Editorial

Theme: Pharmacokinetics, Biopharmaceutics and Bioequivalence: History and Perspectives

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Bioequivalence; Its History, Practice, and Future

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INTRODUCTION

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. It is known that most of the interventions of healthcare are done through medication. Since the cost of medication has also been escalating through the years, the contribution of drug costs to the overall costs of healthcare has received considerable attention. A major strategy for lowering the cost of medication, and thereby reducing its contribution to total healthcare costs, has been the introduction in global markets of generic equivalents of brand-name drugs (innovator drugs). The strategy has been effective. The national average savings through the use of generic drugs from 1997–2000 was approximately 9 billion dollars or 11% of total prescription costs (1). At the same time, generic drugs have captured more than 65% of the global pharmaceutical market. Average prescription spending in the United States topped 286 billion in 2007, prompting calls for greater generic drug use to reduce costs without sacrificing quality. Generic drugs account for 66% of prescriptions filled in the US but less than 13% of the cost (2).

Thus, 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. Assessment of “interchangeability” between the generic and the innovator product is carried out by a study of “*in vivo* equivalence” or “bioequivalence” (BE).

The concept of 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.

HISTORICAL OVERVIEW—US LANDSCAPE

The concepts of bioavailability (BA) and bioequivalence have gained considerable importance during the last three decades because of their application to new brand-name drugs, as well as to generic drugs. During this period, regulatory authorities also started developing and formulating the regulatory requirements for approval of generic drug products. Consequently, tremendous advances have been made in the application of assessment approaches to these scientific concepts. BA and BE have become the cornerstones for the approval of brand-name and generic drugs globally and have been utilized for brand-name drugs to reduce cost of development. It is encouraging to know that there are continuing efforts by regulatory authorities and the scientific community, both nationally and internationally, to understand and develop more efficient and scientifically valid approaches to the assessment of BE of various dosage forms including some of the tough complex special dosage forms.

The concept of BE and approaches to its assessment were developed in various stages over the last 35 years. In the early 1970s, the “United States Food and Drug Administration” (FDA) became interested in biological availability of new drugs. During this period, a drug bioequivalence study panel was formed by the Office of Technology Assessment (OTA) to understand the chemical and therapeutic equivalence relationships of drug products. On the basis of the recommendations put forth by this panel, the FDA formulated regulations for the submission of bioavailability data. These regulations are currently incorporated in the 21st volume of Code of Federal Regulation, Part 320 (21CFR320) (3).

In the early 1980s, attention was paid to statistical methods for assessing BE. Several approaches to data analysis and statistical treatment of data were considered by FDA. The major methods included the power approach (reformation of bioequivalence hypotheses) (4,5), the 75/75 rule, the confidence interval approach (6), and the Bayesian approach (7,8).

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In 1984, United States Congress passed the “Drug Price Competition and Patent Term Restoration Act of 1984” that authorized FDA to approve generic drug products through BA and BE studies. As a result of the passage of this act, several activities were initiated by the FDA for the review and approval of generic drug application (Abbreviated New Drug Application, commonly known as ANDA). During 1984 to 1992, FDA published for the industry a series of drug-specific BA/BE guidances, general guidances on conducting studies, and regulatory recommendations and statistical guidances to document BE (see URL <http://www.fda.gov/cder/guidance/index.htm>). Consequently, these guidances helped the industry to conduct BA/BE studies and receive approval of a large number of generic drug products during that period.

In 1986, public concern was expressed in the US regarding equivalent therapeutic quality of generic drugs that had been approved under existing approaches for assessing BE. The issue here was not solely on the bioequivalence of the products but also included concerns related to the therapeutic equivalence. As a result, FDA addressed these concerns in a hearing on bioequivalence of solid oral dosage forms. Based on the outcome of the hearing, a task force was formed to examine the procedures and statistical approaches applied to assess bioequivalence of solid oral dosage forms.

Since then, and after turn of the century, tremendous advancements have been made by the FDA and other regulatory authorities (national, international, and supranational), and by industry and academia in the area of assessment of bioequivalence. Currently approaches to determine BE of pharmaceutical products has been largely standardized. This has occurred due to discussion and consensus reached among various stakeholders at numerous national and international meetings, conferences, and workshops.

REGULATORY ASPECTS OF BIOEQUIVALENCE

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 following table provides some of the relevant sections in the CFR important from BA/BE standpoint (Table I).

ASSESSMENT OF BIOEQUIVALENCE

Bioequivalence Endpoint

The assessment of BE of different drug products is based on the fundamental assumption that two products are equivalent when the rate and extent of absorption of the test drug does not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. Should the rate of absorption actually differ between products, it would have to be intentional and reflected in the proposed product label and be clearly demonstrated that it is not essential in the attainment of effective body drug concentrations on chronic use or has been shown to be medically insignificant for the drug (9). In practice, equivalence is indicated when key pharmacokinetic parameters used to establish rate and extent of the test, and reference products fall within a preset confidence interval.

The FDA declares a drug product to be therapeutically equivalent to the innovator product if it is pharmaceutically equivalent, i.e., same active ingredient, dosage form, strength and route of administration, and bioequivalent. Products that are therapeutically equivalent can be used interchangeably. Thus, BE studies are construed to be considered surrogates for comparative clinical trials for the assessment of therapeutic equivalence in safety and efficacy between two drug products.

Bioequivalence studies are generally recommended by FDA using the following endpoints, listed in order of preference:

- a. Pharmacokinetic endpoint
- b. Pharmacodynamic endpoint
- c. Clinical endpoint
- d. *In vitro* endpoint

Table I. Relevant Sections of the Code of Federal Regulations Related to BA/BE

21CFR section	Type of provision/information
21CFR 314.94(a)(9)	Chemistry, manufacturing, and controls; permitted changes in inactive ingredients for parenteral, otic, ophthalmic, and topical drug products
21CFR 320.1	Definitions of bioavailability, pharmaceutical equivalents, pharmaceutical alternatives, and bioequivalence
21CFR 320.21	Regulatory requirements related to submission of <i>in vivo</i> bioavailability and bioequivalence data
21CFR 320.22	Criteria for waiver of evidence of <i>in vivo</i> bioavailability or bioequivalence data
21CFR 320.23	Basis for measuring <i>in vivo</i> 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 <i>in vivo</i> bioavailability study
21CFR 320.26	Guidelines on the design of a single dose <i>in vivo</i> bioavailability or bioequivalence study
21CFR 320.27	Guidelines on the design of a multiple-dose <i>in vivo</i> bioavailability study
21CFR 320.28	Correlation of bioavailability with an acute pharmacological effect or clinical evidence
21CFR 320.29	Analytical methods for an <i>in vivo</i> bioavailability or bioequivalence study
21CFR 320.30	Inquiries regarding bioavailability and bioequivalence requirements and review of protocols by the Food and Drug Administration
21CFR 320.38	Retention of bioavailability samples
21CFR 320.63	Retention of bioequivalence samples

Thus, for drug products where drug level can be determined in an easily accessible biological fluid and drug level is correlated with the clinical effect, pharmacokinetic endpoint BE studies are conducted by preference. In general, this endpoint is applicable for most drugs. If this approach is not feasible, other endpoints are recommended, and for certain special drug products, multiple BE studies with different endpoints may be recommended for approval.

General Considerations for Bioequivalence Studies

Because the pharmacokinetic endpoint has been so often used, most of the advances in assessment of bioequivalence have been made in this approach. Areas of advancement include:

1. Study design and protocol
2. Bioanalytical methods and validation
3. Selection of appropriate analyte(s)—parent drug and/or metabolite, prodrug
4. Bioequivalence metrics
5. Data transformation
6. Statistical approaches and analysis
7. Establishment of bioequivalence criteria

Study Design

As with any quantitative technique the source and quality of the samples used in the final evaluation predetermine the quality of the data undergoing evaluation. In other words, if the study design, the protocol, and the manner in which biological fluid samples are collected, processed, and stored are inappropriate, any subsequent analysis will be flawed and potentially meaningless. Consequently, a great deal of time should be spent on designing the bioequivalence study and managing the conduct of that study such that the highest quality samples are obtained. In this regard, specific attention should be paid to properly sizing the study (so that sufficient statistical power is available as discussed later), enrolling subjects who meet all relevant inclusion and do not meet any exclusion criteria, the appropriate overall design (simple two period crossover, replicate design to gain direct information on within-subject variability for both test and reference product or parallel design) is utilized to adequately address the question at hand, adequate control of environmental conditions (fasting, fed, ambulatory, supine etc.) and good clinical practice are strictly adhered to and documented.

In addition, consideration must be given to dose proportionality (especially if biowaivers are to be requested for additional dosage strengths) and the descriptive pharmacokinetics of the drug in question so that adequate samples are collected in a manner that will give the best estimates of the various pharmacokinetic parameters to be evaluated. All of this must be planned *a priori* and embodied in the overall protocol and study plan. In some cases, this may require pilot studies to be conducted or a very comprehensive review of the scientific literature.

Bioanalysis

Subsequent to the conduct of the clinical portion of the study, the bioanalysis must be conducted using fully validated

methodology. Excellent scientific and regulatory guidance documents are available that outline the requirements for a fully validated method. These guidances are updated as technology, and the science evolves through the combined efforts of industry, academia, and regulatory scientists. Readers are directed to the proceedings of the meetings cohosted by the American Association of Pharmaceutical Scientists (AAPS), Federation Internationale Pharmaceutique (FIP), and Food and Drug Administration and international forums such as BioInternational cohosted by FIP, Royal Pharmaceutical Society of Great Britain, and AAPS.

The application of validated methodology presupposes that the most appropriate analyte is monitored to attest to the question of bioequivalence. In this regard, the parent drug is generally the most suitable analyte to monitor. In some cases, however, monitoring a metabolite, or the parent and metabolite(s), may be more appropriate. Some examples of such cases are: (a) when the parent drug is rapidly and extensively metabolized such that only metabolite(s) data is available, (b) the metabolite is more highly correlated to therapeutic efficacy than the parent, or (c) both the parent and metabolite(s) are responsible for therapeutic effect (10). Most commonly, the investigator should consult the relevant regulatory agency for guidance on a particular therapeutic agent.

Bioequivalence Metrics and Data Treatment

The most common data treatment involves analysis of variance using a suitable program such as SAS (SAS 2005, Statistical Analysis System, SAS Institute, Cary, NC) or WINNONLIN (Pharsight Corporation, St. Louis, MO) so that contributions from subject, period, formulation, and interactions between these can be examined. Geometric mean ratios and log transformed data are examined to test the hypothesis that the 90% confidence interval of extent (total exposure, area under the plasma concentration time curve from predose to the last measurable time point, AUC_0 to last extrapolated to infinity) and the maximum concentration (peak exposure, the single point estimate of maximum observed concentration in the plasma concentration time curve) fall within the acceptance limits of 80–125%. In two published reports of the FDA archived studies—the mean values for the key parameters AUC and C_{max} did not vary >4% (11,12). More recently, other data treatments have become popular, especially with specialized dosage forms, with drugs that are highly variable, with drugs having a long terminal half life, and/or with those drugs whose time to C_{max} is considered important (i.e., certain pain medications). These other data treatments include partial area measurements and exposure metrics including C_{max}/AUC . In all of these cases, the goal has been to err on the side of protecting the consumer while at times increasing risk to the manufacturer. Hence, over the last 10–15 years, considerable debate has occurred about the fundamental scientific rationale used to establish bioequivalence for some of these “special” cases. Although at times this debate may have seemed overly specific to some singular drugs or drug products, it has resulted in excellent fundamental research and discovery into the broader issues surrounding BE with extension to our understanding of therapeutic equivalence. This debate has

also offered a platform for global interaction as it relates to issues surrounding bioequivalence and the greater issues associated with harmonization of drug equivalence approaches on a global scale including choice of comparator (reference/brand) and windows of acceptance.

Pertinent Statistical Considerations

Study Power. The conduct of a study that can truly attest to the bioequivalence of two drug products requires some prior knowledge of the performance of the products in the human body so that an appropriate number of test subjects can be enrolled and provide adequate power to test the hypothesis with a reasonable likelihood (i.e., at least 80%) that the two products are indeed bioequivalent. In fact, the alternate hypothesis that two products are not statistically significantly different leads to the conclusion that they are bioequivalent. The two criteria that are considered most important to understand are the inherent variability of the drug and the geometric mean ratio between the test and reference product. Both of these parameters can be determined through the conduct of a pilot study of 6–12 subjects. It should be borne in mind that such determinations will likely overestimate the number of subjects actually required for the final pivotal study. Such overestimation is usually more tolerable than the counter possibility of under sizing the study for obvious reasons.

75/75 Rule. Considerable debate has ensued over the past 20 years related to statistical testing and issues of bioequivalence. Some of this debate is still ongoing and will be further expanded later in this article when we discuss highly variable drugs. The original considerations related to how similar do the results of relative bioavailability between two formulations need to be before there is concern was one based on relative medical risk assessments.

In this regard, the biomedical community felt that unless there was greater than a 20–25% change in the biological system, it would really not pose a significant clinical risk that would invalidate the use of one therapeutic strategy *versus* another (13). This formed the basis for the 75/75 rule that stated that two formulations are equivalent if and only if at least 75% of the individuals being tested had ratios (of the various pharmacokinetic parameters obtained from the individual results) between the 75 %and 125% limits, and the study conducted has the statistical power to detect 20% difference between the two formulations. This statistical treatment of the data was really the first application wherein individual bioequivalence was being tested. The 75/75 rule lost most of its appeal when it was noted that both the test and reference formulations each have their own variability, and therefore, a confidence interval approach was more appropriate so that some consideration can be given to the differential variability between the test and reference products. Application of the 75/75 rule provides a greater probability of acceptance if the coefficient of variation for the reference product is smaller than the test product.

90% Confidence Interval. In July 1992, the guidance on “Statistical Procedures for Bioequivalence Studies Using a Standard Two-treatment Crossover Design” was released by FDA. In this document, the recommended statistical

approach was that based on average bioequivalence (ABE) wherein the average values for the pharmacokinetic parameters were determined for the test and reference products and compared using a 90% confidence interval for the ratio of the averages using two one-sided *t* tests procedure (6). To establish bioequivalence, the calculated confidence interval should fall within a BE limit of 80–125% using logarithm transformed data (adopted since the concentration parameters C_{max} and AUC may or may not be normally distributed). Again this limit was based on clinical judgment that a test product with bioavailability measures outside of this range should be denied market access since it posed an unacceptable risk to the consumer. The concept of using a confidence interval approach was really based on the fact that if the ratios of the two parameters of clinical interest (AUC, C_{max}, etc.) are to be compared, each with their own variability that may or may not be randomly distributed, then such a comparison can only truly be done through a confidence interval approach.

SOME SPECIAL DRUG CLASSES, DOSAGE FORMS

Narrow Therapeutic Index Drugs

Scientists and regulatory agencies throughout the world have certainly recognized that the primary rules to establish bioequivalence for the majority of drug products will not work (or at least have significant short-comings) with some special drug classes or dosage forms. Those drugs which demonstrate considerable consumer risks such as the narrow therapeutic index drugs or critical dose drugs are clear examples where the fundamental biomedical basis used to establish the cornerstone of bioequivalence decision making, “... that unless there was greater than a 20-25% change in the biological system it would really not pose a significant risk...” may not hold. Perhaps tighter restrictions on these drugs would aid in the establishment of truly bioequivalent drug products within this class. For example recent discussion around the equivalency of antiepileptic drugs (AEDs) has created a resurgence in interest of examining individual bioequivalence (IBE) as a measure of product switchability since IBE does consider the within subject variability of both the test and reference products using the replicate study design (14). The lack of concordance between ABE and IBE with such data requires further research in developing appropriate approaches such as IBE.

The traditional 2-formulation, 2-period, 2-sequence cross-over design is used in the conventional average ABE. This approach gives no information about the within-subject variances associated with the test and reference products. For drug products that demonstrate low within-subject variability and demonstrate low variance between subjects, the traditional ABE approach works relatively well. However, when one is concerned with drug product performance within a given subject (drug interchangeability), such as that encountered with AEDs, a more relevant test criterion is individual bioequivalence (IBE) based on the concept of distance ratio, i.e., ratio of difference between test and reference and difference between reference and reference). This concept

includes the consideration of the variance associated with each formulation. It has been quickly shown, however, that when the variance is equal for both formulations, there is no additional risk in accepting an inferior test formulation (15). However, when the variance for the reference formulation is smaller than for the test formulation, this risk is increased as a larger difference between the test and the reference product would show BE. In response to this, a scaled ABE (sABE) approach was presented that would provide an objective means of evaluating the variance of the reference formulation and provide a convenient method of examining the ABE between two formulations with widely disparate variances (16). This approach to evaluating BE is appropriate and becoming increasingly acceptable for those special drugs that are inherently highly variable.

Highly Variable Drugs and Drug Products

This class of drug and drug products exhibits the influence of intrinsic variability of a drug and drug product on the assessment of bioequivalence. The question arises how best to assess bioequivalence of such drug products? It is often required to test with very large numbers of volunteers to achieve sufficient power in order to document bioequivalence. This increases producers' risk in terms of cost and involves unnecessary human testing without concomitantly decreasing consumers' risk.

In fact, the high variability of this class of drugs and yet their inherent safe use within the population is generally manifested in the fact that such drugs generally have an extremely wide therapeutic window. As a consequence, the consumer risk is very low, and it has been proposed that such drugs should have a wider window of acceptance in order to allow conventional approaches towards testing of bioequivalence to be applicable. However, as the consensus for such approaches could not be achieved for various reasons, these concepts were abandoned initially with discussion consistently ending with regulatory opinion not accepting the idea of widening the window of acceptance but certainly now agreeing that an approach based on scaling of ABE may be more reasonable since it relies on the performance of the marketed formulation in helping to set the acceptance window. This approach also stipulates that the point estimate of C_{max} must fall within a geometric mean ratio between the test and reference product of 0.8–1.25 (17).

Other Drug Products

Some examples of other special formulations that have been given scientific and regulatory consideration are those involving chiral drugs, drugs that are present as endogenous entities, drugs exhibiting polymorphic metabolism, poorly absorbed or nonabsorbed drugs, antiepileptic drugs, and cytotoxic drugs. Each of these presents unique difficulties when it comes to establishing the study design, the proper analyte for measurement or the appropriate marker and the statistical testing for truly establishing bioequivalence and hence therapeutic equivalence. Specific interest groups involving international scientists have debated and discussed many of these issues. Most notably FIP through its scientific interest group on bioavailability and bioequivalence was

formed in 1994 to be a global platform for such discussion. Readers are directed to the Bio-International Conferences held to discuss and resolve complex issues in BA/BE in 1989, 1992, 1994, 1996, 1999, 2001, 2003, 2005, and 2008. In addition, regulatory science workshops (see URL http://www.fip.nl/www/index.php?page=pharmacy_sciences&pharmacy_sciences=sciencs_bioavail) have been hosted by FIP in cooperation with AAPS aimed at providing solid knowledge and competences to participants from the global community related to BA/BE.

In addition to the special drug classes mentioned above, we also note that certain dosage forms present unique challenges for the establishment of bioequivalence. Some of these include drugs administered transdermally, respiratory drug products, pulsatile delivery systems, complex intravenous systems, drugs delivered by noninvasive routes, and biotechnology drug products that require the introduction of the concept of biosimilarity as opposed to bioequivalence.

OTHER ISSUES

There are other issues that need resolution when using pharmacokinetic endpoint in BE studies. Some of these issues are:

- a. Bioequivalence of very poorly formulated brand product—when redosing of the same batch of the drug product does not demonstrate bioequivalence.
- b. Similarity between plasma concentrations *versus* time profiles—single peak *versus* multiple peaks, immediate release and modified release combination formulation.
- c. Should T_{MAX} for the generic and the brand products be same/similar, particularly when the drug is intended for chronic use for a considerable length of time?
- d. Should food bioequivalence study be mandatory for all drug products to assess potential dose dumping or reduced bioavailability?
- e. What is the appropriate study population in terms of healthy subjects or patient population, effect of gender, age, ethnicity as it relates to BE study with food?

INTERNATIONAL EFFORT TO HARMONIZE APPROACHES TO BE ASSESSMENT AND EVALUATION OF PRODUCT QUALITY

The magnitude of assessment of bioequivalence of drug product is influenced by the regulatory environment of the country of marketing. Highly regulated markets have more stringent regulatory policy than countries that are not tightly regulated. Magnitude of regulatory influence is often dictated by the availability of resources, expertise, and lack of regulation or its implementation. Thus, there is a greater need to harmonize the regulatory environment globally for bioequivalence 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.

It is clear that currently, the pharmaceutical industry has taken a global dimension. For this reason, bioequivalence assessment approaches should be harmonized with proper understanding of the assessment complexities as it affects the product quality. Thus, by developing a consensus or understanding and harmonizing among the regulatory authorities of different countries, both the consumers and producers can be benefited immensely.

In the recent years, some significant progress has been made towards harmonization. This effort is continued on regional level. In addition to harmonization, some regulatory authorities are also in the process of cooperating with the counterparts of other countries to harmonize the regulatory requirements while streamlining their own regulatory requirements. Tremendous work toward harmonization has been initiated and completed by some organizations. Chief among them is the International Conference on Harmonization (ICH), a consortium of regulatory authorities from Europe, Japan, and USA. Other organizations are also involved in this effort. ICH has primarily focused on developing guidelines for standardizing and harmonizing the regulatory requirements, primarily for the chemistry and manufacturing control, safety, efficacy aspects of new drug product quality. In addition, it has developed specific documents for content and format of drug product dossier. It has not yet focused on harmonizing the requirements for approval of generic equivalents.

Other national and international organizations are also involved in this endeavor. One of the major international organizations is the World Health Organization (WHO). It has made tremendous progress specifically in developing international consensus with regard to the regulatory requirements for assessing bioequivalence for marketing authorization of multisource pharmaceutical products for interchangeability, selection of comparator product for bioequivalence assessment, and other related documents. There are other European and Asian organizations that are also actively involved in the harmonization efforts. Some national, regional, and international organizations are involved in the area of assessment of BE and improving the quality of pharmaceutical products globally. Some of these organizations and regulatory authorities have also developed guidance related to BE and product quality. A brief description of these organizations and Agencies is summarized below:

- World Health Organization [<http://www.who.int/en/>]
- Global Regulatory GMP Effort by ISPE [<http://www.kppub.com/articles/india-Q7A-symposium-2006/ISPE-india-Q7A-symposium-2006.html>]
- Global GMP Harmonization by Japan [<http://www.nihs.go.jp/drug/section3/hiyama070518-3.pdf>]
- Global Harmonization Task Force [<http://www.ghhf.org/>]
- European Union (European Commission and EMEA) [<http://www.emea.europa.eu/htms/human/ich/ichquality.htm>]
- European Agency for the Evaluation of Medicinal Products (EMA) [<http://www.emea.europa.eu/>]
- Committee for Proprietary Medicinal Products [<http://www.emea.europa.eu/pdfs/human/ewp/20094307en.pdf>]
- Therapeutic Good Administration—Australia [<http://www.tga.gov.au/>]
- Association of Southeast Asian Nations Consultative Committee for Standards and Quality [<http://www.aseansec.org/>]
- Middle East Regulatory Conference (MERC)—United Arab Emirates [http://www.blnz.com/news/2008/05/13/Middle_East_Regulatory_Conference_MERC_6132.html]
- U.S. Food and Drug Administration (USFDA) [<http://www.fda.hhs.gov/>]

Some of these organizations have also developed guidelines on assessment of pharmaceutical quality and BE.

- ICH—Extensive guidelines on various aspects of pharmaceutical quality
- WHO
- WHO—Good manufacturing practices for pharmaceutical products
- WHO Guidelines for Good Clinical Practice (GCP)
- Multisource Pharmaceutical Products: WHO Guideline on Registration Requirements
- EMEA (GCPs, GLPs, new draft guidance on BE, see URL <http://www.emea.europa.eu/pdfs/human/qwp/140198enrev1.pdf>)
- USFDA (several general and drug specific regulatory guidance documents)

SUMMARY

The concept of BE has been adopted by the pharmaceutical industry and national regulatory authorities throughout the world for over 20 years. Because of this, thousands of generic drugs have been manufactured and marketed by the industry after regulatory approval. A lot of advances have been made during these years in developing various approaches to assess BE through research that would assure high quality interchangeable and affordable drugs. However, a lot remains to be done. There is a continuing attempt by national regulatory authorities, international public health organization, pharmaceutical, and basic scientists to understand and develop more efficient and scientifically valid approaches to assess bioequivalence of various dosage forms including some of the tough complex special dosage forms.

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