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DEVELOPMENT OF ORALLY ADMINISTERED FIXED DOSE COMBINATION (FDC) PRODUCTS: PHARMACOKINETIC AND BIOPHARMACEUTICAL CONSIDERATIONS

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ABSTRACT: Combination drug therapy has been shown to be beneficial in chronic multifactorial diseases, infectious diseases and in the treatment of comorbid conditions. Some drug combinations have also been developed to improve the bioavailability of the active components by combining with drug metabolizing enzyme inhibitors. Fixed dose combinations (FDC) offer advantages of better efficacy, ease of administration and patient compliance, while combination therapy generally improves efficacy. For the development of FDCs the primary consideration is the approval status of the drugs to be combined to develop an appropriate strategy. Subsequently, the dose strengths of the individual components need to be considered to be able to allow flexibility of dosing. In order to successfully develop FDC products, demonstration of bioequivalence (BE) to the individual free combinations and lack of pharmacokinetic/pharmacodynamic (PK/PD) drug interaction are essential. Therefore, the development of FDCs requires a good understanding of the biopharmaceutical properties, drug pharmacokinetics and their metabolic pathways. The formulation development program involves pilot stage program followed by registration BE studies with a requirement for food effect bioavailability studies. The regulatory requirements may be challenging in scenarios where two new chemical entities (NCE) are to be combined. Developing a good strategy and designing appropriate trials to evaluate the formulations, drug-drug interactions and bioavailability are critical to the development of FDCs. This review article summarizes the clinical and regulatory requirements of clinical pharmacokinetics/ biopharmaceutics studies in the development of FDCs and challenges that arise in conduct with respect to dose selection, sample size calculations and food effects.

INTRODUCTION: Historically, fixed dose combination (FDC) products were developed for improved compliance, better efficacy and reduced adverse events ^{1, 2}. In the current scenario, the strategies for developing FDCs are primarily based on the therapeutic requirements.

Assessments of the desired benefits such as patient adherence, enhanced efficacy and better safety profiles compared to the existent drug therapies and possible limitations (e.g. cumulative toxicity) of the combination product are performed. FDC product development is governed by regulatory recommendations, where clinical, biopharmaceutical and pharmacokinetic (PK) considerations are critical for their development ^{3, 4, 5}. One of the main biopharmaceutical considerations is the dose of each active substance in the FDC which should be appropriately evaluated and clinically justified.

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FDCs are generally developed with components having complementary mechanisms of action with a clear medical rationale. Typically this is the case for an uncontrolled disease or comorbid condition requiring multi-drug therapy resulting in pill burden. Following are the general clinical considerations for the development of FDC products:

- i. To improve efficacy or safety due to additive or synergistic pharmacological activity or to reduce drug resistance (e.g., anti-microbial drug combinations)
- ii. To reduce potential for abuse (e.g., low dose combination of various centrally acting analgesics)
- iii. To improve bioavailability (BA) by inhibiting the metabolism of the active component
- iv. To simplify the dosage regimen making it more convenient from patient compliance in addition to simplified manufacturing and distribution reasons.

While there are advantages of developing FDC products, the scope for development of these

products is limited for situations when the component therapies require dose titration especially in specific patient populations that require various dose adjustment patterns. Occasionally development of the FDC is challenging when the duration of action of active drugs differ significantly. Another limitation of developing FDCs is when unfavorable drug interactions at the level of PK or efficacy/safety exist. In some cases, the challenge of developing an FDC is that the dose becomes too large to administer as single pill⁶. Some of these challenges have been addressed through formulation approaches⁷.

FDC products are available as oral or parenteral drug products (e.g., inhalation products, intravenous/subcutaneous injections etc.), based on the original dosage forms of each active component to be combined. In this article, the emphasis is on the PK and biopharmaceutical considerations in the development of FDC products primarily administered as oral dosage forms. The primary rationale for the development of FDC products along with few examples currently available combinations are listed in **Table 1** and **2**, respectively.

TABLE 1: FEW EXAMPLES REPRESENTING THE RATIONALE FOR THE DEVELOPMENT OF FIXED DOSE COMBINATION PRODUCTS

Rationale	Example of FDC products
Treatment Synergy (complimentary mechanism of actions)	Short term Treatment (Acute therapy): Artemeter/Lumefantrine (Malaria) Everolimus/Cyclosporine (Immune suppression) Long term Treatment (Chronic therapy): Ramipril/Felodipine (Hypertension) Atenolol/Amlodipine (Hypertension) Azidothymidine/Lamivudine /Abacavir/Nevirapine (HIV infection) Pioglitazone/Metformin (Diabetes) Metformin/Glipizide (Diabetes)
Bioavailability Enhancement	Lopinavir/ritonavir (Lopinavir is a CYP and Pgp substrate; Ritonavir inhibits gut CYP and Pgp resulting in higher oral BA of lopinavir) Amoxicillin/Clavulenate (Bacterial infection), Levodopa/Carbidopa/Entacapone(Parkinson's)
Multiple Indications (co-morbid disease states)	Amlodipine/Atorvastatin (Hypertension and Hyperlipidemia) Diclofenac/Chlorzoxazone (Inflammation and muscle sprain)
Adverse Event Management	Ibuprofen/Famotidine (Co administration of proton pump inhibitor to overcome hyperacidity related side effects of ibuprofen) Morphine/Methylnaltrexone (To overcome morphine induced constipation by methylnaltrexone)

TABLE 2: A LIST OF FEW REPRESENTATIVE EXAMPLES OF FIXED DOSE COMBINATION PRODUCTS

Therapeutic Area	Brand	Combination	Dose Combinations, mg (Dosage Form)
Diabetes ⁸	Metaglip TM	Metformin/Glipizide	250/2.5, 500/2.5, 500/5 (Tablet)
Hypertension/ Dyslipidemia ⁹	Caduet [®]	Amlodipine/ Atorvastatin	2.5/10, 2.5/20, 2.5/40, 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, 10/80 (Tablet)
HIV ¹⁰	Kaletra [®]	Lopinavir/Ritonavir	200/50, 100/25 (Tablet)
Bacterial Infection ¹¹	Augmentin [®]	Amoxicillin/ Clavulanate	250/125, 500/125, 875/125 (Tablets) 125/31.25, 200/28.5, 250/62.5, 400/57 mg (chewable tablets or in 5 mL suspension)
Tuberculosis ^{12, 13}	Rifater [®]	Rifampin/Isoniazid/ Pyrazinamide	120/50/300 (Tablet)
Allergy ¹⁴	Clarinet D [®]	Desloratidine / Pseudoephedrine	5/240 (Extended Release Tablets)

Development strategy based on approval status of the drug combination:

An FDC product may be a combination of two or more drugs in different stages of development. The FDA guidance recognizes three types of combinations: two or more marketed/approved drugs, a new molecular entity (NME) with marketed drug(s) or two or more unmarketed/investigational drugs which are being co-developed. Different strategies need to be applied in the development of the FDC depending on the development stages of the products to be combined.

Combination of approved drug products:

For an approved drug product the exposure, safety, efficacy and dose range is usually well characterized in the target patient population. The development of an FDC product that is a combination of two or more approved drug products requires further information in addition to the existing efficacy, safety and PK of each individual approved product. A flow chart of the feasibility assessment for the development of an FDC product is given in **Fig.1** for a scenario of combining two or more drugs that are already approved for mono-therapy. To begin with; lack of undesirable PK and pharmacodynamic (PD) interaction for the targeted indication must be established.

Additionally, the FDC must be bioequivalent to the individual components of the combination administered as individual innovator dosage forms or other dosage forms as per local regulatory requirements. In few countries, the formulation proven to be bioequivalent to the innovator may be used as comparator, if the innovator formulation is not marketed/available for study conduct, however, this is subject to the inter and intra subject

variability associated with the results of study confirming bioequivalence of the comparator with the innovator formulation. In case of bias in the 90% Confidence interval, this might be a regulatory challenge, in terms of approval.

To establish the lack of PK/PD interactions between the individual components, it is important to understand the PK and PD properties of the components of the proposed FDC. In some cases, the FDC is developed based on the PK or PD interaction to enhance therapeutic efficacy. An example of this type of FDC is enhancement of bioavailability of the drug by either maximizing the intestinal uptake of the drug or by protecting the drug from presystemic degradation by combining with inhibitors of enzyme or efflux transporter. This strategy is especially prevalent in HIV and hepatitis C virus (HCV) treatment, where for example, ritonavir is used as an enzyme inhibitor to enhance the bioavailability of other anti-retroviral drug¹⁵.

For an FDC of Drug A and Drug B of defined dose, the following information has to be generated to register the product:

- If Drug A and Drug B have the same pharmacological end point (e.g., both drugs reduce blood pressure), the efficacy of FDC (AB) product should be better than Product A alone or Product B alone, while the safety is better or comparable. This will required clinical evaluation.
- A general requirement is that the FDC(AB) product should be bioequivalent in terms of rate and extent of absorption of Drug A and Drug B following oral administration relative to the co-administration as Product

A + Product B at steady-state. This means that the presence of one drug in the combination is not altering the PK of other drug when co-administered.

- If Drug A and Drug B have independent end points [e.g., Drug A reduces high blood pressure; Drug B addresses dyslipidemia],

then the efficacy of FDC(AB) corresponding to each end point is expected to be similar or better than Product A or Product B administered alone while the safety of each component is expected to be similar. This may not require clinical evaluation.

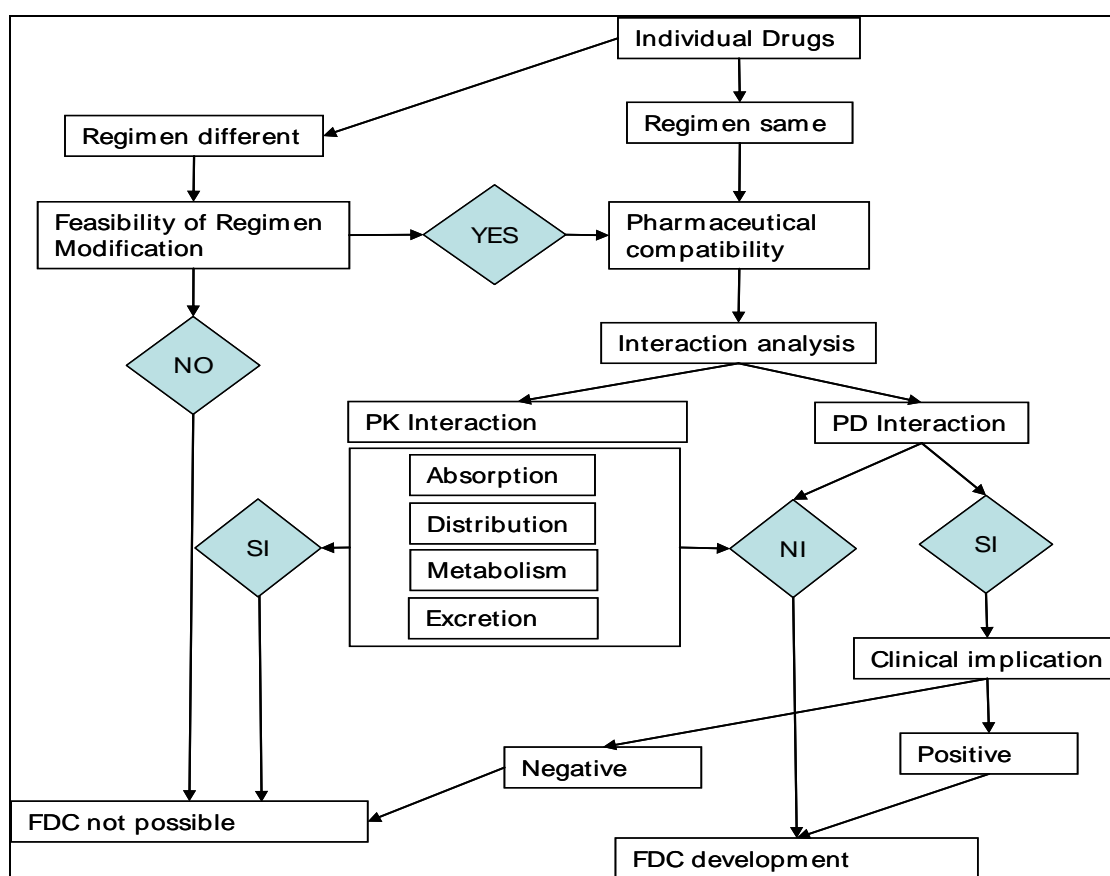


FIG. 1: A FLOW CHART TO GUIDE THE FEASIBILITY ASSESSMENT OF THE DEVELOPMENT OF A FDC PRODUCT CONSISTING OF TWO OR MORE APPROVED INDIVIDUAL PRODUCTS

FDC: Fixed dose combination; NI: No Interaction; PD: Pharmacodynamic; PK: Pharmacokinetic; SI: Significant Interaction

Combination of a new molecular entity (NME) and approved drug product(s) into single FDC product:

One of the most challenging scenarios in FDC product development is when the intended FDC product is to combine an NME(s) and approved product(s). In this case, the safety, efficacy and dose range of NME should be first established independently in a reasonable size of target patient population; however, this may not be possible. For example, in case of Malaria, Tuberculosis or HIV where the World Health Organization (WHO) recommends multi-drug therapy, evaluation of a single molecule (NME) may be a challenge. Often

in such cases, the clinical dose range is not established for the NME. Once the effectiveness and clinical dose range is established with the final market image (FMI) of the NME, the above discussed development considerations for the approved drug combination would apply in this case as well.

Combination of two or more new molecular entity (NME) drugs into single FDC product:

If the intended FDC product is to replace two or more NME products, at first, the safety, efficacy and dose range of each NME should first be established independently in a reasonable size of

target patient population. Some examples of such combinations are described by Britten et al.¹⁶. The International Conference on Harmonisation (ICH) guidance of Technical Requirements for Registration of Pharmaceuticals for Human Use states that data to support a rationale for the combination should be provided prior to starting the clinical study¹⁷. In general, toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with advanced cancer are not warranted. According to the ICH guidance and Food and Drug Administration (FDA) guidance, for combinations of two early stage (Phase II) entities, nonclinical combination toxicity studies are recommended to support clinical trials^{17, 18}.

If the human toxicity profile of the pharmaceuticals has been characterized, a nonclinical study evaluating the combination is not usually warranted. This is a major challenge because often data to support the rationale is not very clear when combining two NMEs. According to the FDA guidance for co-development of two or more unmarketed investigational drugs for use in combination the main criteria are¹⁹:

- i. Combination is intended to treat a serious disease or condition
- ii. Compelling biological rationale for use of the combination
- iii. Novel drug class that has not been previously combined
- iv. Compelling preclinical rationale for

combination: *in vivo* or *in vitro* or short-term clinical study (possible approval in case of unmet medical need) showing combination has more than additive activity or a more durable response

In the above described scenarios, it is a minimum requirement to conduct a single PK drug interaction study, bioavailability/bioequivalence (BA/BE) study and a single well-controlled clinical efficacy/safety study in target patient population to register an FDC product. In the sections below, the study design criteria pertinent to PK drug interaction and BA/BE are discussed in detail.

The clinical study designs pertinent to efficacy and safety end point evaluation primarily depend on the nature of the pharmacology of each drug and type of the target indication (or indications), which are beyond the scope of this review. However, for readers benefit, few literature references on the expert reviews on the FDC products related to various indications are provided in **Table 2**.

The importance of the FDC products and their impact on public health was recognized by the regulatory authorities and relevant guidelines were developed for the industry to assist the development of suitable products (**Table 3**). These guidelines include the considerations for clinical pharmacology and biopharmaceutics, chemistry, manufacturing and controls, microbiology/virology and labeling.

TABLE 3: REGULATORY GUIDELINES FOR THE DEVELOPMENT OF FDC

S. No	Authority/ country	Implementation/ Act
1	FDA ¹⁹	NDA pathways for FDC products for drugs already approved by the FDA. With advances in genomics and cell biology, regulation has also advanced in concert
2	WHO ²⁰	Regulatory landscape outside of the United States, the World Health Organization's Guidelines for Registration of FDC Medicinal Products is a good reference for general advices
3	USA and European Union (EU) ⁴	Development of FDC products/ 21 CFR 300.5 and Art 10b of Directive 2001/83/EC
4	FDA ²¹	Guidance to the industry on the clinical evaluation of estrogen/ progestin combination drug products
5	WHO ⁵	Approved the expedited process to review FDC medicines and co-packaging of existing therapies for the treatment of HIV/ AIDS in developing countries

6	FDA ³	In 2006 to encourage the sponsors to apply for approval of the FDC products and co-packaged versions of previously approved anti-retroviral therapies for the treatment of HIV
7	FDA ²²	Guidance on co-development of two or more un-marketed investigational drugs for use in combination was published in the Federal Register and is soliciting public comments

Clinical Considerations:

Dose strengths:

One of the often cited disadvantages of FDC products is the lack of flexibility due to availability of limited dose strengths. Therefore, it is important to decide the number and dose strength combinations to be developed. In the development of FDC products, it is always important to understand the factors that influence the selection of dose strength of each component of the combination product. The selection of the number of dose strengths depend on the medical rationale and/or the number of doses available for each drug component to be combined. For example, the potential number of possible combination product dose strengths can be generated by combination of the available dose strengths of each individual product as shown in the table below:

TABLE 4: FDC DEVELOPMENT COMBINATION MATRIX

FDC(A/B) = 3x3 = 9 possible dose combinations	Product A (3 doses)			
		x	y	z*
Product B (3 doses)	a	x/a	y/a	z/a
	b	x/b	y/b	z/b
	c*	x/c	y/c	z/c*

* =highest dose in individual products and the FDC

The calculation of number of dose strengths for more than 2 drug combinations (e.g., 3 drugs, 4 drugs) is more complex and therefore, it is not a general rule that number of possible dose strengths depend on the number of doses available for each individual product, but is more dependent on the patient need and the combination of strengths used by majority population. The principle of dose strengths for combinations are much simpler for products such as Kaletra[®] (developed with the intention of enhancing the bioavailability of the active drug by inhibiting the metabolizing enzyme) where the enzyme inhibitor dose is constant while the doses of active component are varied.

In summary, the number of FDC dose strengths to be developed should be guided through medical need and other regulatory guidelines^{3, 4, 18, 20}. The size of the product based on the doses of the individual component also needs to be considered

to determine the feasibility of FDC development. It is essential that a clear development need and rationale for the number of FDC dose strengths should be finalized prior to initiating the FDC development activities as these impact the key clinical study designs pertinent to PK interaction studies, biopharmaceutical studies, pivotal safety and efficacy studies.

Pharmacokinetic Consideration:

Drug interaction studies:

The investigation of PK interaction potential becomes essential especially when the change in drug exposure can explain the PD activities of the active drug components that represents overall efficacy or safety of the combination. When a meaningful PK-PD relationship does not exist even for one drug in the intended combination, an independent PD interaction study or a hybridized PK-PD interaction study can be considered.

Since PD interaction study design considerations are associated with specific disease indication, the discussion on this topic is beyond the scope of this review article. In general, the intent of conducting PK interaction studies is to understand whether the drug components to be combined affect each other's PK profiles in humans (or in a given clinical setting). In the case of FDC development (see **Fig. 1**), it is expected that the pharmacokinetics of the planned combination drugs is not affected in the presence of each other. However, in few cases, a PK interaction may constitute the rationale for the FDC. For example, Kaletra[®], an FDC product, has two active drug components lopinivir and ritonavir, and the choice of this combination was based on low dose ritonavir's (potent CYP3A inhibitor) induced increase in the steady state plasma concentration of lopinavir (a CYP3A substrate) by 15-20 fold at clinical doses^{23, 24}.

The resulting high concentrations of lopinavir are responsible for its anti-viral activity. The PK drug interaction study design (number and nature of subjects, dosage administration, data analysis and

interpretation) considerations in the development of FDC products are not different from the drug interaction studies that are generally conducted to register a single active NME (mono-therapy) product.

The drug-drug interactions study considerations when developing an FDC are same as during a single drug development and will not be covered here. Briefly, the study population is typically healthy subjects except in cases where it is not possible or acceptable as in oncology trials. The sample size in the PK interaction studies is generally determined based on the variability associated with the pharmacokinetics of each drug to be combined. In general, a drug with higher inter/intra-subject variability dictates the sample size to provide adequate power to detect any interaction potential. In majority instances, since the primary objective of the drug interaction study is to understand the trend for interaction potential, a limited sample of 16-24 subjects applies in general.

The development of FDC products are driven by the dosing regimens of the active components of individual products to be combined. For instance, it is easy to combine the products which are administered at the same time (once daily in the AM or PM), same duration (q.d., b.i.d. or t.i.d. for each combining drug) and under similar conditions (each drug administered under fasting conditions or fed conditions). If any of these variables are different for one of the drug components compared to the other drugs of the combination, the development becomes significantly complex and the development program has to be customized accordingly (see Figure 1). From the PK interaction study perspective, it is ideal to use the individual dosage regimen conditions and the study should be conducted first with the highest dose strength of each drug of the combination product. If there is no PK interaction observed at the highest dose strength of each drug to be included in the combination, the lack of interaction could be extrapolated to lower dose strength combinations when each drug component exhibits linear and dose proportional pharmacokinetics. In case there is a significant PK interaction at the highest dose strength of the combination, the development of FDC could be abandoned or if the medical rationale

outweighs the limitation of PK interaction. Pharmacokinetic interaction with different dose combinations has to be evaluated such as with the dose combinations of low/low, low/high, high/low and high/high to assess the effect of dose on the degree of PK interaction. The decision on these number of dose combinations and interaction studies depends on the therapeutic window of each drug and the known PK (exposure) - efficacy/safety (response) relationship of each drug.

The test and reference treatments in the PK interaction study should be defined based on the overall clinical goal of the FDC product and individual drug characteristics of the combination. When possible, PK drug interaction should be studied at steady-state of each drug. The drug with shorter elimination half-life generally sets the steady state duration. Even though a multiple dose steady state PK interaction study is required, sometimes, it may be difficult to conduct study under these conditions due to very long half-life of the one the drug components to be combined, which may limit the establishment of steady state. In such cases, a strong judgment on the utility of single dose PK interaction study should be made or a population PK study in pivotal clinical efficacy or safety study should be considered.

In general, cross-over and open label studies are preferred in these PK interaction studies in healthy subjects or patient population. This design will allow the ability to normalize the inter-subject variability across the treatment types. As discussed above, sometimes, crossover studies are not possible with adequate washout period due to very long half-life of one/more drugs to be combined. In such cases, parallel group design studies can be considered with adequate sample size. A good review on BE challenges and the strategies adopted to address this has been published²⁵.

A typical PK drug interaction study design can be described as follows for two drugs to be combined (Drug A (Product A) and Drug B (Product B)): An open label, three treatment period, three sequence, cross-over design with adequate washout between treatment periods with PK sampling on pre-determined steady state day. Each sequence will receive the following treatments:

Treatment 1: Multiple dose administration of Product A [Reference treatment for Drug A]

Treatment 2: Multiple dose administration of Product B [Reference treatment for Drug B]

Treatment 3: Multiple dose administration of Product A + Product B [Test treatment]

The key PK parameters such as time (T_{max}) to reach steady state maximum plasma concentration ($C_{max_{ss}}$), total systemic exposure during the dosing interval ($AUC_{0-\tau}$), elimination half-life ($t_{1/2}$) and oral clearance (CL/F_{ss}) are compared between the test and reference treatments to assess the extent of interaction between the drugs. The statistical interpretation of the data generally comply with regulatory guidance set for BA/BE studies comprising of the geometric mean ratio of specific PK parameter between test and reference treatment should be within the 90% confidence interval of 0.8 to 1.25 to conclude no PK interaction.

Biopharmaceutical considerations:

Development of a suitable formulation or dosage form that can accommodate all the active drug components at their corresponding doses is critical for the success of FDC product. The final FDC product should possess all the required ideal characteristics of ease of administration, appropriate size/shape and should be able to accommodate the doses to be combined. In some instances, even though medical rationale support the development of FDC product of two or more drug components, an FDC cannot be developed due to technical reasons such as:

- a) large doses of drugs that cannot be combined into a single unit dosage form
- b) physicochemical incompatibility of the drugs to be combined (which ultimately affect the integrity of the FDC and thus may also impact the PK of each drug)
- c) or unique formulation requirements for each active component including requirement of specific excipients, specific manufacturing processes etc.

The starting point for the formulation development activities for the FDC product is usually based on prior experience with the development of the individual drug products of the combination. In many cases, due to the potential for significant differences in the nature of drug components or products to be combined as one single FDC product, the early stages of the formulation development effort involves the development of several prototype FDC formulations.

The development of prototype concepts are primarily based on the physico-chemical compatibility testing (in case of incompatibility, drug components have to be separated from each other through innovative methods), variability in manufacturing processes (e.g., wet granulation for one component versus dry granulation requirement for the other), stability reasons (one process may cause stability issues for one product compared to other) and, at the end, due to economic reasons (more sophisticated method such as multi-layered products require more resources compared to conventional dosage forms). Few technical development aspects of the FDC products are discussed elsewhere^{7,26}.

The selection of final robust and cost-effective FDC formulation is possible from information generated using prototype concepts. After the development of various prototype formulations, suitable number of formulation concepts can be screened and selected for in vivo human testing from the in vitro dissolution information (and its relevance to established IVIVC, if any) or through preclinical studies. Usually, these prototype formulations represent very small laboratory batch sizes and do not represent large commercial batches.

However, all the selected prototype concepts for human testing must be developed under Good Manufacturing Practice (GMP) conditions suitable for clinical use with appropriate regulatory Chemistry Manufacturing and Control (CMC) information. Then the selected prototype formulations should be studied in the relative bioavailability studies.

Relative bioavailability studies to screen prototype FDC formulations:

The relative bioavailability studies are also generally referred to as pilot bioavailability studies. The primary objective of a pilot bioavailability study is to understand the oral bioavailability of active components of the FDC product relative to the free combination of individual products. These pilot studies would help formulation development scientists to test the formulation principles of various prototype concepts and to finally select one formulation as is or with further modifications for commercial scale development. If the results of pilot bioavailability study are very different from the expected outcome, new prototypes could be developed and tested further in separate pilot bioavailability studies followed by selecting the final formulation for commercial scale. In any case, the study design considerations are the same for any pilot bioavailability study.

The study design generally includes open-label, single dose, cross-over study in healthy subjects. The limitations for use of cross-over study and healthy subjects are similar to what is described in PK interaction study. The sample size is generally estimated based on the inter/intra-subject variability associated with the PK of active components of the combination product and also follows the guidelines described for PK interaction studies. The overall goal of the pilot bioavailability studies is to observe the trend for differences in the rate and extent of absorption for various prototype formulations relative to the reference treatment of free combination. Thus, the size of the study could be smaller than the pivotal/definitive BE studies.

The conclusions from the pilot bioavailability study are help in making the decision to move forward with next phase of formulation development. The pilot bioavailability studies are generally conducted under fasting conditions (overnight) unless otherwise required by design. The highest dose strength of the planned FDC combination products is generally studied in the development of prototype formulations.

A general study design for pilot bioavailability study containing three prototype formulations of FDC(A/B) product can be described as follows: an open label, four treatment, four sequence, cross

over study to evaluate the bioavailability of 3 prototype formulations of FDC(A/B) relative to the free combination of individual drug products of A and B:

Treatment 1: Prototype-1 formulation of FDC(A/B) (test 1)

Treatment 2: Prototype-2 formulation of FDC(A/B) (test 2)

Treatment 3: Prototype-3 formulation of FDC(A/B) (test 3)

Treatment 4: Free combination of individual Product A + Product B (reference)

The treatment duration and washout period are determined by the drug component with the highest elimination half-life value. The PK sampling must cover five half-lives of the drug with highest elimination half-life followed by adequate washout period. The key PK parameters such as Tmax, Cmax and AUC from 0 to last measurable concentration and infinity are compared between each test treatment and reference treatment. The statistical interpretation of the data generally comply with regulatory guidance set for BA/BE studies comprising of the geometric mean ratio of specific PK parameter between test and reference treatment should be within the 90% confidence interval of 0.8 to 1.25 to describe the differences in bioavailability³.

The *in vivo* PK parameters of a prototype formulation which are similar to the reference treatment are generally considered for further development (scale-up) and will be studied for definitive BE. The prototype formulation that is scaled-up according to the commercial batch requirements is referred as Final Market Image (FMI) formulation.

Pivotal bioequivalence studies (registration bioequivalence studies):

It is expected that the Final Market Image (FMI) formulation should be bioequivalent to the free combination of respective individual drug products of active drug components of the combination. As described in the three potential scenarios of FDC product development, the individual drug products of the free combination could be the

marketed/approved drug products of the active drug components (in case of approved products scenario) or the formulations that are used in the pivotal clinical efficacy/safety trials.

The formulations used in the clinical trials are generally referred to as clinical service formulations (CSFs). The CSFs may be different from the marketed individual products in terms of composition (over encapsulation) and appearance relative to the marketed products to allow blinding in clinical efficacy/safety trials. In such cases, respective BE studies should be conducted between CSF formulations and marketed products as per the requirements of BE studies for formulation changes²⁷.

In the sections below, it is assumed that the reference treatment of free combination of individual products meet the appropriate standards to bridge to the FMI formulation of FDC. The FMI formulation must meet the registration and commercial batch size criteria, which are defined in the regulatory guidance set for the BE studies²⁷. In most instances, one BE study is conducted with the highest dose strength of the FDC product series, and the BE is extrapolated to lower dose strengths when the drug components exhibit dose proportional PK and the composition and method of manufacture of lower doses strengths are very much similar to the highest dose strength.

The BE study design with the FMI formulation is similar to studies done for registration of generic products¹⁸. The FMI product should meet the registration criteria of geometric mean ratios and the corresponding 90% CI should fall in the range of 0.8 to 1.25. In case of deviations of the results from this window, appropriate clinical efficacy/safety related aspects to be provided in order to justify that such excursions do not impact safety or efficacy of the FDC product. The BE studies are generally conducted under fasting conditions following single dose administration unless the drug components/products to be combined have special food restrictions in their use and the individual products are special dosage forms such as enteric coated formulations or sustained/modified release formulations (For specific guidance please refer to **Table 3**).

The sample size in BE studies is strictly governed by the drug component with the highest inter/intra-subject variability. The sample size is also determined by the assumptions regarding the difference between test and reference products (5% or 10%) and the power of study (80% or 90%). More in-depth discussion on this could be found elsewhere^{28, 29, 30}, however, all these sample size determinants should be pre-specified in the protocol of the BE study. In case of highly variable drugs with the intra-subject variability >50% requiring very high number of subjects, replicate study design is generally recommended. In the replicated design, each subject receives the test FMI treatment and the reference of free combination of individual products twice. The PK sampling and wash-out treatment durations are similar as described in PK interaction study and pilot bioavailability studies.

A general study design for registration BE study with the FMI formulation of FDC(A/B) product can be described as follows:

an open label, two treatment, two sequence (in case of replicate 4-sequence), cross over study to evaluate the BE of FMI formulation of FDC(A/B) relative to the free combination of individual drug products of A and B:

Treatment 1: FMI formulation of FDC (A/B) (test)

Treatment 2: Free combination of individual Product A + Product B (reference)

In order to claim BE, the rate and extent of the absorption of each component of the FDC product should be equivalent to that of the corresponding components in the free combinations. The rate and extent of absorption are assessed based on the area under the plasma concentration-time curve to the last quantifiable (above the lower limit of quantification, based on a fully validated and documented bioanalytical method) time point (AUC_{0-t}) and the area extrapolated to infinity ($AUC_{0-\infty}$), peak plasma concentration (C_{max}) and time to peak plasma concentration (T_{max}).

Statistical analysis of the PK parameters is recommended using two way one-sided analysis of variance (ANOVA) for log transformed AUC and C_{max} , while T_{max} only requires descriptive

statistics. Calculation of point estimate and 90% confidence interval of the ratio of the parameters AUC and C_{max} for the test and reference formulations are recommended. Bioequivalence criteria set by the health authorities is a confidence interval 80 to 125 percent, with the AUC and C_{max} values of all the active moieties in the new product entirely falling within the pre-specified range.

Food effect bioavailability studies:

Since the FDC product is a combination of individual drug products of active drug components, evaluating the effect of food on the oral bioavailability of each active component in the FDC product is generally recommended by the EMA. However, the FDA does not require a fed BE study for the combination.

The food effect data is important to provide guidance on the administration of FDC product. A food effect study is also considered at the time of prototype development stage in the selection of FMI formulation when food plays a critical role in the bioavailability of active drug components and their formulations.

Typically food effect bioavailability studies are conducted after single dose administration in healthy subjects in a cross-over design fashion between fed and fasting conditions. A high fat breakfast meal is generally used in these studies²⁶. The sample size requirements and study design considerations are very much similar to that is described in the BA/BE studies.

A general study design for a food effect bioavailability study with the FMI formulation of FDC(A/B) product is as follows: an open label, two treatment, two sequence, cross over study to assess the effect of food on the bioavailability of orally administered of FMI formulation of FDC(A/B):

Treatment 1: FMI formulation of FDC(A/B) – under fed conditions (test)

Treatment 2: FMI formulation of FDC(A/B) – under fasting conditions (reference)

The PK parameters are compared between the test and reference treatments for each drug component. The data analysis and interpretation are similar to

that described in the BA/BE studies. If there is a significant food effect (using high fat meal) on the bioavailability of FDC product, then the effect of different meal types (such as low fat, low calorie) should be considered to identify the optimal meal type that is required for dosing of FDC product as needed.

Requirement of number of bioequivalence studies and Biowaivers:

It is essential to recognize that a biopharmaceutics development plan is required early on to determine the number of BE studies required to register an FDC product consisting of several dose strengths. In general, the need for specific number of BE studies depend up on the PK characteristics of each drug component, the quality and quantity of excipients used across all dose strengths, and the applied manufacturing process across all the dose strengths.

A limited (one or very few) number of BE studies would be sufficient under the following conditions:

- If the drug components in the FDC exhibit dose proportional PK within the developed FDC dose strengths
- When the qualitative composition of excipients (e.g., nature of the excipients) and quantitative composition of excipients (e.g., excipients to active drug components ratio) is related across all the dose strengths
- When the manufacturing process and equipment are similar across all dose strengths.

In these instances, limited number of BE studies can be conducted with few dose strengths and obtain the waiver for conducting BE studies for the other (low) dose strengths by demonstrating similarity of in vitro dissolution profiles. More information on the biowaiver requirements and specifications for similarity of dissolution profiles is available in the regulatory guidances^{31, 32}.

In general, it is expected that in vitro dissolution similarity should be established in three pH media (pH 1.0, 4.5 and 6.8) which simulate gastro intestinal pH conditions. The dissolution specifications such as apparatus (paddle or basket), speed of the basket/paddle (rpm) and volume of

dissolution media could be defined as per the general requirements of regulatory guidance for setting dissolution method specifications for each active component³³. The similarity of dissolution profiles are compared through f2 similarity factors, which is reviewed elsewhere³¹.

An example where the biowaiver strategy was successfully implemented was for a combination of amlodipine and atorvastatin (Caduet®)³⁴. Amlodipine/atorvastatin FDC is available in 11 different dose proportions including 2.5/10, 2.5/20, 2.5/40, 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, and 10/80 mg. Bioequivalence for C_{max} and AUC with reference to the free combination was established in 126 healthy volunteers in a randomized, open label, two way cross over study design with a 14 day wash out at the highest dose combination (10 mg amlodipine besylate and 80 mg atorvastatin calcium, n=62) and one lower dose combination (5 mg amlodipine besylate and 10 mg atorvastatin calcium, n=64) in two separate studies. A total of 11 dose strengths were registered using the data from 2 BE studies and biowaiver approach³¹.

CONCLUSION: The development of FDC products is driven by the medical need and patient compliance in multi-drug therapy. The development of FDC product involves the assessment of potential for PK interaction, formulation development dependent biopharmaceutics studies and appropriate clinical efficacy/safety studies. The potential for PK interaction between the individual drugs in a proposed FDC product must be assessed similar to the traditional PK interaction studies designed during the development of new molecular entities. The recent increase in the development of FDC products have been helpful to gain understanding the general development considerations including formulation development and associated biopharmaceutics aspects. The formulation development program involves pilot stage program followed by registration BE studies with a requirement for food effect bioavailability studies. Based on the nature of the drug components of the FDC product, a limited number of BE studies are adequate to register several dose strengths.

Future Recommendations:

Based on the current FDC development, new technologies for formulation, novel probability of successful assessments for BE studies; and better understanding of the PK of the individual drug components for drug-drug interactions are warranted before venturing the development of the FDC. The application of in-silico methods to evaluate the feasibility of development and thereby reduction of number of clinical studies, specifically for NMEs could be further explored as a realistic approach to rational drug development in terms of combination therapy. Further, the in-silico methods could also help in debating the need for the clinical drug-drug interaction study, and if justifiable based on strong existing data, could be critical in either waiving the interaction study, or conducting a study in minimum population.

The advances in mathematical modeling by simulating clinical trial data using “Trial Simulator” might enhance the likelihood of success of outcome of the trial. In summary, it is important to rationalize the development of an FDC based on patient need and during development, apply all available technologies to minimize the exposure of subjects to trials in terms of number of subjects or number of trials.

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