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BRIDGING THE GAP OF INDIAN REGULATIONS AND MAJOR GLOBAL REGULATIONS FOR BIOEQUIVALENCE STUDIES WITH EMPHASIS ON ADAPTIVE SEQUENTIAL DESIGN AND TWO-STAGE BIOEQUIVALENCE STUDIES

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ABSTRACT

The cost of healthcare has been escalating globally during the last two decades, and this has prompted efforts in most countries to reduce those costs. Because of the importance of generic drugs in healthcare, it is imperative that the pharmaceutical quality and in vivo performance of generic drugs be reliably assessed. Because generic drugs would be interchanged with innovator products in the market place, it must be demonstrated that the safety and efficacy of generics are comparable to the safety and efficacy of the corresponding innovator drugs. The concept of bioavailability (BA) and bioequivalence (BE) has been accepted worldwide by the pharmaceutical industry and national regulatory authorities for over 20 years and is applied to new as well as generic products. As a result, thousands of high-quality generic drugs at reduced costs have become available in every corner of the globe. The assessment of BE is not a simple issue, however, and much of the research has been done in recent years to develop new and more effective approaches to the assessment of BE. There are several approaches to assess BE and each regulatory authority has its own regulations/guidance for conducting BA/BE studies before approving generic products for marketing in their country. Therefore, a thorough understanding is required of these BA/BE concepts and basic regulatory requirements for conduct of BA/BE studies. In this article, the regulatory guidelines are compared on the basis of various parameters involving the clinical conduct of the BA/BE studies. Harmonization of these approaches may decrease the number of in vivo bioequivalence studies and avoid unnecessary drug exposure to humans. Another upcoming approach for conduct of bioequivalence studies is Adaptive design, which is a relatively new approach. This innovation is becoming accepted by the regulators and has been taken up by the pharmaceutical industry to reduce product development times and costs. There is a need for raising the awareness of these design approaches because they could be used to make dramatic improvements to clinical research in developing countries.

Keywords: bioavailability (BA), bioequivalence (BE), generic drugs, regulatory authority, US FDA, EMA, WHO, CDSCO.

INTRODUCTION

Over the last 30 years, India's pharmaceutical industry has evolved from almost non-existent to a world leader in the production of high quality generic drugs. India has garnered a worldwide reputation for producing high quality, low cost generic drugs. The industry currently meets India's demand for bulk drugs and nearly all its demand for formulations. Overall, the Indian market for pharmaceuticals is projected to grow at an average annual rate of between 15 and 20 percent during 2005-2010.The surge in production has been driven by legislative reforms, the growth in contract manufacturing and outsourcing, value added foreign acquisitions and joint ventures, India's mastery of reverse engineering of patented drug molecules, and India's efforts to comply with its World Trade Organization (WTO) Trade Related Intellectual Property Agreement (TRIPs) obligations. Globally, India ranks third in terms of manufacturing pharma products by volume. According to McKinsey, the Pharmaceutical Market is ranked 14th in the world. By 2015 it is expected to reach top 10 in the world beating Brazil, Mexico, South Korea and Turkey.[1]

The rising cost of medication and overall cost of health care receive considerable attention globally. During last couple of years, patients' life span has increased significantly due to the new drug discovery as well as generic drug production. The push for international harmonization of regulatory standards is leading to worldwide discussions and changes regarding bioequivalence and other components of the drug approval process.[2,3]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 branded drugs (innovator drugs).[4] This strategy has been effective in reducing total prescription cost by 11% without sacrificing quality.[5] Generic drugs have captured more than 65% of the global market and account for 66% of prescriptions filled in the United States but for less than 13% of the cost.[6]

Bioequivalence (BE), defined by the US Food and Drug Administration's (FDA's) Orange Book[7] as the "display of comparable bioavailability when studied under similar experimental conditions," serves as a central scientific and regulatory standard for virtually all oral pharmaceutical products.[8] The most recent regulatory statement on BE, the European Medicines Agency's "Guideline on the Investigation of Bioequivalence" (2010), defines the term similarly.[9] The Orange Book further follows the language of the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) of 1984: "Bioequivalent drug products are therapeutically equivalent and, therefore, interchangeable."[7] Historically the *in vivo* matching of human systemic concentrations of active drug-and, when important for therapeutic efficacy, metabolite(s)-and comparison with a reference product (e.g., the Reference Listed Drug[7]) has been the gold standard for BE and therapeutic inter-changeability. This standard is widely accepted.

Science for Conduct of BE Studies

BE is an essential drug product standard for both innovator and generic products. For innovator products, BE is used to

establish therapeutic equivalence between the commercialized, marketed product and the clinical-scale product that underwent phase III safety and efficacy testing. The pivotal phase III studies that establish the evidence for the label indication(s), use(s), and dosing require that the clinically tested phase III product show evidence of bioavailability. All subsequent products that contain the same "drug," or "active pharmaceutical ingredient," and label must be bioequivalent to that clinically tested product. For example, additional BE evidence on the innovator product is required when the product undergoes various scale-up or post-approval changes (e.g., FDA SUPAC guidances[10]). Therefore, BE is the essential continuing standard for ensuring the therapeutic inter-changeability and efficacy of pharmaceutical products.

REGULATORY OVERVIEW & PRESENT SCENARIO

Historically, generic substitution has been a topic of heated debate among health care professionals, members of the pharmaceutical industry, consumers, and government officials. Thus, because of the importance of generic drugs in health care, it is imperative that the pharmaceutical quality, safety, and efficacy of generics should be reliably compared with the corresponding innovator drugs (branded drugs). The US Food and Drug Administration (FDA) publish a list of drug products and equivalents, *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the "Orange Book". The US FDA has also provided product specific guidance which are nonbinding recommendations for different products and explain study designs, analyse to be measured, no. of studies required etc. The US FDA periodically revises this guidance and modifies its requirements based on the new information available and regulation changes if any. Because the generic product must be pharmaceutically equivalent and bioequivalent to the innovator product, it is expected that the two products will also be therapeutically equivalent.[7]The term "therapeutic equivalents" applies only to products that are pharmaceutical equivalents, not to different therapeutic agents used to treat the same condition. The pertinent situations in which bioequivalence studies are required include 1) when the proposed marketed dosage form is different from that used in pivotal clinical trials; 2) when significant changes are made in the manufacture of the marketed formulation; and 3) when a new generic product is tested against the innovator's marketed product. Based on this background, bioavailability (BA) and bioequivalence (BE) information has been determined to have practical and public health value for pharmaceutical industries, regulatory agencies, patients, and practitioners.

In India, currently lots of outsourcing for bioavailability and bioequivalence studies is being carried out. Clinical Research Organization and Pharmaceutical companies are conducting bioavailability and bioequivalence studies for generic submission to regulatory authorities such as FDA (USA), EMA (European medicines agency), ANVISA (National Health Surveillance Agency -Brazil), CDSCO (Central Drugs Standard Control Organisation - India), TGA (Therapeutic Goods Administration-Australia) etc. Before conducting bioequivalence studies, one must have a thorough understanding of the terms associated with the generic drug approval process. A lack of understanding of the approval process may lead to complication. Every country now has its own individual regulatory authority and guidance for BA/BE studies, and the magnitude of assessment of BE of drug product is influenced by the regulatory environment of the respective country of marketing. 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). The requirements mentioned in the guidelines for conduct of such studies by these regulatory authorities vary. The magnitude of regulatory influence is often dictated by the availability of resources, expertise, and lack of regulation or its implementation. If the bioavailability and bioequivalence study is not conducted according to the requirements, obtaining an approval for the generic drug becomes difficult. Besides specific BE guidelines, companies have to follow other relevant regulations for clinical research i.e. DCGI has recently released couple of new regulations about pharmacovigilance, consent documents related changes etc. which are also important while conducting studies.

The regulatory requirements for conduct of bioavailability-bioequivalence studies are not uniform across the globe. Thus there is a greater need to harmonize the regulatory environment globally for BE assessment as far as practicable so that the drug product marketed in different parts and regions of the world would have optimum drug product quality in terms of interchangeability. In the recent years, some significant progress has been made towards harmonization; in addition some regulatory authorities are also in the process of cooperating with their counterparts from other countries to harmonize the regulatory requirements while streamlining their own regulatory requirements. Thus, it is necessary that all the regulatory guidelines for bioavailability-bioequivalence studies, authorized by the regulatory authorities of various countries are compared and all the differences in the same are present in a common platform.

TABLE 1: REGULATORY REQUIREMENTS FOR DEMOGRAPHICS (BE STUDIES) [9, 11-17]

Regulatory Authority	Age	Sex	BMI (kg/m^2)
India	≥ 18 years; If the drug product is intended for use in elderly, attempt should be made to include as many subjects of 60 years of age or older.	Male/female; the choice of gender should be consistent with usage and safety criteria.	Not specified
USA	18 years of age or older	Male/female	Not specified
Europe (EMA)	18 years of age or older	Male/female	18.5 - 30 kg/m^2
Canada	18- 55 years	Male/females	Height/weight ratio for healthy volunteers should be within 15% of the normal range
ASEAN[#]	18-55 years	Male/females	18 -25 kg/m^2
South Africa	18-55 years	Male/females	Accepted normal BMI or Within 15% of the ideal body mass or any other recognized reference
Brazil (ANVISA)	18-50 years	Male/females	within 15% of the normal range

- Association of Southeast Asian Nations

Sample size requirements: Number of subject will be selected depend up on the variability of drug and acceptance criteria of drug. The minimum number of subject for crossover design will be generally 12 but appropriate sample size will be determined based on previous available data or data available from pilot study.

TABLE 2: REGULATORY REQUIREMENTS FOR SAMPLE SIZE [9, 11-17]

Regulatory authority	Minimum	Sample size specifications
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 withdrawals or removals (drop outs) from the study.
USA	12	The total number of subject in the study should provide adequate power for BE demonstration.
Europe	Not less than 12	The number of subjects to be included in the study should be based on an appropriate sample size calculation
Brazil	Not less than 12. 24 in case of non-availability of inter subject variation.	The number of healthy volunteers shall all times assure an adequate statistical power to guarantee reliability of BE study results.
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 BE (delta, i.e., percentage difference from 100%); and d) the required power
South Africa	Not less than 12 subjects for immediate release and 20 subjects for modified release oral dosage forms	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.

TABLE 3: FASTING AND FED STUDY REQUIREMENTS[9, 11-17]

Regulatory authority	Fating requirements
India	Overnight fast (at least 10 h), with a subsequent fast of 4 h following dosing For multiple-dose fasting studies, when an evening dose must be given, 2 h before and after the dosing
Europe and Brazil	At least 8 hours prior to administration of the products and no food is allowed for at least 4 hours post-dose.
USA and Canada	At least 10 hours of fasting which is continued for at least 4 hours post-dose
ASEAN	At least 8 hours prior to administration of the products. If the Summary of Product Characteristics of the reference product contains specific recommendations in relation with food intake related to food interaction effects the study should be designed accordingly.
South Africa	Fasting prior to dosing and after dosing should be standardized.

Fed study requirements: As per US, Europe, India, Australia (TGA) a high fat and a high caloric meal are recommended as test meal for Fed BE study. Fat should be 50 % of total caloric content of the meal and 800 to 1000 calories considered as high calories. As per US, Europe, India and Australia regulation meal should contain 150 calories of protein, 250 calories of carbohydrates and 500-600 calories of fat. But In NIHS (Japanese, 2000) guidance the low fat and high caloric food is recommended. The caloric content is approximately 700 kcal out of which not more than 20% (140 kcal) is derived from the fat.

Regulatory criteria on number of studies required for conducting BA/BE studies: The number of studies and study design depend on the physicochemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly. Various regulatory provide detail regarding type of study required to be carried out shown below.

TABLE 4: REGULATORY REQUIREMENTS FOR NO. OF STUDIES REQUIRED [9, 11-17]

Regulatory agency	Immediate release products	Modified release products
India	Generally a single-dose, nonreplicate, fasting study Food-effect studies are required 1) when it is recommended that the study drug should be taken with food (as would be in routine clinical practice); 2) when fasting state studies make assessment of C_{max} and T_{max} difficult If multiple-study design is important, appropriate dosage administered and sampling be carried out to document attainment of steady state	Should conduct fasting as well as food-effect studies If multiple-study design is important, appropriate dosage administered and sampling carried out to document attainment of steady state.
USA	Generally two studies • A single-dose, nonreplicate fasting study • A food-effect, nonreplicate study Food effect study can be excepted in the following cases: 1) When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I);or 2) when the dosage and administration section of the RLD label states that the product should be taken only on an empty stomach; or 3) When the RLD label does not make any statements about the effectof food on absorption or administration. If food effect mentioned in RLD label and if multiple-study design is important, appropriate dosage administered and sampling be carried out to document attainment of steady state.	Fasting and fed studies. If multiple-study design is important, appropriate dosage administered and sampling be carried out to document attainment of steady state.
Europe and Australia	Generally a single-dose, nonreplicate, fasting study and fed studies are required if the Summary of Product Characteristics of the reference product contains specific recommendations in relation with food interaction.	Fasting, fed and steady state studies
Canada	Generally recommend fasting studies, fed studies are required for safety concern (toxicity, narrow therapeutic drugs etc.)	Fasting and fed studies. If multiple-study design is important, appropriate dosage administered and sampling be carried out to document attainment of steady state level.
South Africa	Should be done under fasting conditions unless food effects affect bioavailability of drug or reference product dosage recommended	Both fed and fasted studies are required. If multiple-study design is important, it should be carried out as per regulatory specifications.

TABLE 5: REGULATORY ACCEPTANCE CRITERIA FOR BIOEQUIVALENCE[9, 11-17]

Regulatory authority	90% confidence interval on Log transformed data		
	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$
India	80-125	80-125	80-125
USA	80-125	80-125	80-125
Europe and Australia	80-125	80-125	Not applicable
South Africa	75-133 80-125 (for narrow therapeutic range)	80-125	Not applicable
ASEAN	80-125	80-125	80-125

TABLE 6: OTHER IMPORTANT PARAMETERS [9, 11-17]

Regulatory authority	Water intake at time of dosing	No. of samples	Highly variable drug	Narrow therapy drugs
India	Not specified	at least 3elimination half-lives. There should be at least 3 sampling points during the absorption phase, 3-4 at the projected T_{max}& 4 points during the elimination phase.	Not specified	Not much specified (tighter limits are required).
USA	240 ml (8 ounces)	12-18 samples including Pre-dose sample per subject per dose, duration of at least 3 or more elimination half-life of drug/metabolite.	GMR (80 -125) 95% upper bound for (μT - μR) / σWR ≤ 0.7976 (Using Scaled Average Approach, for and AUC)	C_{max} – 80-125% AUC- 80-125% (Additional test/controls required).
Europe	At least 150 ml	frequent samples around predicted T_{max}, AUC(0-t) covers at least 80% of AUC(0-∞), 3-4 samples during the terminal log-linear phase.	#C_{max} - maximum of 69.84%–143.19%. AUC- 80-125%	C_{max} – 90 -111.11 AUC – 90 -111.11
South Africa	volume of fluid should be constant (e.g., 200 mL)	12 -18 samples, max. conc. of drug/API in blood (C_{max}) and the terminal elimination rate constant (K_{el}) should be estimated.	C_{max} – 75 -133% AUC - wider acceptance range may be acceptable and this should be justified clinically	C_{max} – 80-125%

- refer EMA guidance for better clarity.

ADAPTIVE TRIAL DESIGN

Adaptive design is a relatively new approach to clinical studies that is being increasingly used within the pharmaceutical industry.[18] It is recognized that conventional randomization can be ethically infeasible as it gathers information and ignores current knowledge.[19] This design approach has an in-built capacity to change the study; in fact, the very point is to change the study while it is in process without compromising the integrity of the trial. In drug and vaccine development the use of adaptive design shortens product development time. Adaptive design is still not main-stream, which many find it surprising. Adaptive clinical trial design is defined as a design that allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity. The role of adaptive design is to make clinical trials more flexible, efficient, and fast. Because of the level of flexibility involved, these trial designs are also termed as flexible designs. In essence a clinical trial that uses adaptive design allows, and indeed plans for, substantial change as the trial progresses without the need for a separate new study or a protocol amendment.

In February 2010, draft guidance on adaptive design clinical trials by the FDA was circulated for comments. This draft guidance is a document describing the potential use of adaptive designs in clinical trials. It is generally viewed as supportive of the use of adaptive designs if they are employed properly. The FDA draft guidance is not a specific guidance for the implementation of adaptive designs in clinical trials.[20] It, however, should be noted that adaptive designs have been used at times in confirmatory contexts, for the most part cautiously, limited to changes such as sample size re-estimation and treatment arm consolidation in the early phase of clinical development where there is more uncertainty and regulatory concerns are minimized. The FDA classifies adaptive designs into well-understood designs and less well-understood designs. Well-understood design refers to the typical group sequential design, which has been employed in clinical research for years. Less well-understood designs include the adaptive dose finding and two-stage phase I/II (or II/III) seamless adaptive designs. Many scientific issues surrounding the less well-understood designs are posted in the draft guidance without recommendations for resolution. This raises the question whether the use of adaptive design methods in clinical trials (especially for those less well understood designs) is ready for implementation in practice.

Table 7 describes three possible adaptive trial designs. These examples are not finite, any number of approaches could be used in adaptive design because the aim is to be flexible and adapt the design as the data is gathered and knowledge is gained.

TABLE 7: ADAPTIVE DESIGNS–VARIOUS FORMS

Types of adaptive design	Description	Objective of design
Dose finding	Data is reported and extracted in interim reports. The data is reviewed as it accumulates and then decisions can be taken on lowering or increasing doses as per protocol. It is adaptive as there will not have been a set point where the dose is changed; the design is purposefully flexible and adaptive.	To avoid giving therapeutic doses, or to overdose.
Response adapting	Safety and efficacy data are captured as near to live as possible and further participants are randomized according to outcome of earlier participants. (subsequent participants are assigned to the treatment arm that has the best efficacy or fewer side effects)	To reduce exposure to an ineffective arm or to side effects.
sample size change	Sample sizes are based on assumptions. Therefore, many protocols set a sample size that may be too high or too small. The former results in a trial that exposes participants unnecessarily as the question has been answered and the latter results in the trial being unable to answer the question. In an adaptive design the limitation on the power calculations are acknowledged and as the trial begins to inform that assumption so the power calculation can be amended.	Allow the trial to run until the question has been answered and to avoid exposing participants to an experimental therapy unnecessarily.

In January 2010, EMA in its latest guideline on the investigation of bioequivalence has clearly specified about acceptance of Two-stage design studies. The guideline mentions that it is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis. If his approach is adopted appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined prior to the study. The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%). For example, using 94.12% confidence intervals for both the analysis of stage 1 and the combined data from stage 1 and stage 2 would be acceptable, but there are many acceptable alternatives and the choice of how much alpha to spend at the interim analysis is at the company's discretion. The plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses.

When analysing the combined data from the two stages, a term for stage should be included in the ANOVA model.

Two Stage Design in Bioequivalence Studies

As in case of planning a clinical trial, Planning BE studies also requires some prior estimate of the appropriate variance and a decision regarding the effect size at which to determine power (probability of meeting the pre-established BE criteria). The most commonly accepted BE study design world over are crossover designs, so the variance needed is within subject. The effect size is specified by choosing a ratio of the geometric means of the two formulations. Minimum sample size is obtained if the 'effect size' is chosen to be 100%, i.e. perfect equivalence. It is common practice to allow for some departure from perfect equivalence, with a resulting statement like, 'We will have power of at least 80% to conclude the two formulations to be bioequivalent as long as the true ratio of geometric means lies between 95.0% and 105.3%.'BE studies are also no different from other clinical trials in that prior information regarding the variance may be poor or non-existent. The choice of the effect size may also be overly optimistic. If the variance used in the power calculation is too low or the chosen effect size overly optimistic, the study is underpowered; conversely, if the variance estimate is too high, the sample size may be unnecessarily large.[21]

Few Regulatory agencies for example, Canada and WHO permit 'add-on' designs. With these designs, if the failure to declare the two formulations bioequivalent appears to be due to insufficient power, it is permissible to add additional subjects and pool results of the additional subjects with the original trial. The argument in favour of add-on designs is that they do make use of the data already collected, and the inflation of the type I error rate is 'acceptable.' The TGA (Australia) discourages sequential designs and indicates that, if used, must be in the protocol and a Bonferroni correction applied.[22] (In statistics, the Bonferroni correction is a method used to counteract the problem of multiple comparisons. It is considered the simplest and most conservative method). In the US, the study may be repeated, but the data from the second study are not pooled with those from the first study. The second study has to stand on its own merits.

In a group sequential trial, interim analyses are conducted on the data available at one or more intermediate stages, where the sample size (n_i) and allowed type I error rate (α_i), at each stage are pre-established according to some rules. Application of group sequential approaches to BE studies differs from their application to most other types of clinical studies because the former generally involves crossover designs, testing of equivalence hypotheses, and testing based on t-distributions, whereas the latter generally involves parallel designs with testing of difference hypotheses.

Potvin D. and his group has described four methods in detail in the 2008 paper.[21]In 2012, this group has published another paper providing additional results on sequential designs.[23]The four methods (A–D) are described in detail in the 2008 paper and 2012 paper. The methods in 2012 paper differ from those in the 2008 paper in that the assumed GMR that is part of the methods (for determining stage 1 power and stage 2 sample size) is 0.90 instead of 0.95 used in the 2008 paper.

FORWARD PATH AND FUTURE PROSPECTS

Although regulations intended to ensure bioequivalence have been in place for two decades, controversies still continue. The guidelines and regulations continue to evolve as science and technology change. The adaptation of the BA/BE concept worldwide for over 20 years has enabled the production and approval of quality generic products through profound scientific, technical, and regulatory advances (especially through two-stage designs, application of BCS, scaled

average BE) to assess BE for various complex and special groups of drugs. Clinicians and scientists need to understand the generic drug approval process and the issues surrounding bioequivalence, as well as the foundation upon which decisions regarding drug selection rest.

The success story of BA/BE is based on the contribution by global regulatory agencies, pharma industry and indeed the efforts from ICH, and various international health organizations. WHO has made remarkable progress specifically in developing international consensus on the regulatory requirements for assessing BE for marketing authorization of multisource pharmaceutical products for interchange ability, selection of comparator product for BE assessment and other related regulatory documents. However, a lot remains to be done, especially to promote global harmonization of BA/BE approaches, which should focus on uniformity, harmony on general concepts, standardisation of designs, outlier issues, consideration of BE criteria etc. To achieve these objectives efforts should continue from international health organizations, pharmaceutical industries and regulatory agencies to understand and to develop more efficient and scientifically valid approaches to assess BE, and develop generic drugs in a cost-effective manner. Harmonization of these approaches may decrease the number of in vivo bioequivalence studies and avoid unnecessary drug exposure to humans. Global harmonization for regulatory requirements may be promoted by a better understanding of factors underlying product performance and expectations from different regulatory authorities. Existence of these regulations is to guarantee the safety and efficacy of the drugs and thereby protecting the end users and consumers.

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