitution indication primarily because they are not subjected to clinical trial to confirm their safety and efficacy, a new FDCP scheduled to undergo a clinical trial may require some different approach. This can be in form of consulting clinical team if such marginal deviation in CI would necessarily impact the PD of drug leading to undesired safety/efficacy outcome. Unless the drug has narrow therapeutic window, such deviations are considered acceptable. However, such conclusion needs to be based on a thorough evaluation of dose–response relation. If the dose of the active in FDCP (e.g., 10 mg) lies between the highest and lowest approved dose of monocomponent product (e.g., 5 and 40 mg), it is very likely that the respective C_{max} and $AUC_{0\text{-last}}$ of the active in FDC would also lie between the minimum and maximum values which have already been approved and have a proven safety and efficacy data. Such cases provide a very convincing rationale to proceed for further development. However, in most of the cases, bioequivalence studies are commonly conducted with formulation containing highest or lowest strength of the active. For such product, while the PK parameters may lie outside the approved limits, it may be worthwhile to evaluate possible clinical impact. If it is concluded that marginally higher or lower C_{max} or $AUC_{0\text{-last}}$ are clinically non-significant, it would be logical to proceed to the next level of development rather than reformulating the product.

On the other hand, a large variation in the CI for the C_{max} and $AUC_{0\text{-last}}$, as in case of formulation 'B', may not be justifiable as such products may have higher probability of adverse safety/efficacy outcome in clinical trials. Similarly, such an approach cannot be recommended for drugs with narrow therapeutic window. One may ask if there is a definition of high and low variation in the CI for C_{max} and $AUC_{0\text{-last}}$ which can facilitate decision-making. The answer is no. It entirely depends on the actives, therapeutic class, its dose–response relation, clinical knowledge, etc. Given below are three cases of approved FDC formulations that could not meet bioequivalence for one or more of the combined actives but were still approved through clinical development route.

A. Micardis Plus tablets (telmisartan 80 mg, hydrochlorothiazide 12.5 mg): In a single does, randomized, four-way crossover replicate bioequivalence study between the

FDCP and the individual monocomponent product of telmisartan and hydrochlorothiazide administered together, the CI for C_{max} of telmisartan was 106.8 – 129% indicating that the upper level breached the acceptable limit of 125%. It implies that the rate of absorption of telmisartan from FDC formulation was higher than that from approved market formulation of telmisartan. However, the same formulation was evaluated for safety and efficacy and was finally approved by FDA. In its review comment, FDA noted that the observed higher rate of absorption is clinically non-significant [4].

B. Tekturna HCT capsules (aliskiren 300 mg, hydrochlorothiazide 12.5 mg): In a single dose, randomized, two-way crossover bioequivalence study between the FDCP and the approved monocomponent product of respective actives, the CI for C_{max} of aliskiren was 75 – 104%, indicating lower rate of absorption of alsikiren from the FDC formulation than that from the approved monocomponent product. However, the reviewer concluded it to be clinically non-significant due to wide therapeutic window of aliskiren [5].

C. Simcor tablets (niacin extended release 1000 mg, simvastatin 20 mg): In a single dose, randomized, four-way, crossover study comparing Simcor against the monocompnent product of niacin extended release and simvastatin dosed separately and concomitantly, simvastatin absorption rate as well as extent was found to be higher (CI for C_{max}: 102.95 – 133.45%; CI for $AUC_{0\text{-last}}$: 112.36 – 133.57%). Higher rate and extent of absorption were attributed to formulation as well as drug–drug interaction. However, they were concluded to be clinically non-significant and the product was approved based on the clinical trial results [6].

While the above examples indicate that some FDCPs, which may fail the bioequivalence test against the monocomponent reference products marginally, may still be considered for the clinical evaluation, it is important to have a clinical justification that the observed non-equivalence would not negatively impact the product to meet its clinical end points of safety and efficacy. Pre-Investigational New Drug Application (IND) consultations with FDA to discuss clinical implication of products' formulation and PK attributes, proposal of clinical study and design and risk mitigation strategies are very helpful to arrive at such decisions.

7. Expert opinion

Speed of development of pharmaceutical products is a global concern in pharmaceutical industry. Increasing competitive pressure and diminishing growth opportunities have overwhelmed pharmaceutical firms not only to carve out niche area that provides respite from competition but also to rethink various strategies, including those related to product development. The focus is on winning the race of bringing new products to market. In this context, development of FDCPs that provides multimodal treatment options to patients resulting in improved efficacy and/or lower adverse events has become an obvious choice as it promises faster development with lower risks as compared with other options.

While development of FDCPs with previously approved molecules simplifies the development program by reducing preclinical study requirement, it often gets complicated due to formulation challenges to meet certain regulatory requirement. Bioequivalence of each of the actives against their respective reference products is considered to be one critical requirement. In the face of failure of bioequivalence studies for one or more of the combined molecules, a simplistic approach involves reformulation followed by the repeated bioequivalence studies. This approach is fraught with huge risk of increasing development time, cost and at times may also lead to discontinuation of development program for challenging molecules as those in BCS class IV. While the reformulation approach is adopted to meet bioequivalence requirement, it is seldom questioned whether a non-bioequivalent product will run any additional risk as compared with a bioequivalent product.

The bioequivalence merely informs the lack of PK interaction between the combined actives which is an early, and indirect, indication that the combined actives can be expected to have adverse events no worse than respective approved market product of each active. It does not offer any indication about PD interaction of the combined actives which ultimately determines the safety and efficacy. While bioequivalence should always be the initial goal in the formulation development, failure to meet bioequivalence should not immediately lead to reformulation. Instead, evaluating the PK of actives in FDCPs vis-à-vis PK of actives in approved market products, and consequent clinical implications would help to take a rationale and pragmatic decision. Such an approach will facilitate clinical study initiation without increasing the risk of failing to meet safety and efficacy end points, and in turn will significantly improve the productivity.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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