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Fed Bioequivalence Studies for Immediate Release Drug Products: Beneficial or Wastage?

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SSK and SVS designed the study and wrote the first draft of the manuscript. Author TVD collected the data, performed the statistical analysis and collated the findings. Authors FMS, USK and RVS managed the literature searches and participated in the final write-up. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: The present study was undertaken to understand the need of fed bioequivalence studies for immediate release pharmaceutical products and thereby evaluating the relative appropriateness of guidelines given by the European Medicines Agency (EMA) and the United States Food and Drug Administration (USFDA). Vulnerability to show bioequivalent or non-bioequivalent results on the basis of type of drugs was also assessed.
Study Design: The present work is a meta-analysis involving 162 bioequivalence studies conducted on healthy human subjects.
Place and Duration of Study: Accutest Research Laboratories (I) Pvt Ltd, A-31, Khairne MIDC, TTC Industrial Area, Khairne, Navi Mumbai, 400 709, India, between June 2013 and February 2014.
Methodology: The present meta-analysis included a total of 162 bioequivalence studies of which 81 were conducted under fasted condition and the other 81 studies were conducted under fed condition. The drug products were fixed dose combinations and mono drug products for 22 and 140 studies respectively representing all the classes of Biopharmaceutics Classification System (BCS). The bioequivalence was assessed by standard criteria laid down by regulatory authorities. The results were correlated with the

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respective condition of study (fasted or fed) and the corresponding BCS class of the drug product. The observations were discussed in the light of available literature.
Results: A total of 78 and 74 studies conducted under fasting and fed conditions respectively had bioequivalent results. All studies conducted on fixed dose combination products had bioequivalent results. Five drug products had bioequivalent results only under fasting condition which proportionately contributed to 6.17% (5/81 fasting studies). These drug products complied only with the EMA guidelines and not USFDA defined passing criteria. All drug products belonging to BCS classes I and III showed bioequivalent results whereas drug products belonging to BCS class IV contributed to 80% of the total non-bioequivalent studies.
Conclusion: The EMA approach can be followed for BCS class I drugs while USFDA approach looks better for remaining drug products. Further research work is required to confirm the trend observed in our meta-analysis.

Keywords: Bioequivalence; immediate release products; solubility; permeability.

1. INTRODUCTION

Life expectancy of human beings has increased globally during the last few decades due to the new drug discovery (brand-name drugs) as well as generic drug production. The rising cost of medication has been contributing to the overall cost of health care and thus receives considerable attention globally. A major strategy for lowering the cost of medication, and thereby reducing its contribution to total health care costs, has been the introduction of generic equivalents of brand-name drugs [1]. This strategy has been effective in reducing total prescription cost significantly without compromising quality [2]. Recently the generic pharmaceutical industry has become increasingly more global and is manufacturing multisource drug products for both domestic and international markets. Multisource drug products are products marketed by more than one manufacturer that contain the same active pharmaceutical ingredient (API) or drug substance in the same dosage form, the same strength and are given by the same route of administration [3,4].

According to the World Health Organization (WHO), multisource or generic drug products are pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent [3]. Multisource pharmaceutical products that are both pharmaceutically equivalent and bioequivalent (thus therapeutically equivalent) are considered interchangeable. Documentation of therapeutic equivalence may be shown directly or indirectly by various test methods deemed suitable by regulatory authorities. Among these, determination of bioequivalence is the most important for therapeutic equivalence, which is also the most difficult part of generic drug product development [5].

Bioequivalence (BE) studies are the commonly accepted method to demonstrate therapeutic equivalence between two medicinal products. This approach resets on the understanding that measuring the active moiety or ingredient at the site of action is not generally possible and, furthermore, that some relationship exists between the efficacy/safety and concentration of the active moiety and/or its important metabolite or metabolites in the systemic circulation. Though accepted worldwide, measurement of drug levels in biological matrix is not a full proof method to prove bioequivalence and subsequently therapeutic equivalence. Savings in time and cost are substantial when using bioequivalence as an established surrogate marker of therapeutic equivalence. For this reason, the design,

performance and evaluation of bioequivalence studies have received major attention from academia, the pharmaceutical industry and also the health authorities. Bioequivalence studies need to be carefully designed to take into account biopharmaceutical, ethical, medical, pharmacokinetic, analytical and statistical considerations.

Designation of multisource (or generic) drug products as therapeutic equivalents to a reference drug product (usually the brand product) requires regulatory approval. However, approaches for regulatory approval of these drug products vary among different regions and/or countries, which in some cases, may render additional bioequivalence studies necessary to meet the requirements of each of these regulatory agencies [5]. With respect to the administration of food during BE studies, majority of the regulatory authorities ask for bioequivalence studies under fasting as well as fed conditions for modified release drug products. However, there is no such consistency for immediate release drug products. Surprisingly, for immediate release multisource drug products, different regulatory bodies have different recommendations or requirements to conduct bioequivalence study. The European Medicines agency (EMA) guidelines or the United States Food and Drug Administration (USFDA) regulations are commonly referred by several other regulatory authorities while deriving specific requirements or recommendations. However, the revised EMA guideline still differs from the USFDA regulations with respect to the administration of food during the conduct of BE studies. The major difference lies in the requirement of fed bioequivalence study in addition to the fasting BE study.

The approach of the USFDA is that in order to demonstrate BE, a study conducted under fed conditions is required in addition to a fasted study except for in the following situations: (i) Drugs belonging to class I of Biopharmaceutics Classification system (BCS) where both test product and Reference Listed Drug (RLD) are rapidly dissolving and have similar dissolution profiles, (ii) when the label of the RLD states that the product should be taken only on an empty stomach, or (iii) when the RLD label does not make any statement about the effect of food on absorption or administration [6]. In contrast, only a single study conducted in fasting state is required by EMA assuming that it is the most sensitive condition to detect formulation differences. Therefore, the food effect may exist but it is not believed that products with conventional pharmaceutical technology will be equivalent in fasting state and non-bioequivalent in fed state as the fasting state is considered more discriminative. Consequently, it is not considered necessary to increase the regulatory burden for such products. Based on this principle, for drugs that are taken only in the fasted state or irrespective of food, a BE study with that drug must be conducted in fasted state. However, in situations where it is recommended in it's labeling that a reference product be taken only in the fed state, a BE study conducted with that product should generally be conducted in fed state. This "generally" means that if the fed state is recommended in the Summary of Product Characteristics (SPC) in order to avoid tolerability problems associated with chronic use in patients, a fasted state study is acceptable as a single dose in healthy volunteers but, if the fed state is required for pharmacokinetic reasons resulting in a systemic exposure that is notably different, the study should be performed in fed state. There is an exception to this approach for products (test or reference) employing special (not conventional) technology (e.g., micro-emulsions and solid dispersions) that can be taken irrespective of food in that for these products BE has to be shown in both fasted and fed state [7].

The advantage of testing the performance of products in the fasted state and the fed state with a high-fat, high-calorie meal, such as is required for many conventional products in the United States of America (USA), is that the extremes of the food effect are tested and BE with intermediate meals can be assumed. In European Union (EU), if the SPC of the

reference product indicates administration with food but does not make specific recommendations with respect to the composition of the meal, studies should employ a high-fat, high-calorie meal and hence, bioequivalence when products are taken with meals with a different more moderate composition, which might be more realistic, is not investigated. The demonstration of bioequivalence in the fasting state and after a high-fat high-calorie meal would represent a bracketing approach where all intermediate meal compositions could be assumed [8].

The demonstration of bioequivalence in the worst-case scenario of a high-fat high calorie meal could be considered debatable and not representative of all possible meal compositions. The high-fat, high-calorie meal might be representative of a dinner or a lunch of some European countries but, would not normally be considered a typical breakfast. Another issue of debate is the composition of the high fat, high-calorie meal. In the USFDA, the ingredients of the high-fat, high-calorie meal are specified, i.e., an example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. In the EU, however, only the caloric content of each component of the meal is specified, which leaves room to employ different types of food according to the dietary habits of the study site. Consequently, the volume, texture, and viscosity of the meal may vary markedly, which could affect the extent of the food effect [8]. The first pass effect and variation in food composition are equally important factors influencing the outcome of fed bioequivalence studies.

Considering the inconsistent approach by regulatory authorities for underlining the need of a fed bioequivalence study for the same drug product in the same dose and dosage form, we planned the present meta-analysis with a primary objective to evaluate the actual need and value addition of fed bioequivalence study. This was considered essential to avoid unnecessary exposure of subjects to the study drugs, cut down cost and time on multiple BE studies if fed studies didn't add any value. On the contrary, if fed studies revealed some value addition, conduction of fed studies would be necessary to ensure entry of truly bioequivalent product in the market though the work load or burden on regulatory authority is increased.

As a secondary objective, we correlated the outcome of every study with the BCS class of the involved drug product. The BCS categorizes active pharmaceutical substances into four different groups according to their aqueous solubility at the highest dose in a volume of 250 ml and intestinal permeability [9]. We expected that failed studies should not be constituted by BCS class I drugs as they have high solubility and high permeability and should be comprised of BCS class IV and II drugs having poor solubility. This was done taking in to account the fact that BCS provides a basis for avoiding unnecessary in vivo bioequivalence studies and significantly reduces the cost and time of developing drug products. BCS has gained importance worldwide as a drug product regulation tool; the system has been formally adopted by the USFDA and EMA [10]. Various drugs are handled separately by the regulatory authorities depending upon their BCS class. Example: BCS I drugs can be considered suitable for bio-waiver based on the comparative in vitro dissolution data.

2. MATERIALS AND METHODS

Various in vivo bioequivalence studies conducted at Accutest Research Laboratories Limited, Navi Mumbai for USFDA submission from year 2005 to 2013 on different drug products belonging to various therapeutic categories and involving at least 24 healthy human subjects per study were included in this meta-analysis. For each drug product, it was necessary to have bioequivalence studies conducted under fasting as well as fed conditions separately. A total of 162 (81 fasting and 81 fed) studies irrespective of the study outcome (bioequivalent or non-bioequivalent) were included in this analysis. For all the drug products included in this meta-analysis, the USFDA recommended fasting as well as fed studies while the EMA required only fasting study.

In addition, these studies had following common features.

a. Conducted adhering to the guidelines documented in International Conference on Harmonization of Good Clinical Practice (ICH GCP) and schedule Y.
b. Conducted with a single dose, two period, two treatment, two sequence, and cross over approach wherein the subjects were dosed with the test product in one period and reference product in another as per the randomization code.
c. All the drug products were immediate release in nature.
d. Calculation of area under curve (AUC_{0-t} and AUC_{0-inf}) and maximum plasma concentration (C_{max}) was done by using the plasma concentration data for each drug product in each treatment.
e. Presence of 90% confidence interval (CI) limits between 80-125% for AUC_{0-t}, AUC_{0-inf} and C_{max} was considered as passing criteria for concluding bioequivalence.
f. Written approval from the independent ethics committee was obtained prior to execution of the clinical phase for every study.
g. All the fed bioequivalent studies involved administration of high calorie, high fat breakfast within 30 minutes of drug administration in each period.
h. The conduction of fasting and fed studies for every drug product was conducted in the same clinical facility with all standard and similar procedures with regards to inclusion of participants and conduction of clinical, bio-analytical and statistical phases. This ensured procedural uniformity thereby avoiding addition of any variability inducing factor.

The results of fasting study with regards to 90% CI for AUC_{0-t}, AUC_{0-inf} and C_{max} were tabulated and compared with those of fed study for each drug product separately. The following observations were made from this comparison.

Observation A: Both fasting and fed studies passing for the given drug product
Observation B: Both fasting and fed studies failing for the given drug product
Observation C: Fasting study passing but fed study failing for the given drug product
Observation D: Fed study passing but fasting study failing for the given drug product

It was decided to conclude that fasting bioequivalence study alone is sufficient if observations ‘A’ and ‘B’ are present and ‘C’ is absent. This would strengthen the approach laid down by the EMA. The need of fasting as well as fed bioequivalence studies was to be underlined if observation ‘C’ is noted for the given drug products in considerable number. This would strengthen the approach laid down by the USFDA.

In case of failed bioequivalence study, we also investigated the presence of any confounding factor (other than those related to food effect) thereby avoiding false conclusion. The drug failing in fasting and/or fed condition was further correlated with its BCS class in order to understand which BCS class is more vulnerable for failure. Though studied, the parameter AUC_{inf} was not considered to judge the passing or failing of any study as it is not considered a primary pharmacokinetic parameter by EMA.

3. RESULTS AND DISCUSSION

A total of 162 studies (81 fasting and 81 fed) were included in the meta-analysis. The drugs formulated in their immediate release dosage form irrespective of their BCS class were included in this study. A total of 22 studies (11 each under fasting and fed conditions) were conducted on fixed dose combination products while remaining studies were conducted on mono drug products (Table 1).

Table 1. Break up of all studies considered in meta-analysis

Total studies involved (n=162)							
Fasting condition (n=81)				Fed condition (n=81)			
MDP (n=70)		FDC (n=11)		MDP (n=70)		FDC (n=11)	
BEQ (n=67)	N-BEQ (n=3)	BEQ (n=11)	N-BEQ (n=0)	BEQ (n=63)	N-BEQ n=7)	BEQ (n=11)	N-BEQ (n=0)

MDP: Mono Drug Product, FDC: Fixed dose combination, BEQ: Bioequivalent, N-BEQ: Non-bioequivalent

The drugs represented various therapeutic categories. The highest number of studies (20.98%) was conducted for drugs acting on musculoskeletal system and the least number of studies (7.40%) was conducted for drugs acting on central nervous system (Table 2).

Table 2. Classification of studies according to therapeutic class of drugs

Sr. no.	**Category**	**No. of studies**	**Proportion (%)**
1.	Cardiovascular system	24	14.81
2.	Central Nervous system	12	07.40
3.	Musculoskeletal system	34	20.98
4.	Endocrinology	20	12.34
5.	Anti-retroviral	24	14.81
6.	Respiratory system	20	12.34
7.	Others	28	17.28
Total		162	100

The passing rate was more in the studies conducted under fasting condition. A total of 78 studies comprising 67 for mono drug products and 11 for fixed dose combinations had shown bioequivalent results under fasting condition. Thus, the passing rate was 96.31% (78/81 studies) under fasting condition. A total of 74 studies comprising 63 for mono drug products and 11 for fixed dose combinations had shown bioequivalent results under fed condition. Thus, the passing rate was 91.35 % (74/81 studies) under fed condition. The fed condition is slightly difficult to meet the bioequivalence criteria for the drug products (Table 1). No study involving fixed dose combination failed either in fasting or fed condition.

We noted following observations from this dataset (Table 3).

(a) A total of 73 drug products had bioequivalent results under fasting as well as fed conditions thereby complying with the passing criteria of the USFDA and EMA. These studies constitute 90.12% of the total studies. These drug products are eligible to seek marketing permission in both territories.

Table 3. Outcome of all studies

Study status	No. of studies	Percentage
Both fasted and fed passing	146 out of 162 total studies	90.12
Only fasted passing	5 out of total 81 fasted studies	6.17
Only fed passing	01 out of total 81 fed studies	1.23
Both fasted and fed failing	04 (2 fasted + 2 fed) out of total 162 studies	2.47
Total		100

(b) Five drug products had bioequivalent results only under fasting condition which proportionately contributed to 6.17% (5/81 fasting studies). These drug products complied only with the EMA and not USFDA defined passing criteria. These studies offer a serious concern as far as the therapeutic outcome is concerned. These studies are suitable to seek marketing approval in European Union but not in the United States. The proportion (6.17%) is very high as far as this risk is concerned. The patients are likely to get benefit of the generic products only under fasting condition though the label mentions to consume it with or without regards to food.

(c) One study (1.23%) had bioequivalent results only under fed condition while 4 studies (2.47%) had non-bioequivalent results under fasting as well as fed condition. These studies were not in compliance with the USFDA as well as EMA defined passing criteria and hence not eligible to seek marketing approval in either territory.

Upon further investigation of all the studies, we noticed that none of the drugs belonging to BCS class I had non-bioequivalent results either in fasting or fed condition. The sub-analysis of failed studies revealed that the failure rate was the highest in BCS class IV. Drug products belonging to BCS class IV contributed to 80% of the total non-bioequivalent studies. This is presented as category A1 showing studies failing under fed condition and category C showing studies failing under fasting as well as fed conditions (Fig. 1). A total of 2 of 10 comprising 20% of the failed studies represented BCS II. This is presented as category A2 showing studies failing under fed condition and category B showing studies failing under fasting condition (Fig. 1).

Administration of a drug product with food may change the bioavailability (BA) by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the BA of a drug product without performing specific mechanistic studies.

Change in gastric emptying time is the most important factor. Presence of food in stomach changes gastric motility to typical postprandial pattern, during which gastric secretion and residence time are increased. Consequently it is usual for rate of absorption of drugs to be slower when taken with meals as compared with fasted state [11]. Food can contain, or become contaminated with xenobiotic which affect hepatic or gut wall drug metabolizing enzymes [12]. Drug chelation, change in splanchnic blood flow and plasma protein binding

are other factors which add to pharmacokinetic variability under fed condition. Our result that the failure rate was marginally higher under fed condition against fasting condition (96.29% vs 91.35%) could be because of collective impact of all these factors.

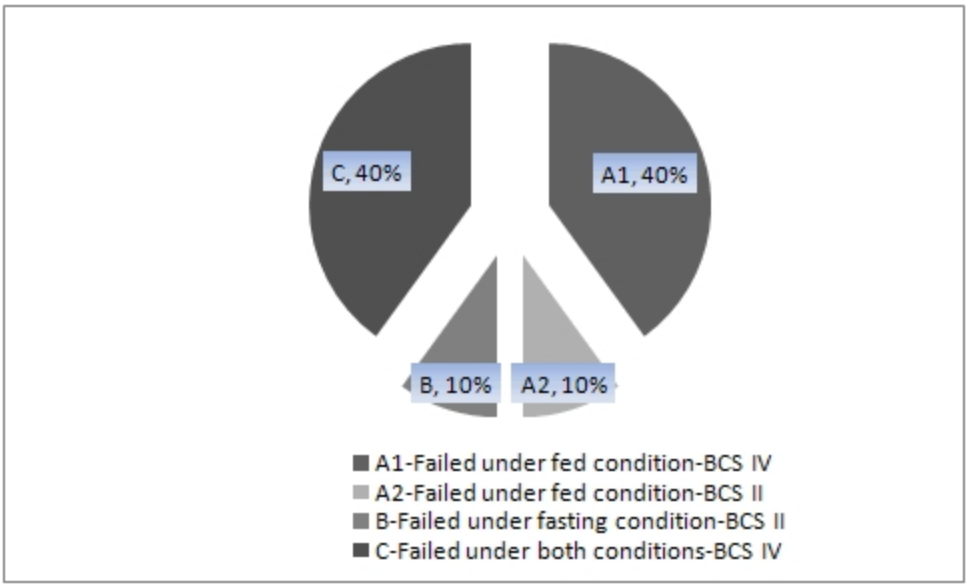

Fig. 1. Distribution of all failed studies as per study condition and biopharmaceutics classification system (BCS) of related drug

Important food effects on BA are least likely to occur with many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) because absorption of the drug substances in Class I is usually pH- and site-independent and thus insensitive to differences in dissolution [13]. Probably, this was the reason why we did not get any failed study either in fasting or fed condition for drugs belonging to BCS class I.

Few drugs are absorbed to an important extent by the stomach, both acidic and basic drug are mainly absorbed in small bowel. In fasting state, gastric motility is not uniform but passes through cycles termed migrating motor complexes (MMC). These MMC last about 2h in total, but are divided into four phases, of which phase III results in strongest contractions but last only about 15 min. Non nutrient liquids are moved quickly from stomach throughout the MMC, but solids of particle size 2mm are only moved into intestine during brief phase III. Consequently readily soluble drugs are cleared rapidly from fasting stomach to their site of absorption, but poorly soluble drugs may take longer [14]. Thus, a greater inconsistency in absorption can be observed in drugs belonging to BCS class II and IV which have poor solubility. We can attribute this reason why all the drugs failing in fasting and/or fed conditions were from BCS class II and IV.

The meta-analysis conducted by Elena Ramirez et al. (2010) involving 124 studies observed that pharmaceutical products in classes I and III were similar as far as BE outcome is concerned. The failure rate was 15.38% and 13.63% in BCS class I and III respectively. The highest and lowest failure rate was observed for products belonging to BCS class II and IV respectively [15]. In contrast to their results, our study could not find any failed

pharmaceutical product belonging to BCS class I and III. The highest failure rate was observed for pharmaceutical products of BCS class IV. The meta-analysis conducted by Elena Ramirez et al. and our study are similar in many regards however the results obtained in both these studies are entirely different. Their study included 124 studies of which only 89 were classified by BCS while 35 were non-classified by BCS. The reference to the condition of study (fasted or fed) and dosage form (immediate release or modified release) is not mentioned anywhere in their paper. It is difficult to understand the impact of dosage form on the study outcome. Our meta-analysis included 162 studies involving only immediate release drug products, all of them were classified by BCS and each drug product was exposed to fasting as well as fed conditions for evaluating bioequivalence. Though difficult to quantify, the collective impact of these factors might have resulted in different outcome in our study and the study conducted by Elena Ramirez et al. Our results interpret that the chances of meeting BE criteria are more if the drug has high solubility. This possibility is further strengthened if high solubility is coupled with high permeability.

4. CONCLUSION

The pharmacokinetic parameters C_{max} and AUC are only helpful representatives and not the absolute true indicators of therapeutic equivalence for all the drugs. We conclude our results cautiously in the background of these limitations for any bioequivalence study. The present meta-analysis revealed that the stringent requirement of USFDA to conduct BE studies under fasting and fed conditions is free of any consumer's risk while that of EMA may have some consumer's risk while using immediate release drug products belonging to BCS class II and IV. Hence, due consideration in asking for fasting as well as fed bioequivalence studies for such products by EMA (similar to USFDA recommendations) may be given. Though we did not find any such finding for BCS class III drugs, it cannot be ruled out that these drugs don't require bioequivalence study under fed condition. Drugs belonging to BCS class I can be treated with EMA recommendations rather than stringent USFDA recommendations. The present meta-analysis involved less than 200 studies and hence the conclusions drawn need to be confirmed through few more studies involving large number of studies. The conclusions drawn in this meta-analysis can be interpreted as signals to identify the appropriate direction for further research.

CONSENT

All authors declare that written informed consent was obtained from all the participants who participated in all the studies included in this meta-analysis.

ETHICAL APPROVAL

All authors hereby declare that all studies included in this meta-analysis have been thoroughly reviewed and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki (1964).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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