

Research Article



Bioavailability and Bioequivalence: The Past, Present and Costly Affairs of a Global Concept Used Locally

Priyanka Harbola*

Department of Pharmaceutical Sciences, Bhimtal Campus, Kumaun University, Nainital, India.

*Corresponding author's E-mail: priyanka_harbola@yahoo.com

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ABSTRACT

The information on recommendations for conductance of bioavailability and bioequivalence is required for filing of Investigational New Drug, New Drug Application and Abbreviated New Drug Application. The guidelines for these studies differ as the drug product applicant moves from one country to the other. A sound knowledge of these is therefore mandatory for availing the benefits of timely and economic drug product approvals. The current scenario of the bioavailability and bioequivalence studies has its roots in the age old years where the Upjohn's friable pills reflected the desire for efficient drug delivery. The scientific developments date back to the late 1950's and early 1960's with the landmark Kefauver Harris Amendments and the Hatch-Waxman Act. The fast pace pharmaceutical industry is exploring the vistas for drug discovery and innovation. The pharmaceutical firms all over the world are burning the candle at both ends for attainment of market authorizations in various nations. This review explores the history of the bioavailability and bioequivalence studies. In addition it details the important aspects of these studies in the United States, European Union, South Africa, India, ASEAN and Brazil. The study highlights the global pharmaceutical expenditures and depicts current market scenario along with statistics up to 2013 for global generics market. The study concludes to suggest the harmonization of bioavailability and bioequivalence studies worldwide for achieving the benefits of what the author labels as the three M's – service to mankind, monetary gains and saving of precious minutes.

Keywords: Bioavailability, Bioequivalence, Hatch-Waxman Act, Pharmaceutical expenditure, Regulatory Guidelines.

INTRODUCTION

Biopharmaceutics is the science that forms the basis of formulation of various pharmaceutical dosage forms by a precise examination and understanding of the chemical and physical properties of the drug substance along with the intended route of administration. The last decades have witnessed a revolutionary change in Biopharmaceutics in respect of drug discovery and drug regulation worldwide. The thalidomide tragedy of the late 1950's and early 1960's, the Kelsey Report, the Kefauver Harris Amendments of 1962, the Hatch Waxman act of 1984 represent the changing scenario of pharmaceutical regulation and somewhere hidden among these changes are the seeds of bioavailability and bioequivalence that are an integral part of the current drug regulations worldwide. The BA/BE guidelines differ in various countries and companies use these for screening drug products and introducing them into the market.

The recent fast pace drug discovery and innovation on one hand is striving to boost up the healthcare status but on the other hand for a sustained market growth, the cost of discovered and innovated products needs to be recovered by the company. Thus, pharmaceutical sector intends to both give and receive. Also, the drugs must be affordable to the consumers. Thus, the task of striking a balance among the drug innovator, the generic drug producer and the consumers is undoubtedly a difficult one. This is where bioavailability and bioequivalence come into the play. In this report an overview of the

history and current status of bioavailability and bioequivalence regulations worldwide has been detailed with reference to current statistics.

The Historical Background: Pondering Over The Past

A General Overview

The Upjohn's friable pills (Upjohn, circa 1880) which were advertised as 'can be reduced to a powder under the thumb' reflect that back in the 1880's too drug delivery held importance. Thus, even 100 years ago, biopharmaceutical quality of a drug product was a significant selling point.¹ With the passage of time, in the mid 1950's, the bioanalytical capacity witnessed a growth which led to the expression of product performance in terms of bioavailability measures. The related data's drew national and international interest. The efforts were then made for defining BA and BE and determining appropriate procedures for their measurement.² The Congressional Office of Technology Assessment in the United states issued a key report recommending significance of BA and BE studies and indicated steps to make certain that the information became part of regulatory processes and drug development.³ The FDA subsequently adopted many recommendations of this report which were published as regulations entitled *Part 320—Bioavailability and Bioequivalence Requirements*, which contain subparts A (*General Provisions*) and B (*Procedures for Determining the Bioavailability or Bioequivalence of Drug Products*) in 1977.⁴



An alternative means of testing the bioequivalence of two formulations of a pharmaceutical agent was originally proposed in the 75/75 or 75/75-125 Rule. In accordance with this rule the ratio of test to reference formulation in a bioequivalent study was to range between 75-125% of unity in at least 75% of subjects for establishment of the two formulations as bioequivalent. The rule did amass criticism and a "power approach" was applied to the AUC and Cmax in the early 1980's. This approach consisted of two tests to detect 20% mean difference in treatment and was used in alliance with the 75/75 rule sometimes. In 1986 the use of these methods was declined by the agency and a public hearing on BE was conducted due to public demand. The scientific investigations of the hearing were performed by a BE Task Force whose report was released in 1989. Subsequently a guidance on the statistical procedures for BE studies was issued in July 1992.⁵

THE HATCH-WAXMAN ACT

Pre-1962 Scenario

Prior to the Kefauver Harris Amendments of 1962, drug safety was the sole basis of drug approval. Also, 'paper NDAs' helped approve generic versions of drug products. The paper NDA consisted of published scientific or medical literature that demonstrated the safety of a chemical. This NDA could be presented by a generic drug manufacturer for getting an approval.^{6,7}

Thalidomide, had been sold as OTC drug in Germany by 1957 and by 1960 it was sold in many parts of the world including Europe, South America and Canada. It was when the Richardson-Merrell pharmaceutical company of Cincinnati submitted an application in September 1960 to FDA for marketing it in US that Miss Kelsey, a one month fresh medical officer at FDA, raised concerns about its safety. She detailed deficiencies in the application and demanded for more detailed and well executed studies. On finding the data re-submitted unsatisfactory, she denied approval to market the drug in US. Meanwhile, the European physicians started reporting the miscarriage or birth of terribly deformed babies and it was in 1961 that a German pediatrician, Widukind Lenz, determined the cause of these birth defects and abnormalities (phocomelia) to be thalidomide. Subsequently, Richard Merrell withdrew their application from FDA and a new more stringent drug regulation emerged.

Senator Estes Kefauver had strived for years to add the efficacy requirement for drug approval but due to logical disconcert, his proposal lied in a state of limbo. However, it was in 1962 that the tables turned and the controversial bill once passed by Kefauver was rewritten, signed by President Kennedy and introduced into law as Kefauver-Harris Amendments on October 10, 1962. The Thalidomide tragedy thus revolutionized drug regulation.^{8,9}

Post-1962 Scenario

The post-1962 times required submission of drug efficacy data along with the data for safety. This meant elaborate drug testing extended time period and a burden of raised costs of drug testing. For the generic drug industry, this meant havoc. There were only 15 paper NDAs submitted after 1962 by generic drug makers although 150 drugs had gone off patent.⁷

Hatch-Waxman-The draft

President Carter of the US in 1978 launched a major domestic policy for patent term restoration and President Reagan's Council on Trade and Commerce also supported him. An intellectual property committee was set up by the then-US secretary of Commerce Malcolm Baldrige. The committee's recommendations on patent term restoration were turned into a bill XX S.255XX.¹⁰ The bill failed due to lack of majority votes but set ripples into the generic drug industry. Henry A. Waxman, an effective Congressman and the then-Chairman of Health Subcommittee held the reigns of the issue and soon the complexity of the patent term restoration bill was furthered by the addition of drug price competition. Consequently, the bill emerged as the patent term restoration and drug price competition bill which by Public Law 98-417 (the Hatch-Waxman) was enacted in 1984. The animal drugs were first added with the 1988 Generic Animal Drug and Patent Term Extension Act.¹¹

Hatch Waxman Act and Bioequivalence

The Hatch-Waxman Act reduced the drug testing requirements for the generic drug makers by introducing the abbreviated New Drug Application (ANDA) which emphasized production of bioequivalent data by the generic drug maker. The act 'created an abbreviated mechanism for approval of generic copies of all drugs originally approved after 1962, by stating that pre clinical and clinical testing does not have to be repeated for generics'.¹² The applicants were then required to state in the ANDA, any of the four patent certifications labeled from I to IV as laid down by section 505(j)(2)(A)(vii) the Act. These certifications are under mentioned:

- No patent information on the drug product that is the subject of the ANDA has been submitted to FDA;
- That such patent has expired;
- The date on which such patent expires; or
- That such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted.¹³

The Hatch Waxman Act led to a new era of generic drug industry with novel filing requirements (Table 1) and the increased number of ANDA filings (Figure 1) in the coming times reflected the fast pace of a developing global generic drug industry.



REFLECTIONS OF THE PRESENT: CURRENT STATUS OF BA AND BE STUDIES

Definitions

Bioavailability (BA)

Bioavailability has been defined in § 320.1 as ‘the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action’.

Bioequivalence (BE)

Bioequivalence has been defined in § 320.1 as ‘the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study’.¹⁴

Generic Drug

A generic drug product has been defined as a “drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use”.¹²

Reference listed drug

This refers to ‘the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application’.¹⁵

Pharmaceutical Equivalent

Pharmaceutical equivalents are drug products that are formulated to contain the same amount of active ingredient in the same dosage form for meeting the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity). They may, however, differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.¹⁶

BA and BE Guidelines across the World

BA and BE is a global concept used within and among the countries worldwide. The FDA guidelines are always in prime focus of drug regulation and the BA & BE perspectives show slight yet significant variation of expression and understanding in other nations. Keeping in mind the same a few guidelines are further discussed.

The SADC (Southern African Development Community) and EMEA Guidelines for BA and BE

The SADC guideline ranges from sections between 1 and 8 and comprises of various subsections. Similarly, the

European Agency for Evaluation of Medicinal Products and CPMP lay down guidelines under sections 1-5 with various subsections and two appendices. Hence, detailing the minute details of every section is not an easy task. However, an attempt has been made to project a comparison of the important aspects of the various guidelines. A comparative study of SADC and EMEA guidelines (Table 2) marks the difference in BA/BE studies in Southern Africa and Europe.¹⁷⁻²²

Table 1: Filing Requirements- Branded Vs. Generic Drugs

Generic Drugs	Branded Drug
Labeling	Labeling
Pharm/Toxicity	Pharm/Toxicity
Chemistry	Chemistry
Manufacturing	Manufacturing
Controls	Controls
Microbiology	Microbiology
Inspection	Inspection
Testing	Testing
Animal Studies Clinical Studies Bioavailability	Bioequivalence

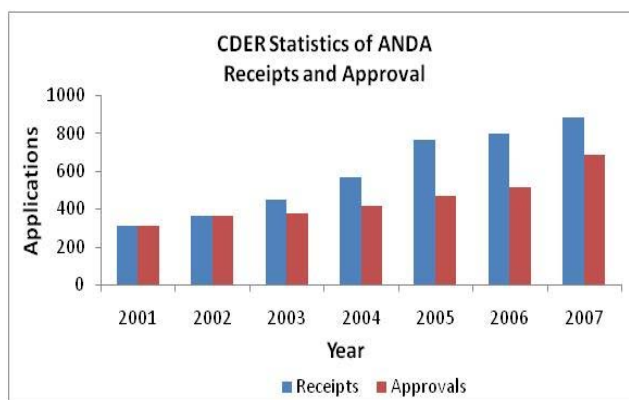


Figure 1: ANDA Receipts and Approvals- Rise of the Generics

The tabulated data mentioned so far clearly indicates that although quite similar there exist certain differences in the guidelines provided by SADC and EMEA. Also, notable is that the guidelines do undergo amendments from time to time.

For getting marketing approvals in different countries, their BA and BE guidelines are to be followed. Considering the same, a few BA/BE requirements in India, USA, Brazil and ASEAN countries is highlighted below (Table 3).²³⁻²⁶

India is developing and so is its pharmaceutical sector. A glimpse of the Indian Regulations relating to conductance of BA/BE studies (Table 4) is therefore presented.^{23, 25}

Bioequivalence and Brazil

Bioequivalence requirements were stated in ANVISA resolution number 391/1999. At the budding stage of bioequivalence in Brazil, more than 80% of bioequivalence studies sent to ANVISA were performed



by international CRO's using an international reference product. This was referred to as 'special registration'. At the first registry revalidation (after 5 years), the sponsors that had got marketing authorization based on special

registration were asked to present another set of bioequivalence studies using a national reference product of the ANVISA list.

Table 2: BA and BE Guidelines: A comparison between SADC and EMEA Perspectives

Contents	SADC Guidelines	EMEA Guidelines
Objectives	<p>Section 1 Defines when bioavailability or bioequivalence data will be required in order to prove safety and efficacy. Provides guidance on the design and conduct of studies and the evaluation of data. Provides guidance when <i>in vitro</i> instead of <i>in vivo</i> data may be used. Provides guidance when suitably validated pharmacodynamic methods can be used to demonstrate bioequivalence.</p>	<p>Section 1 Defines for products with systemic effect, when bioavailability or bioequivalence studies are necessary and to formulate requirements for their design, conduct and evaluation. The guideline also envisages the possibility of using <i>in vitro</i> in place of <i>in vivo</i> studies with pharmacokinetic end points. The guidelines are said to be read in conjunction with other EU, ICH and other relevant guidelines along with Directive 75-318/EEC.</p>
Bioequivalence	<p>Bioequivalence is defined as the absence of a significant difference in bioavailability between two pharmaceutically equivalent products or pharmaceutical alternatives under similar conditions in an appropriately designed study. Comparative studies using clinical or pharmacodynamic end points may also be used to demonstrate bioequivalence.</p>	<p>States, two medicinal products are bioequivalent if they are pharmaceutically equivalent of pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degrees that their effects, with respect to both, efficacy and safety, will be essentially the same.</p>
Other Definitions	<p>Section 3 (Subsections 3.1-3.13) The guidelines define Proportionally Similar Dosage Forms/Products in addition to other definitions.</p>	<p>Section 2 (Subsections 2.1-2.6) The guidelines define essentially Similar products in addition to others.</p>
Design and Conduct of Studies	<p>Section 4 (Subsections 4.1-4.9.4) Design Formulation effect to be distinguished from other effects.</p> <ul style="list-style-type: none"> ➤ A balanced two period, two sequence carry over design to be considered for comparison of two formulations. ➤ Parallel designs for very long half-life substances can be considered in some cases. ➤ Single dose studies suffice but in some cases steady-state studies must be motivated. ➤ Adequate wash-out periods suggested to avoid carry over effects. ➤ For a reliable estimate of extent of absorption the AUC derived from measurements is at least 80 % of the AUC extrapolated to infinity and sampling plan is based on it. ➤ If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples above the LOQ during the terminal log linear phase. ➤ For long half-life drugs (> 24 hours) the study should cover a minimum of 72 hours unless 80 % is recovered before 72 hours. 	<p>Section 3 (Subsections 3.1-3.8) Design The design of the study is similar to that prescribed in SADC guidelines. Yet some details render a difference like: Examples of conditions in which steady state studies 'are required' or 'can be considered'. '...replicate designs for substances with highly variable disposition' is stated along with that for parallel design. For drugs with long half lives relative bioavailability can be adequately estimated using truncated AUC as long as the total collection period is justified. In this case the sample collection time should be adequate to ensure comparison of absorption process.</p>
Design and Conduct of Studies	<p>No. of Subjects</p> <ul style="list-style-type: none"> ➤ Must be justified on the basis of providing at least 80 % power of meeting the acceptance criteria. ➤ The minimum number of subjects should not be less than 12. If 12 subjects do not provide 80 % power, more subjects should be included. ➤ A minimum of 20 subjects is required for modified release oral 	<p>No. of Subjects and their Selection Number of subjects not to be less than 12 unless justified. Studies normally performed using healthy volunteers. Subjects can be male or female but risk to child bearing women must be</p>



	<p>dosage forms.</p> <ul style="list-style-type: none"> ➤ The number of subjects required to provide an 80 % power of meeting and passing the acceptance criteria for the 0,8 to 1,25 acceptable interval, can be determined from Reference 1. ➤ Alternatively, the sample size can be calculated using appropriate power equations, which should be presented in the protocol. ➤ The provision for add-ons should be made in the protocol <i>a priori</i> clearly reflecting the maximum number of subjects to be included. <p>Selection of Subjects Similar with only slight additions like: Subject's weight must be within normal values of BMI or within 15 % of the ideal body mass, or any other recognized reference. Informed consent to be given by subjects.</p>	<p>considered. Inclusion/exclusion criteria to be clearly stated. Age generally 18-55 years with weight within normal range with values accepted normal according to Body Mass Index. Proper screening of subjects. Preferably non-smokers with no history of alcohol or drug abuse. Moderate smokers if included must be identified and consequences of results must be discussed. Genetic phenotyping mentioned.</p>
<p>Design and Conduct of Studies</p>	<p>Standardization of Study Conditions Stated in terms of dosing, fluid intake at dosing, food and fluid intake, concomitant medication and posture and physical activity. Fluid Intake at Dosing: As fluid intake may profoundly influence the gastric transit of orally administered dosage forms, the volume of fluid administered at the time of dosing should be constant (e.g. 200 ml).</p> <p>Sample Collection and Sampling Times Specifies When blood is collected When urine is collected</p> <p>Characteristics To Be Investigated Includes: <ul style="list-style-type: none"> ➤ Blood/Plasma/Serum Concentration <i>versus</i> Time Profiles ➤ Urinary Excretion Profiles ➤ Pharmacodynamic Studies ➤ Chirality </p> <p>Evaluation of BA and BE to be based upon measured concentrations of the parent compound (i.e. the API) where the shape of, and the area under, the plasma concentration <i>versus</i> time curves are generally used to assess the rate and extent of absorption. In some situations, measurements of an active or inactive metabolite may be necessary instead of the parent compound.</p> <p>The following bioavailability parameters are to be estimated: a) AUC_t, AUC_{∞}, C_{max}, t_{max} for plasma concentration <i>versus</i> time profiles. b) AUC_{∞}, C_{max}, C_{min}, fluctuation (% PTF) and swing (% Swing) for studies conducted at steady state. c) Any other justifiable characteristics d) The method of estimating AUC-values should be specified.</p> <p>BioAnalysis <ul style="list-style-type: none"> ➤ States bioequivalence studies must be conducted in accordance with GLP and cGMP. ➤ Focuses on use of validated methods and use of pre-established SOP's ➤ Suggests generation of calibration curve for each analyte in each analytical run. ➤ States submission and discussion of all relevant procedures and formulae, used to validate the bioanalytical method. ➤ Any modification of the bioanalytical method, before and during analysis of study specimens, may require adequate revalidation, and all modifications should be reported and the scope of revalidation justified. </p>	<p>Standardization of Study Conditions The basis of standardization is near about similar. Only this guideline states at least 150 ml of fluid intake.</p> <p>Sample Collection and Sampling Times A separate section for this has not been given</p> <p>Characteristics To Be Investigated It proposes the measurement of following parameters. AUC_t, AUC_{∞}, C_{max}, t_{max}, Ae_t, Ae_{∞}. Or any other justifiable characteristic (cf. Appendix I). It also states that method of estimating AUC-values must be specified.</p> <p>For additional information $t_{1/2}$ and MRT can be estimated. For studies in steady-state, AUC_r, C_{max}, C_{min} and fluctuation should be provided. Also it states, 'the exclusive use of modeled characteristics is not recommended.'</p> <p>Chemical Analysis Similar indications of method validation, SOP's and calibration curve etc. Additionally provides for two phases: the pre-study phase and the study phase for validation of a bioanalytical method.</p>

<p>Design and Conduct of Studies</p>	<p>Study Products Details Reference and test products, retention samples and sample handling. States in the case of oral solid forms for systemic action the test product should usually originate from a batch of at least one tenth (1/10) of the production scale unless otherwise justified.</p> <p>Data and Statistical Analysis The statistical method for testing relative bioavailability (i.e. average bioequivalence) is based upon the 90 % confidence interval for the ratio of the population means (Test/Reference) for the parameters under consideration. Pharmacokinetic parameters derived from measures of concentration, e.g. AUC_t, AUC_{∞} and C_{max} should be analyzed using ANOVA. Data for these parameters should be transformed prior to analysis using a logarithmic transformation. If appropriate to the evaluation, the analysis technique for t_{max} should be non-parametric and should be applied to untransformed data. In addition to the appropriate 90 % confidence intervals, summary statistics such as geometric and arithmetic means, SD and % RSD, as well as ranges for pharmacokinetic parameters (minimum and maximum), should be provided.</p>	<p>Study Products States in addition that if the batch is less than 100,000 units, a full production batch will be required. Also states that the reference and test product must be packed in an individual way for each subject included in the bioequivalence trial in accordance with Annexure 13 to the EU guide to GMP. Also states about efforts for precise tracking of administration of test and reference products to subjects.</p> <p>Data and Statistical Analysis The guideline proposes same provisions with only a few extra comments on ANOVA.</p>
<p>Design and Conduct of Studies</p>	<p>Acceptance Range for Pharmacokinetic Procedures These have been provided for single and steady-state studies</p> <p>Single Dose Study</p> <p>For AUC_t-ratio The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,80-1,25 (80 – 125 %).</p> <p>For C_{max}-ratio The 90 % confidence interval for the test/reference ratio should lie within an acceptance interval of 75 – 133 %, calculated using log-transformed data, except for narrow therapeutic range API's when an acceptance interval of 80 – 125 % will apply. In certain cases, e.g. in the case of highly variable API's, a wider interval or other appropriate measure may be acceptable, but should be stated <i>a priori</i> and justified in the protocol. The Section 4 of the guideline further includes study Reports:</p> <ul style="list-style-type: none"> ➤ Clinical report ➤ Analytical report ➤ Pharmacokinetic and statistical report ➤ QA statement 	<p>Acceptance Range for Pharmacokinetic Procedures</p> <p>States the same (80-125%) except for further defining that in case of acceptance of a wider interval for C_{max} ratio, the interval must be prospectively defined e.g., 0.75-1.35</p> <p>The Section 3 of guideline further comments on the following: Handling deviations from the study plan A remark on individual and population bioequivalence In vitro dissolution complementary to a bioequivalent study Reporting of results The reports must comply with GCP Rules and related EU and ICH E3 Guidelines.</p>
<p>The Differing Sections</p>	<p>Section 5 gives the BA and BE requirements for:</p> <ul style="list-style-type: none"> ➤ Orally administered products with systemic action ➤ Orally administered drugs with local action ➤ Parenteral solutions ➤ Topical Products ➤ Products intended for other routes of administration ➤ Variations or Post-Registration Amendments <p>Section 6 discusses Waivers of <i>in vivo</i> Bioequivalence studies</p> <p>Section 7 covers References</p> <p>Section 8 covers Abbreviations</p>	<p>Section 4 states BA and BE related information with reference to applications for products containing new active substances.</p> <p>Section 5 states BE provisions relating to the following: Oral immediate release forms with systemic action Oral solutions Non oral immediate release forms with systemic action Modified release and transdermal dosage form Fixed combination products Parenteral solutions Gases (Bioequivalence study is not required for inhalation or gas product) Locally applied Products The guidelines in the end discuss the</p>

		following: In vitro dissolution Variations Dose proportionality in immediate release oral dosage forms Suprabioavailability
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Table 3: Regulatory Authorities and the Requirements for BE Studies

Regulatory Authority	Age	BMI (kg/m ²)	Min. Sample Size	90% Confidence interval on log transformed data		
				C _{max}	AUC _{0-t}	AUC _{0-∞}
India	≥18 years; as many subjects of 60 years or older must be included if drug product is intended for use in elderly	Not Specified	Not less than 16 unless justified for ethical reason	80-125	80-125	80-125
USA	18 years or older	Not Specified	12	80-125	80-125	80-125
Brazil (ANVISA)	18-50 years	Within 15% of the normal range	Not less than 12; 24 in case of non availability of inter-subject variation
ASEAN	18-55 years	18-25 kg/m ²	Not less than 12	80-125	80-125	80-125

Table 4: A Glimpse of the Indian Regulations Scenario of BA/BE Studies

Sample Size Specifications	Requirements for Fasting	Fed Study Requirements	Immediate-Release Products	Modified Release Products
<p>The number of subjects required for study should be statistically significant.</p> <p>The number of subjects should be sufficient to allow for possible withdrawals or removals (drop-outs) from study.</p>	<p>Overnight fast of at least 10 hrs followed by a 4 hr fast after dosing.</p> <p>In multiple-dose fasting studies, an evening dose must be given 2 hrs before or after dosing.</p>	<p>Fat must be 50% of total caloric content of meal.</p> <p>800-1000 calories are considered as high in calories.</p> <p>150 calories of proteins, 250 calories of carbohydrates and 500-600 calories of fat form a regulation meal</p>	<p>A non replicate, single dose, fasting study is generally prescribed.</p> <p>Food effect studies are required under circumstances like: Recommendation that the study drug is to be taken with food as in general clinical practice. When assessment of C_{max} and t_{max} becomes difficult in fasting studies. If multiple study design is important, appropriate sampling and dosage administration must be carried out for documentation of attainment of steady-state.</p>	<p>Food effect and fasting studies should be conducted.</p> <p>If multiple study design is important, appropriate sampling and dosage administration must be carried out for documentation of attainment of steady-state.</p>

2000-2001

ANVISA created CRO's by funding 9 institutions for supplying the national demand of bioequivalence studies. The ANVISA resolution number 41 in year 2000 established the criteria for habilitation of CRO's. The increased demand for BE studies led to the formation of 'Coordination of Inspection', CIBIO in 2001 for keeping an eye on the CRO's.

2003

- ANVISA Resolution no. 103 stated that only results of BE studies conducted in certified CRO's can be accepted for a generic drug registration.
- ANVISA Resolution no. 899/2003 established the guidance for validation of analytical and bioanalytical methods.



- ANVISA Resolution no. 895/2003 established the guidance for BE Report.
- ANVISA Resolution no. 134/2003 stated that already registered similar medicines must produce BE studies. Narrow therapeutic range drugs data was to be submitted by December 2004; Antiretrovirals, antineoplastics and antibiotics by 2008 and others until may 2013(10 years later second revalidation).

2005

ANVISA resolution no. 406 created the bioequivalence unit (UABBE) inside the General Office of Drugs (GGMED) which had the following attributes:

- Evaluation of BA/BE study protocols and reports for market authorization of similar, generic and new medicines.
- Evaluation of dissolution profile for biowaiver intermediate strength.

2006

ANVISA Resolution no. 1170 established the guidance for BA/BE Proof.²⁷

The rising BE report approvals in Brazil during the year 2000-2008 (Figure 2) are the fruitful results of efforts of Brazilian pharmaceutical sector.²⁷

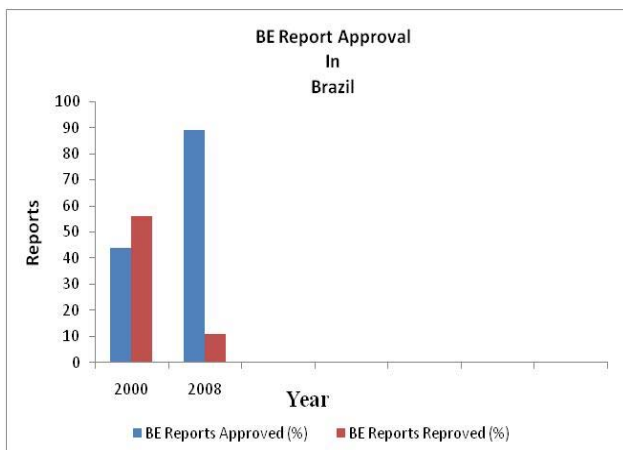


Figure 2: The BE Report Approvals in Brazil

The Costly Affairs

The pharmaceutical industry is a billion dollar global business empire. According to an OECD (Organization for Economic Cooperation and Development) report, an average OECD country spent 1.5% of its GDP on pharmaceuticals in the year 2005. Among the top spending countries in the year 2005 were three Hungarian, the Slovakian Republic and Portugal which spent around 2% of their GDP on pharmaceuticals. The report unravels the fact that the pace of pharmaceutical expenditure is faster than the economic growth. The average rate of real annual growth rate in health (net of pharmaceutical expenditure) was equivalent to the real annual growth in pharmaceutical spending during the period 1997-2005 was 5.3%.

‘The rate of growth of pharmaceutical spending surpassed that of total health expenditures in ten of 25 countries, while being roughly equal in six countries. Both pharmaceutical and total health expenditures grew at a higher rate than the mean annual growth rate of GDP for the countries’ that include Ireland, Hungary, United States, Mexico, Australia, Korea, Canada, Slovak Republic, Spain, Luxembourg, OECD, Finland, Iceland, Netherlands, France, Sweden, Portugal, UK, Austria, Czech Republic, New Zealand, Germany, Switzerland, Norway, Denmark, Italy and Japan. Thus, pharmaceutical sector beyond doubt is moving swiftly.²⁸

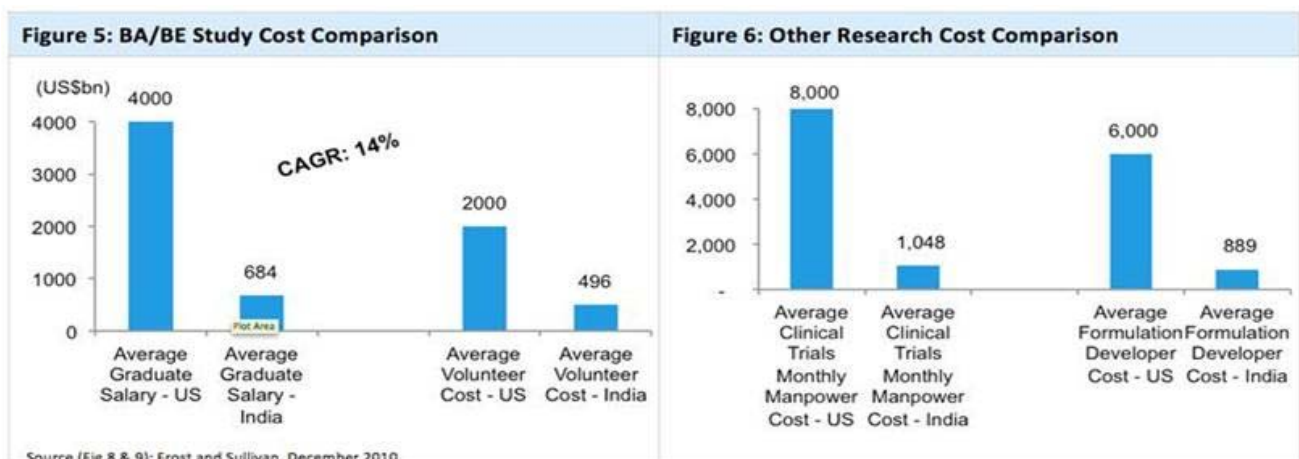


Figure 3: Cost Comparison of BA/BE and other Research Study



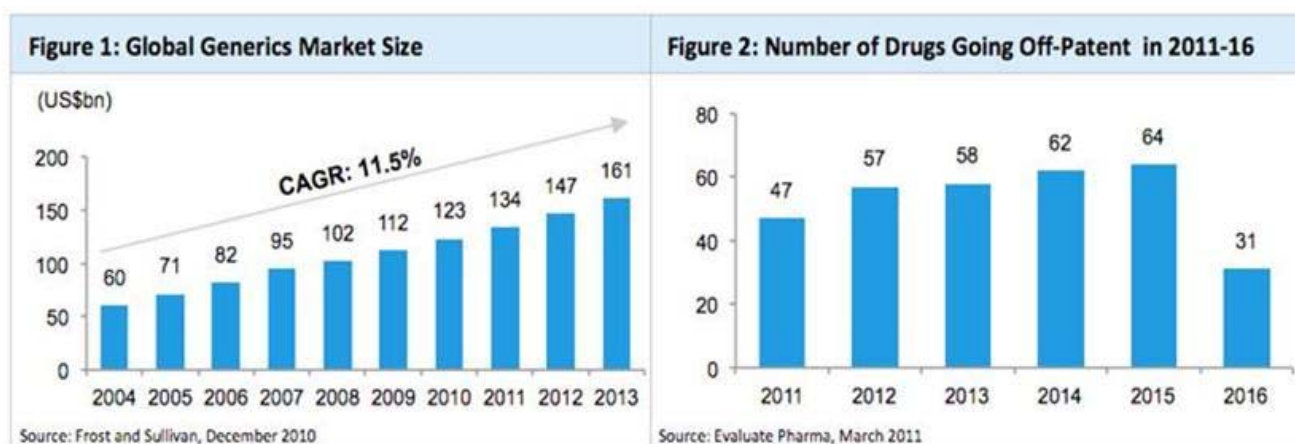


Figure 4: Current Global Generic market size and Drugs going Off- Patent in 2011-16

CONCLUSION

A lot has been already discussed in conferences and seminars all across the world on the concepts of BA/BE and the world has still to discourse in great lengths on BA/BE studies and drug regulation. The pharmaceutical expenditures are moving with long strides trying to cover up for different drug regulations worldwide. It has already been demonstrated by the author that there exist variations in conductance of BE studies worldwide and so the need of the hour is to harmonize drug regulations on BE so that conductance of different tests in different nations following different regulations is discouraged.

A unified bioequivalent scenario can help the pharmaceutical industries to avail the benefits of the three M's – service to mankind, monetary gains and saving of precious minutes, the three undeniable truths every pharmaceutical company would nod a 'yes' to. The unification will also help improve the overall world health scenario by availability of timely and economically feasible healthcare products. Now is the hour for the global pharmaceutical industry to work together for mutual benefits.

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Corresponding Author's Biography: Ms. Priyanka harbola



Ms. Priyanka graduated and post-graduated from the Dept. of Pharmaceutical Sciences, Bhimtal Campus, Kumaun University, Nainital. At post-graduation she chose to specialize in pharmaceutics and completed her master's thesis in "Process validation of Lisininopril Tablets" from Jubilant Life Sciences Ltd. With a 2.5 year teaching experience, she is currently a Research Scholar at Kumaun University.