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The Basic Regulatory Considerations for Generic Drugs and Bioequivalence Studies an Overview

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ABSTRACT

Bioavailability and Bioequivalence studies play a vital role in drug development process for new drug products and generic drugs. The main aim of abbreviated new drug application is to show that the generic drug is bioequivalent to innovator product in terms of quality, safety, and efficacy. There are several approaches to study bioequivalence and each country has its own regulations for conducting Bioavailability and Bioequivalence studies. The present review gives information about abbreviated new drug application submission and important aspects involved in bioequivalence and Regulatory requirement for various countries.

Keywords: FDA: Food and Drug Administration, EMA: European medical agency, BA/BE: Bioavailability and Bioequivalence, AUC: Area under Curve, ANDA: Abbreviated new drug application.

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INTRODUCTION

A generic drug is a pharmaceutical product usually intended to be interchangeable with an innovator product, and marketed after expiry date of the patent of innovator product or exclusive rights. These are same as innovator drugs in dosage form, safety, and strength, route of administration, quality, performance characteristics and intended use.

Hatch-wax man act :

History:-

Prior to 1962, as per Federal Food, Drug and cosmetic act, all the applications i.e.; new drugs were scrutinized for marketing approval by USFDA on the basis of the safety profile. Later in 1962 Congress passed another act (the Kefauver-Harris Drug Amendments), which added the requirement that drugs must also be proven effective for their intended use. As per this amendment proof of efficacy was also required along with the safety profile. As a result, all drug products approved before 1962 by the USFDA were reviewed again for efficacy through the Drug Efficacy Study Implementation (DESI) program. DESI was a program hosted by the USFDA resulting Kefauver-Harris Amendments to establish safety and efficacy requirements for approval of new drugs as well as for reconsidering the safety and efficacy of prior approved drugs [1]

To seek FDA Marketing approval for generic drugs there is need to submit clinical data to prove efficacy. Even with this, before expiration of patent no generic drugs company was allowed to use patented product even for experimental purpose for generic drug approval process. In order to address the above mentioned problems, a provision in the law was needed which would allow the generic manufacturers to use the clinical trial data of the innovator drug for USFDA approval process.

Amendment of Hatch- Waxman act 1984:

To overcome the drawback of Kefauver- Harris amendment, in year of 1984, Drug Price Competition and Patent Term Restoration act was implemented in FD&C act, also known as Hatch-Waxman act. “The Hatch-Waxman Act is an act dealing with the approval of generic drugs and associated conditions for getting their approval from the Food and Drug Administration (FDA)”.

Due to the high costs involved in conducting clinical trials, only a few generic companies came forward in launching generic drug products. The Hatch-Waxman Act focused on this issue and proposed many changes, and started the generic drugs approval procedure as Abbreviated New Drug Application (ANDA), for the purpose of market authorization.

General provisions of the Act:

Bioavailability studies are needed in place of clinical trials for approval of generics. While filing an ANDA, a generic drug must certify any one of the authorization certifications [2], i.e. Para I, II, III and IV certifications. Abbreviated new drug application (ANDA) submission procedure was shown in Table 1.

Table 1 Abbreviated new drug application submission procedure [2]

Type	ANDA filing
Paragraph-I,II	If a generic drug manufacturer certifies I and II then FDA starts processing the generic abbreviated New Drug Application (ANDA) immediately.
Paragraph-III	If a generic drug manufacture certifies III then an abbreviated New Drug Application (ANDA) may finally approved when the patent expires.
Paragraph-IV	If a generic company files an abbreviated New Drug Application (ANDA) with paragraph-IV Certification then the innovator Product company is notified within 20 days, after the notice the Innovator Product Company has 45 days to file patent infringement action against the generic Company. If the patent holder sues FDA must withhold approval for 30 months.

Code of Federal Regulations (CFR):-

The Code of Federal Regulations (CFR) is the codification of the general and permanent rules and regulations. It is published by the federal government of United States. CFR can be called as administrative law.

CFR Title 21 administrates the food and drugs within the United States for the Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), and the Office of National Drug Control Policy (ONDCP). 21CFR is majorly divided in to three chapters, Chapter-I gives information regarding FDA Chapter-II deals with the Drug Enforcement administration, Chapter-III give information regarding Office of National Drug Control Policy.

Harmonization in bioavailability and bioequivalence studies:

There are several approaches to assess Bioequivalence and each country has its own regulatory authority as well as regulatory guidelines for conducting BA/BE studies, before approving generic products for marketing. Thus, there is need to harmonize the regulatory environment globally for bioequivalence assessment practically so that the drug product marketed in different parts and regions of the world. [3]

The regulatory authorities of various countries and international organizations are listed and briefly described in Table 3. In the United States, the FDA approves and grants marketing

authorization of generic drugs by applying the regulatory requirements provided in the Code of Federal Regulations (CFR). Table 4 lists some of the relevant sections in the CFR related to BA/BE. The FDA framed regulations for the submission of bioavailability data. These regulations are currently incorporated in the 21st volume of Code of Federal Regulation, Part 320 (21CFR320).

Table 3 A brief descriptions of regulatory authorities of various countries

Country	Regulatory authority	Website
India	Central Drugs Standard Control Organization (CDSCO)	http://cdsco.nic.in/
Europe	European Medicines Agency (EMEA)	http://www.ema.europa.eu/
Australia	Therapeutic Goods Administration TGA)	http://www.tga.gov.au/
USA	US Food and Drug Administration (FDA)	http://www.fda.gov/
Saudi	Ministry of Health	http://www.moh.gov.sa/
South Africa	Medicines Control Council (MCC)	http://www.mccza.com/
Canada	Health Canada	
Asean	Association of Southeast Asian Nation	http://www.hc-sc.gc.ca/
Brazil	National Agency for Sanitary Monitoring (ANVISA)	http://www.asean.org/
		http://www.anvisa.gov.br/

Table 4 Some of relevant sections in the code of federal regulations related to Bioavailability and Bioequivalence studies [16]

21CFR section	Type of provision/information
21CFR 320.1	Definitions of bioavailability, pharmaceutical equivalents, pharmaceutical alternatives, And bioequivalence
21CFR 320.21	Regulatory requirements for submission of bioavailability and bioequivalence data.
21CFR 320.22	Criteria for waiver of evidence of in vivo bioavailability or bioequivalence
21CFR 320.23	Basis for measuring in vivo bioavailability or demonstrating bioequivalence.
21CFR 320.24	Types of evidence to measure bioavailability or establish bioequivalence.
21CFR 320.25	Guidelines for the conduct of an in vivo bioavailability study.
21CFR 320.26	Guidelines on the design of a single-dose in vivo bioavailability or bioequivalence study.
21CFR 320.27	Guidelines on the design of a multiple-dose in vivo bioavailability study.
21CFR 320.28	Correlation of bioavailability with an acute pharmacological effect or clinical evidence.
21CFR 320.29	Analytical methods for an in vivo bioavailability or bioequivalence study.
21CFR 320.30	Inquiries regarding bioavailability and bioequivalence requirements and review of protocols by the FDA
21CFR 320.32	Procedures for establishing or amending a bioequivalence requirement
21CFR 320.33	Criteria and evidence to assess actual or potential bioequivalence problems.
21CFR 320.36	Requirements for maintenance of records of bioequivalence testing.
21CFR 320.38	Retention of bioavailability samples.

Regulatory aspects of bioequivalence:

The Significance of Bioavailability and Bioequivalence have grown a considerable importance due to their application to new brand name drugs and generic drugs. During this period, regulatory authorities also started developing and formulating the regulatory requirements for

approval of generic drug products. In the United States, the FDA approves and grants marketing authorization of generic drugs by applying the regulatory requirements provided in the Code of Federal Regulations (CFR) as specified in Table 2.

Table 2 Some of the relevant sections in the code of federal regulations related to Abbreviated New Drug Application submissions [4, 6, 16]

21CFR section	Type of provision/information
21CFR 5.80	Approvals of New Drug Applications and their supplements.
21CFR 10.30	Citizen Petition.
21CFR 50	Protection of Human Subjects.
21 CFR 56	Institutional review boards.
21CFR 310.305	Records and reports concerning ADEs on marketed prescription drugs for human use without approved new drug applications.
21CFR 314.70	Supplements and other changes to an approved application
21CFR 320	BA/BE Requirements.

Table 5 Demographic requirements [5-14]

Country	**Age**	**BMI(kg/m^2)**	**Gender**
India	If the drug product is intended for use is elderly attempt should be made to include as many subjects of 60 years of age or older	Not specified	Both sex
Europe	18 years of age or older	18.5 - 30	Both sex
Australia	Between 18-55	Accepted Normal BMI	Both sex
USA	18 years of age or older	Not specified	Both sex
Saudi	Between 18-50 .	Within 15% of ideal body weight, height and body build	If females are included in the study, the effects of gender differences and menstrual cycle (if applicable) are examined statistically.
South Africa	Between 18-55	within 15 % of the ideal body mass	both sex
Japan		18.5-25.0	Both sex
Canada	Healthy adult volunteers Between 18-55	18.5 - 30	Both sex
Asean	Between 18-55	18.5 and 25 kg/m2	Both sex

Assessment of bioequivalence:

Standardization of study:

The number of subjects required for a study should be taken considerable significance. The studies should be normally performed on healthy adult volunteers. Subjects may be male or

females, however the choice of gender should be consistent with usage safety control. The requirements for Demographic study are shown in Table 5

Fasting study requirements:

Drugs show more sensitive and reliable results during fasting studies, so most of the BA/BE studies are conducted under fasting condition, for this the fasting requirements are desirable as given in Table 6.

Table 6 Fasting study requirements [5-14]

Country	Fasting requirements
India	Overnight fast (at least 10 hours) with subsequent fast of 4 hours followed by dosing. For multiple dose fasting state studies, when an evening dose must be given ,two hours of fasting before and after the dose
Europe	Overnight fast (at least 08 hours) with subsequent fast of 4 hours followed by dosing. For multiple dose fasting state studies, when an evening dose must be given ,two hours of fasting before and after the dose
Australia	Overnight fast (at least 08 hours) with subsequent fast of 4 hours followed by dosing. For multiple dose fasting state studies, when an evening dose must be given ,two hours of fasting before and after the dose
USA	Overnight fast (at least 10 hours) with subsequent fast of 4 hours followed by dosing. For multiple dose fasting state studies, when an evening dose must be given ,two hours of fasting before and after the dose
Saudi	subjects should be at least 10 hours of fasting before drug administration
South Africa	Overnight fast (at least 10 hours) with subsequent fast of 4 hours followed by dosing. For multiple dose fasting state studies, when an evening dose must be given ,two hours of fasting before and after the dose
Japan	Subjects should fast for more than 10 hours for single dose studies and multiple dose studies
Canada	subjects should fast for 8 hours before drug administration
Asian	Subjects should preferably be fasting at least during the night prior to administration of the products.

Fed study requirements:-

Fed BE studies are conducted for ANDAs to demonstrate their bioequivalence to the reference listed drug (RLD) under fed conditions. As per US, Europe, India, Australia a high fat and high caloric meal are recommended as test meal for Food effect BA and fed BE Studies. Fat should be 50% of total caloric content of meal and 800 to 1000 calories meal is recommended. As per US, India ,Europe and Australia regulations meal should contain 150 calories of protein,250 calories of carbohydrates and 500-600 Calories of fat, but in National Institute of Health

Sciences(NIHS)(Japanese) guidance low fat and high caloric food is recommended. The Caloric content is 700 kcal or less containing not more than 20 % (140 k Cal) is derived from the fat [15].

Sample size requirements:

A sufficient number of subjects for assessing bioequivalence should be included. The subject population for bioequivalence studies should be selected with the aim to minimize variability and permit detection of differences between pharmaceutical products. Sample size requirement mainly based on the Intra subject variability, if the drug shows more Intra subject variability it require more number of subjects to complete the study. Sometimes have to conduct partial replicate (3-period) or fully replicate (4-period) studies also. Sample size requirements to conduct Bioavailability and Bioequivalence studies are given in Table7.

Table 7 Sample size requirements [5-14]

Country	Minimum	Sample size specification
India	Not less than 16 unless justified for ethical reason	The number of subjects required for a study should be statistically significant and should be sufficient to allow for possible with drawls or removals (drop out) from the study.
Europe Australia	Not less than 12	The number of subjects to be included in the study should be based on an appropriate sample size calculation
USA	Minimum 12	The total number of subjects in the study provide adequate power for BE demonstration
Saudi	12-24	The total number of subjects in the study provide adequate power for BE demonstration
South Africa	Not less than12	The number of subjects should be justified on the basis of providing at least 80 % power of meeting the acceptance criteria, alternatively the sample size can be calculated using appropriate power equations, which should be presented in the protocol.
Japan	20	The total number of subjects in the study provide adequate power for BE demonstration
Canada	Not less than 12	The total number of subjects in the study provide adequate power for BE demonstration
Asean	Not less than 12	The number of subjects required is determined by a) the error variance associated with the primary characteristic to be studied as estimated from a pilot experiment, from previous studies or from published data, b) the significance level desired, c) the expected deviation from the reference product compatible with bioequivalence (delta , ie percentage difference from 100 %)and d) the required power.

Diet and fluid requirement:

The test conditions should be standardized in order to minimize the variability of all factors involved except that of the products being tested. Therefore, it is recommended to standardize diet, fluid intake and exercise. The subjects should abstain from food and drinks, which may

interact with circulatory, gastrointestinal, hepatic or renal function (e.g. alcoholic drinks or certain fruit juices such as grapefruit Juice) during a suitable period before and during the study.

Acceptance criteria for bioequivalence:-

The acceptance criteria for bioequivalence are fabricated up on internationally recognized standards .For oral drugs bioequivalence is determined by comparing the relative bioavailability of brand name drug versus generic drug. There must be not more than 20% difference between AUC and C max of reference product versus generic products. Bioequivalence is based on comparison of ratios where the ratio of generic drug to reference drug for each pharmacokinetic variable does not differ by more than 8:10.This is how the range of confidence interval is defined by two formulas those are 8/10 = 0.8(gives the lower limit of 80%) and 10/8=0.25(gives the upper limit of 125%).The ratio of C_{max} and 90% confidence interval for the ratio of AUC should be contained within the limits of 0.8 to 0.25.The acceptance criteria for bioequivalence is shown in Table 8.

Table 8 Regulatory acceptance criteria for bioequivalence [5-14]

Country	90%Confidence interval on log transformed data		
	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$
India	80-125	80-125	80-125
Europe	80-125	80-125	Not applicable
Australia	80-125	80-125	Not applicable
USA	80-125	80-125	80-125
Saudi	80-125	80-125	80-125
South Africa	75-133	80-125	Not applicable
Japan	80-125	80-125	80-125
Canada	80-125	80-125	80-125
Asean	80-125	80-125	Not applicable

CONCLUSION:

At present many pharmaceutical companies developing generic drug products and the world has witnessed a sharp increase in the demand for cost-effect generic drugs in a decade. Bioequivalence study is important for generic drug approval process. This review will provide an over glance of major aspects of bioequivalence study and regulatory considerations in different countries.

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