Bioequivalence study: Similarities and Differences Among EMA, FDA,WHO & GCC Requirements

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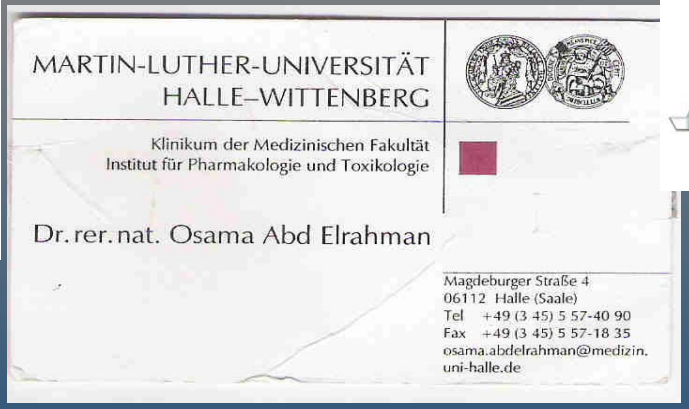


Outlines

- **Introduction to Bioequivalence Study**
- **GL's (BE,BMV & BCS based Biowaivers) Similarities & differences**
- **The new era (anomalies) of BE Product- specific Guidance**
- **Consequence's**
- **The important Need of Harmoniz(s)ation.**
- **Conclusion**

Bioequivalence Study

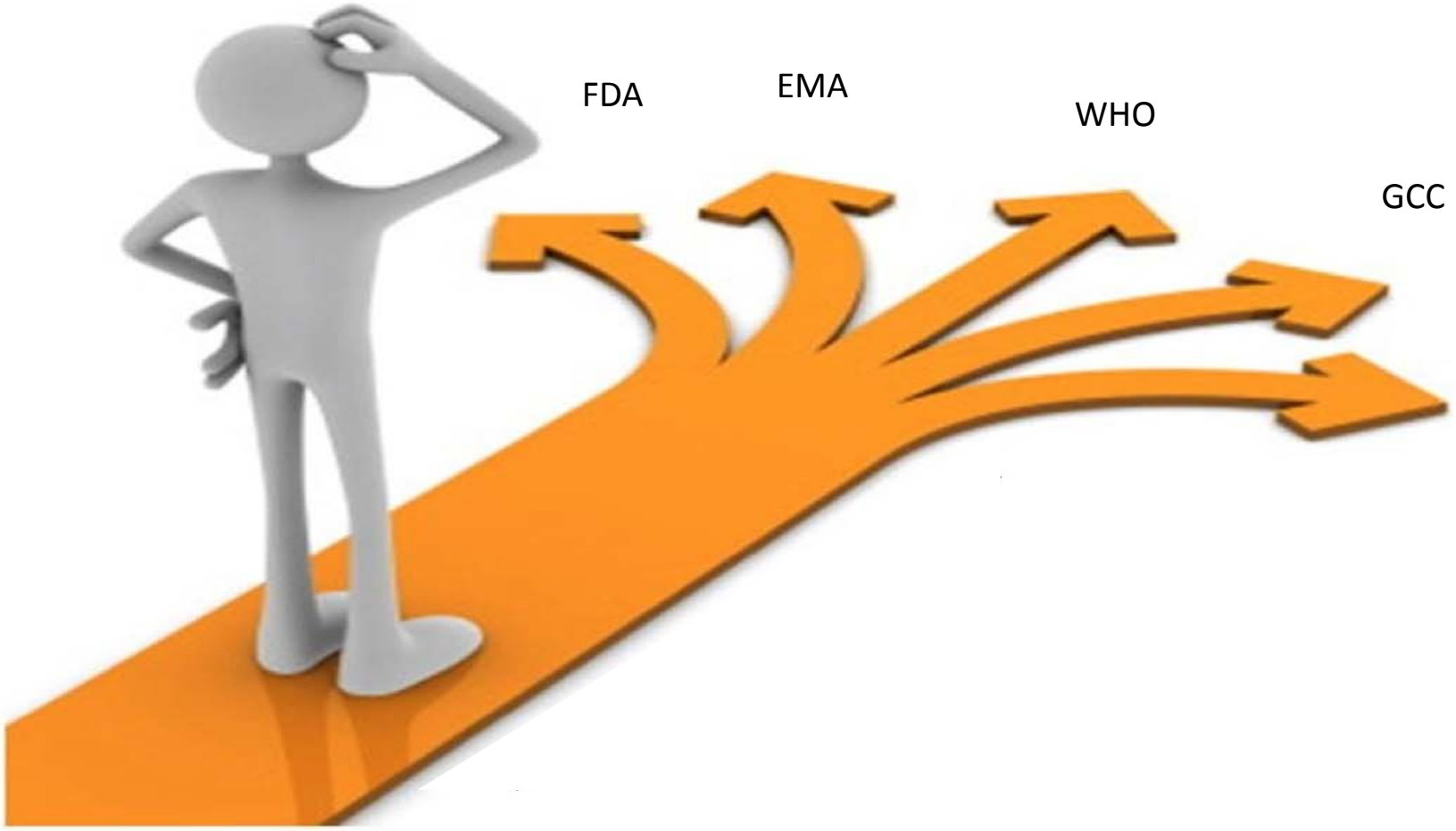
Science ®Regulations

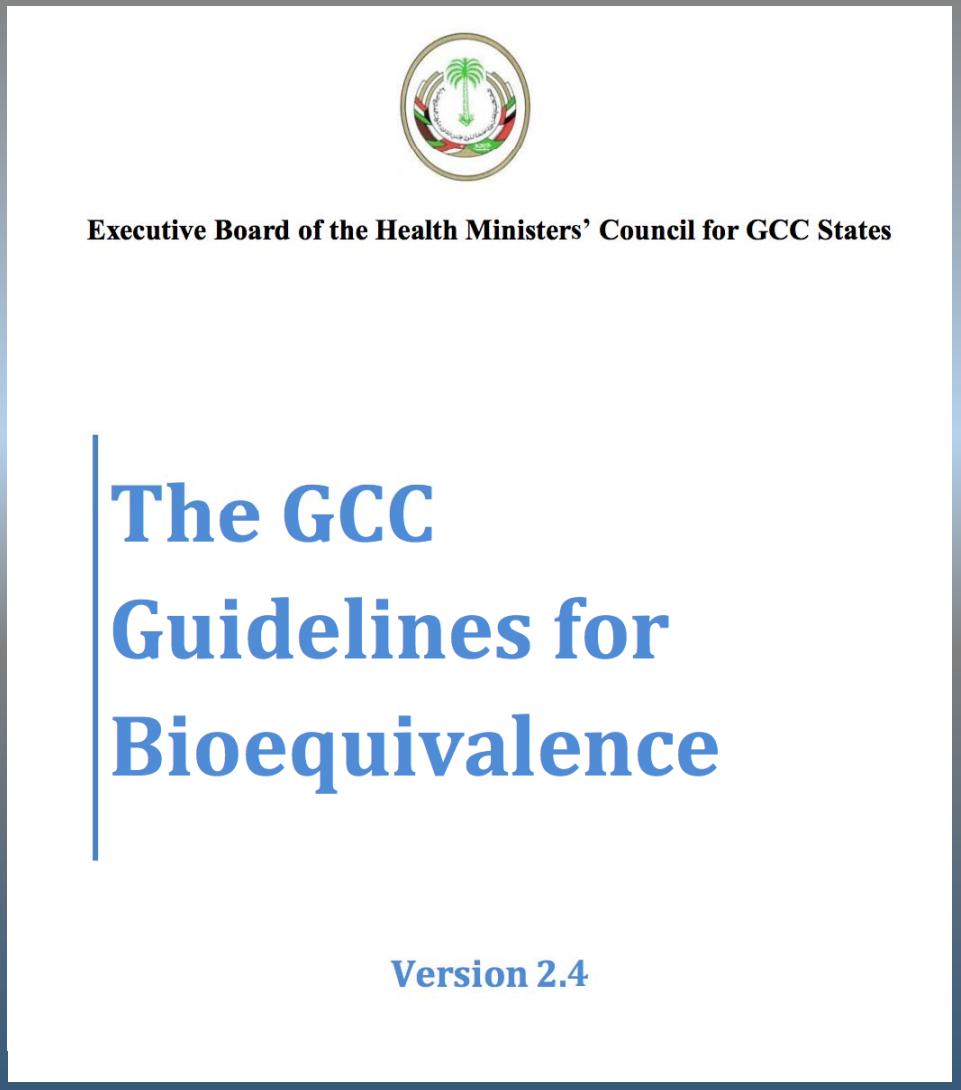
In vivo comparison using humans as dissolution models

- *‚Biologicl quality control‘*
- Comparative evaluation of the formulation effect

Bioequivalence *therapeutic equivalence*

Guidance





1. Introduction

This guideline is adapted from the **EMEA guideline** on the investigation of bioequivalence,
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.

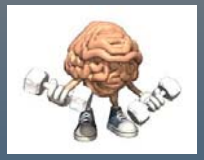
BE requirements: Test and reference products

Regulatory Agency	Generic drug (Test)	Reference product
EMA	• Pharmaceutically Equivalent :qualitatively and quantitatively the same API in the same pharmaceutical form as the reference product. • pharmaceutical alternatives: Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered the same active substance, unless they differ significantly in properties in regards to safety and/or efficacy. • different oral IR pharmaceutical forms like tablets, coated tablets and capsules are defined to be the "same"	A drug product whose marketing authorization in the EU has been granted on the basis of a complete dossier. If there are several dosage forms of this medicinal product (MP) on the market, the reference should be the dosage form used for the initial approval of the concerned MP and which was used in the clinical efficacy and safety studies (if available).
FDA	• Pharmaceutically Equivalent (same salt or ester) • Not considering pharmaceutical alternatives (different salt or ester)	An RLD means the listed drug identified by the FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

BE requirements: Test and reference products

Regulatory Agency	Generic drug	Reference product
G CC	• should be representative of the product to be marketed • should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. In case of a production batch smaller than 100,000 units, a full production batch will be required. • Unless otherwise justified, the assayed content of the batch used as test product should not differ more than 5% from that of the batch used as reference product. (EMA) • Nothing mentioned about the use of pharmaceutical alternatives.	Reference Products must be the original brand-name (i.e. manufactured in the country of origin of the original brand name); if this is not available in the market then the brand-name regarding the same company but different country of origin is used, marketed in GCC region, ICH region, or in any stringent regulatory authority. • If the original brand-name is not available in the market or no longer produced, then the product which is the local market leader may be used as a reference product.

"this challenged my walnut-sized brain"



Bio- Creep phenomenon
(FDA Suitability Petition route)

GCC & Russia:

— Possible to use another generic as reference.
Example: T1/R = 0.894 (*CV* 20%, *n* 20, 90% CI 80.20–99.66% and is approved).
Subsequently, T1 is used as the 'reference' for another generic T2.
T2/T1 = 0.894 (passes 'BE' and is approved). But: T1/R *would be* 0.8942 or only 0.799 (90% CI 71.70–89.09%)!

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Global Harmonization of Comparator Products for Bioequivalence Studies

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Commentary
First Online: 06 March 2017
4
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Abstract

Comparator products should be the products that were shown to be safe and efficacious in pivotal clinical trials to ensure prescribability of generics. The use of a common comparator ensures switchability between generics. The selection of the comparator is a national responsibility and may be different between countries. This paper discusses the current recommendations on selection of comparators, the associated problems, and the possibility of harmonization. Most countries follow the World Health Organization (WHO)

- The exclusive use of the **local comparator** to ensure switchability is **ethically** and **scientifically questionable.**
- **Standardizing comparator products** is not only of interest and benefit for development of generic products but also in clinical documentation of **combination treatments** and for use as comparator product in **clinical phase III trials.**
- Ideally, globally accepted comparator products would **decrease the number of in vivo bioequivalence studies** and reduce the **cost of generic drug development.**
- **The innovator product from well- regulated markets should be the global comparator.**

BE requirements: Demographic Characteristics

Topic	Similarities	Differences
Subjects	**Healthy normal subjects, unless – for reasons of safety – it becomes necessary to employ patients.**	**Japan: Subjects with low gastric acidity (achlorhydric subjects) in cases where the use of the drug is not limited to a specific population and the test and reference products show a significant difference in in vitro dissolution at around pH 6.8, or between pH 3.0–6.8 for basic drugs. Not applicable for enteric coated products.** **The high rate of achlorhydric subjects in the Japanese population is an important factor for assessing bioequivalence, as this parameter indicate an ethnic difference that must be considered in bioequivalence studies.**

What is the justification for studying bioequivalence in healthy volunteers?

"Variability is the enemy of therapeutics" and is also the enemy of bioequivalence. We are trying to determine if two dosage forms of the same drug behave similarly. Therefore we want to keep any other variability not due to the dosage forms at a minimum. We choose the least variable "test tube", that is, a healthy volunteer. Disease states can definitely change bioavailability, but we are testing for bioequivalence, not bioavailability. **Benet LZ**

1st MENA Regulatory Conference on Bioequivalence, Bio waivers, Bio analysis and Dissolution. Amman, Jordan, 23 September 2013.

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Virtual bioequivalence for achlorhydric subjects: The use of PBPK modelling to assess the formulation-dependent effect of achlorhydria

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ABSTRACT

Majority of bioequivalence studies are conducted in healthy volunteers. It has been argued that bioequivalence may not necessarily hold true in relevant patient populations due to a variety of reasons which affect one formulation more than the other for instance in achlorhydric patients where elevated gastric pH may lead to differential effects on formulations which are pH-sensitive with respect to release or dissolution. We therefore examined achlorhydria-related disparity in bioequivalence of levothyroxine and nifedipine formulations using virtual bioequivalence within a physiologically-based pharmacokinetic (PBPK) modelling framework. The *in vitro* dissolution profiles at neutral pH were incorporated into PBPK models to mimic the achlorhydria with *in vitro–in vivo* relationship established using bio-relevant pH media. The PBPK models successfully reproduced the outcome of the bioequivalence studies in healthy volunteers under the normal conditions as well as under proton pump inhibitor-induced achlorhydria. The geometric mean test/reference ratios for C_{max} and AUC between levothyroxine tablet and capsule in patients receiving proton pump inhibitor were 1.21 (90%CI, 1.13–1.29) and 1.09 (90%CI, 1.02–1.17), respectively. Extension of the virtual bioequivalence study to Japanese elderly, who show high incidence of achlorhydria, indicated bio-inequivalence which C_{max} and AUC ratios between nifedipine control-released reference and test formulations were 3.08 (90%CI, 2.81–3.38) and 1.57 (90%CI, 1.43–1.74), respectively. Virtual bioequivalence studies through the PBPK models can highlight the need for conduct of specific studies in elderly Japanese populations where there are discrepancies in pH-sensitivity of dissolution between the test and reference formulations.

1. Introduction

A generic pharmaceutical product is marketed if it is therapeutically

silico modelling of the target population is a new concept materialized with the advent of mechanistic models of oral drug absorption which combines *in vitro* information with the physiologically-based pharma-

formulation more than the other for instance in achlorhydric patients where elevated gastric pH may lead to differential effects on formulations which are pH-sensitive with respect to release or dissolution. We therefore

BE requirements: Demographic Characteristics

Topic	Similarities	Differences
Number of Subjects	**Minimum of 12 subjects (with few exceptions)**	**GCC: A number of subjects of less than 24 may be accepted (with a minimum of 18 subjects) when statistically justifiable.**
Geno-/phenotyping	**Should be considered for safety or pharmacokinetic reasons, as genetics play an important role in determining the intra-individual variability.**	**EMA followed the same rationale in their GL – minimize variability. This idea is even more clear for parallel designs, where geno-/phenotyping is mandatory. GCC : not mentioned**

Yong Chung et al. (2010)
Tacrolimus in healthy subjects (2×2 cross-over), subgroup analysis
CYP3A5*1/*1+CYP3A5*1/*3 (n=16) and
CYP3A5*3/*3 (n=13); %CVW.

PK metric	G1	G2
—expressors—		Non-Exp.–
AUC0-t	30	42
Cmax	29	44

Gonzales-Vacarezza et al. (2013)
Mirtazapine is eliminated by CYP2D6 and CYP3A and undergoes significant presystemic elimination following oral administration. PMs (subjects with no active CYP2D genes) have a higher **AUC (+79%)** compared to EMs (extensive/fast,one or more active genes). FMs show a higher first-pass effect following oral administration. %CVW from two 2×2 cross-over studies:
Group 0: no active CYP2D6 genes (n=7) PM
Group 1: 1 active CYP2D6 gene (n=26) FM
Group 2: ≥2 active CYP2D6 genes (n=35) FM

PK metric	G1	G2	G0	total
	FM–	FM–	PM–	
AUC0-t	7.7	8.5	15.0	12.3
Cmax	21.4	22.2	24.9	23.4

BE requirements: Demographic Characteristics

Standardization to determine *formulation factors !*

Topic	Similarities	Differences
Age	Adults	EMA, FDA: At least 18 years. FDA: If the drug product is to be used primarily in the elderly, the study should include as many subjects as possible **of 60 years of age or older.** WHO: 18–55 years. GCC: **18-50 Years.**
BMI (kg/m^2)	Most specify a body weight range.	EMA, : BMI within 18.5 and 30 kg/m^2. FDA: Individuals representative of the general population. WHO: Within an acceptable range according to accepted life tables. GCC: **Within 15% of ideal body weight, height and body build.**
Sex, ethnicity	Females in the BE should not be pregnant.	EMA, FDA, WHO: Subjects can belong to **either sex.** GCC: **If females are included in the study, the effects of gender differences and menstrual cycle (if applicable) are examined statistically.**

Type of study: The number of studies and study design depend on the physico-chemical characteristics of the API, its PK properties and proportionality in composition.

Regulatory Agency	Immediate Release	Modified Release
U.S.A	Total of 2 studies: 1 single dose crossover study fasted 1 single dose crossover study, fed (If food mentioned in the product Monograph) if a multiple-dose study design is important, appropriate dosage administration and sampling be carried out to document attainment of steady state.	Fasting and fed If a multiple-dose study design is important, appropriate dosage administration and sampling be carried out to document attainment of steady state.
Europe & Australia	Total of 1-2 studies: 1 single dose crossover study, Fasted. OR Fed condition according to SmPC Recommendations related with food interaction effects.	Fasting, fed and steady state
Japan	Fasting and fed	Fasting, fed and steady state
Canada	Fasting	Fasting and fed If Steady-state studies are required, the food and fluid conditions and restrictions noted above should apply on the preceding evening and on the day the plasma profiles are to be obtained.
GCC	Fasting and if food effect from document evidence or drug requires to be administered in fed condition in this case fed study required.	Fasting and fed
South Korea	Fasting	Fasting fed and steady state

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Investigation on the need of multiple dose bioequivalence studies for prolonged-release generic products

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ABSTRACT

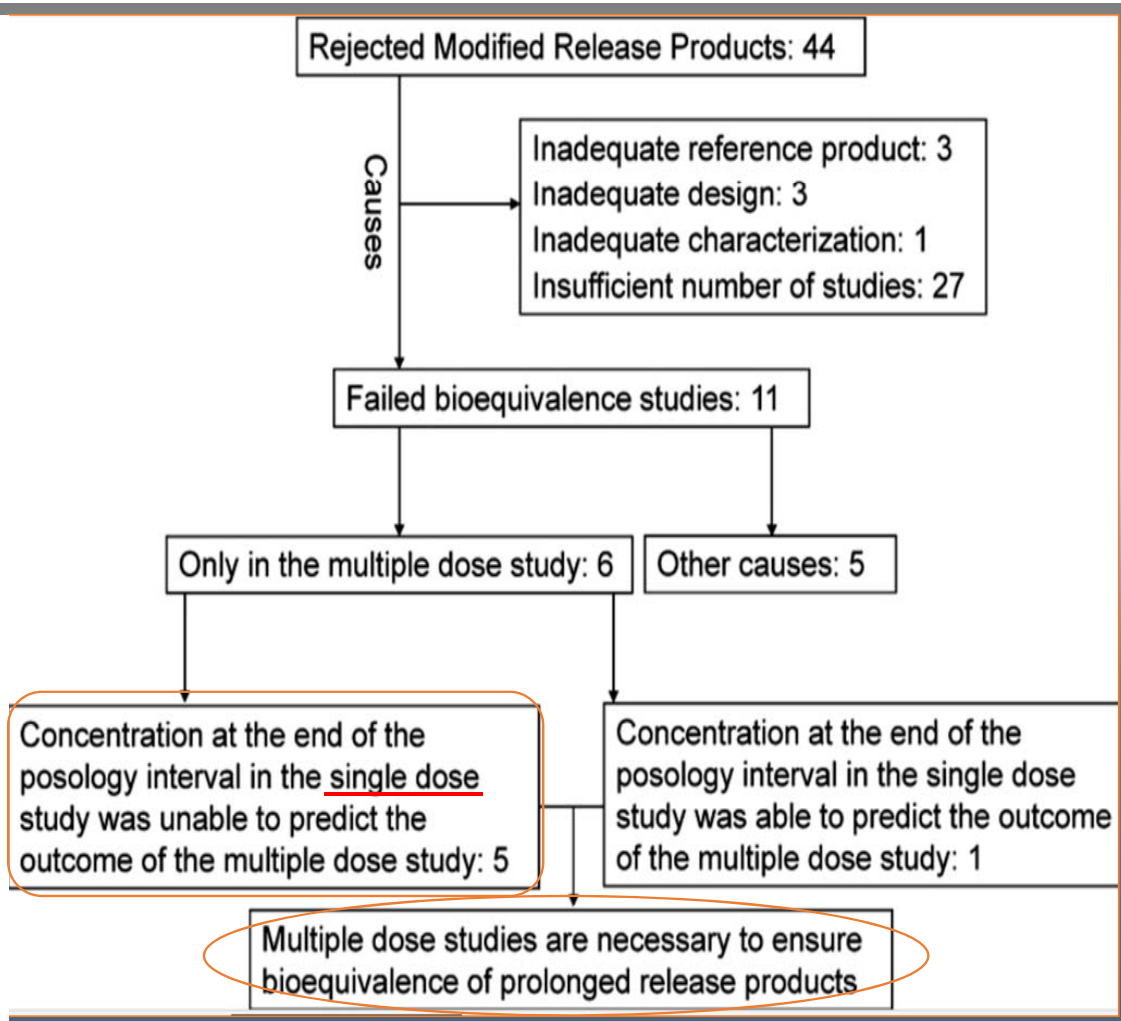
In the European Union multiple dose bioequivalence studies are required for the approval of generic prolonged-release products, but they are not required by the US-FDA. In order to investigate if the multiple dose bioequivalence studies are necessary, the bioequivalence studies assessed in the Spanish Agency for Medicines and Health Care Products in the last 10 years were searched to find all reasons for rejection and identify those cases where the multiple dose study had failed to show bioequivalence and the single dose study had shown bioequivalence. In these latter cases, the plasma concentration at the end of the dosing interval (C_τ) in the single dose study was assessed to investigate its sensitivity to predict non-bioequivalence in the steady state.

The search identified six cases where the non-equivalence in the multiple dose study was not detected by the corresponding single dose study. C_τ was not able to detect the difference in five cases and in general it was more variable than conventional metrics. In conclusion, the multiple dose bioequivalence study is necessary to ensure therapeutic equivalence and the use of C_τ would be counterproductive, increasing the sample size of the studies without enough sensitivity to detect differences in the steady state.

1. Introduction

The present CHMP Guideline on Modified Release Oral and Transdermal Dosage Forms (Committee for Proprietary Medicinal Products (CPMP), 1999) requires the investigation of bioequivalence of generic/hybrid prolonged release products in a single dose study in fasted state, a multiple dose study in fasted state and in presence of a high fat meal in those cases where the product is to be taken irrespective of the food intake, or only a single dose study

After the announcement of the update of the present guideline (Committee for Medicinal Products for Human Use (CHMP), 2010a), EUFEPS sponsored recently a conference to address the pharmacokinetic requirements of this guideline (EUFEPS BABP Network Open Discussion Forum. Revision of BE Requirements for Modified Release Products). The need for multiple dose studies was one of the topics addressed (Becker, 2011). The literature was reviewed to identify cases where multiple dose studies were necessary, i.e. cases where the difference between products was detected more



Unless we have performed steady state studies – at different dose levels –we do know nothing about the PK of a drug.

AUC_{tau}=AUC_{inf} in the case of accumulation.

AUC_{tau}>AUC_{inf} indicate nonlinear PK. ***"Superposition Principle"***

BE with which strength?

Regulatory Agency	Linear Pharmacokinetics	Non- Linear Pharmacokinetics
FDA	Reference Listed Drug (RLD) in the Orange Book* *usually the highest strength if formulations are proportionally	Depends upon the type of nonlinearity. • If the nonlinearity is characterized by greater than proportional increase in AUC with increasing dose → highest therapeutic dose. • If the nonlinearity is less than proportional due to saturable absorption → lowest strength or a strength in the linear part of the curve.
EMA	 • Highly soluble drug and any safety concern: Lower strength acceptable • Problems of sensitivity of the analytical method: Highest strength acceptable	 • If the nonlinearity is less than proportional due to limited solubility of the API, on two strengths.
WHO, GCC	• at the highest strength	Not addressed in Guidance's

Topic	Similarities	Differences
Add-on, GSD (Group-Sequential Design), TSD Two-Stage Design	EMA, FDA, WHO, GCC: Two-Stage Design (instead of Add-on) acceptable, adjusted significance levels predefined in the protocol.	Japan: Add-on Design acceptable.
PK-metrics	SD: AUC0–t, AUC0–∞, Cmax, tmax, t1⁄2, λz. AUC0–72 instead of AUC0–t. MD: (Shape & AUC) AUC0–τ (AUC part.in specific cases), Cmax,ss, tmax,ss, Cτ,ss (Shape)	EMA, GCC: SD AUC(0–72h) instead of AUC0–t for all IR products (not acceptable for MD) MD Cτ,ss. FDA: SD AUC0–72 instead of AUC0–t if long half life drug and low variability. FDA, HC: MD Cmin,ss.
Statistic	Parametric Log-transformation (except tmax, non-parametric, based on therapeutic relevance). ANOVA or mixed-effects model on log-transformed PK-metrics, post-hoc exclusion of outliers is generally not accepted.	EMA, GCC: Fixed-effects model. FDA, HC: Mixed (Fixed +random)-effects model.

Topic	Similarities	Differences
BE-limits and assessment Of BE	90% confidence interval (CI) of GMR SD: AUC_{0-t} and C_{max}, MD: $AUC_{0-\tau}$ and $C_{max,ss}$ within 80.00–125.00%.	FDA, GCC: $AUC_{0-\infty}$additionally for SD. EMA: $AUC_{0-\infty}$ additionally for SD of MR. WHO, Russia, China: Nonparametric test of tmax if clinically relevant. HC: BE-limits 80.0–125.0% for AUCs. GMR of Cmax within 80.0–125.0% (i.e., no CI is required).
HVD(P)s	Reference-scaling acceptable in some countries/regions. If acceptable, restriction of the GMR (within 80.00–125.00%).	EMA,WHO, GCC: Only Cmax, CVwR >30% demonstrated in a replicate design, upper cap of scaling 50%, method ABEL. High variability not caused by outliers. (not mentioned in GCC) FDA: Cmax and AUC, CVwR ≥30% demonstrated in a replicate design, method RSABE. GCC: a wider acceptance range (i.e. 75-133%) for Cmax can be used.

4.1.10 Highly variable drugs or drug products

Highly variable drug products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a drug product can be considered as highly variable in its rate and/or extent of absorption, a replicate cross-over design study can be carried out.

Those HVDP for which a wider difference in C_{max} is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case the acceptance criteria for C_{max} can be widened to a maximum of 69.84 – 143.19%. For the acceptance interval to be widened the bioequivalence study must be of a replicate design where it has been demonstrated that the within-subject variability for C_{max} of the reference compound in the study is >30%. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers. The request for widened interval must be prospectively specified in the protocol.

The extent of the widening is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to $[U, L] = \exp[\pm k \cdot s_{WR}]$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and s_{WR} is the within-subject standard deviation of the log-transformed values of C_{max} of the reference product. The table below gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Within-subject CV (%)*	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

$$* CV(\%) = 100\sqrt{e^{s_{WR}^2} - 1}$$

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00-125.00%.

The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC where the acceptance range should remain at 80.00 – 125.00% regardless of variability.

It is acceptable to apply either a 3-period or a 4-period crossover scheme in the replicate design study.

Bioanalytical Part

Topic	Similarities	Differences
BMV Guidance	**deviation from recommendations presented in the guidance document**	**FDA 2013 BMV draft: justification Not mandatory** **FDA May 2018 BMV Guidance: justification is mandatory**
By using LC-MS, recommendations on the determination of ion suppression or ion enhancement effects	**Presented**	**FDA 2018:** **missing Recommendations on how the experimental procedure should be designed .** **EMA: protocol is described**
Analyate Recovery	**The sponsor should optimize the recovery of the analyte to ensure that the extraction is efficient and reproducible.** **Recovery need not be 100 percent, but the extent of the recovery of an analyte and of the ISs should be consistent and reproducible.**	**EMA: Not addressed** **FDA: May 2018** **WHO:** MHLW guidelines for BMV (2013) **GCC:** **Annex 1 Bioequivalence Study Summary Template: Bioanalytical Method Summary** **Average recovery of drug (%)** **Average recovery of IS (%)** **Annex 2 Updates: What's New in The GCC Guidelines for Bioequivalence (version 2.4)?** **Refer to "Guideline on bioanalytical method validation" published by (EMA). ??**

Topic	Similarities	Differences
Incurred sample reanalysis (ISR)	When: • all pivotal bioequivalence trials • How, How many samples& results: 10% of the samples should be reanalysed in case the number of samples is less than 1000 samples and 5% of the number of samples exceeding 1000 samples. It is advised to obtain samples around Cmax and in the elimination phase. initial analysis and reanalysis should be within 20% of their mean for at least 67% of the repeats. Large differences between results may indicate analytical issues and should be investigated. Samples should not be pooled, as pooling may limit anomalous findings.	FDA: now(May,2018) sample size Similar to EMA, (draft 2013, 7%) GCC: *(Mandatory for studies that were conducted beyond 2013)* *When , How, How many samples, results, ……..??????* WHO: WHO Technical Report, 2015 The extent of testing done should be based on an in-depth understanding of the analytical method and analyte used ???

in-study analysis and reporting		**FDA (BMV) May 2018 :** ***Study samples with concentrations listed below the LLOQ should be reported as (BQL)*** ***Concentrations below the LLOQ should be reported as zeros (2013 draft)***
System suitability		**EMA (BMV) 2012: Not addressed** **FDA (BMV) May 2018 : If system suitability is assessed, a specific SOP should be used. System suitability, including apparatus conditioning and instrument performance, should be determined using samples that are independent of the current study calibrators, QCs, and study samples. Records of system suitability should be maintained and available for audits.** **WHO: Not addressed** **GCC: Not addressed**

Endogenous analytes	• **The biological matrix used to prepare calibration standards should be the same as the study samples and free of the endogenous analyte.** • **The endogenous concentrations of the analyte in the biological matrix should be evaluated prior to QC preparation (e.g., by replicate analysis).** • **Parallelism should be evaluated for assays for endogenous compounds.** ***(Parallelism is a test for demonstrating potential matrix effects by using a serial dilution of (incurred) study samples)***	**EMA: Not addressed** **FDA (BMV): May 2018 section on Endogenous Compounds.** **WHO: Not addressed** **GCC: Not addressed**

BCS- based Biowaivers

BCS- based Biowaivers

FDA EMA WHO

- Dose/Solubility ratio ≤ 250mL in aqueous buffers pHs 1(1.2) – 6.8 (7.5) at 37 ± 1°C (± 0.5°C) (± 0.5°C)
- Dose is defined differently in different guidance's
- WHO- highest dose strength mentioned in the EML

ICH M9, June 2018 draft: highest single therapeutic dose (X EML) or when not meet solubility criterion then the highest strength ,additional data (dose propotional Pk over a dose range that includes the highest therapeutic dose) are required)

- US FDA – maximum dose strength that is marketed
- EMA- highest single therapeutic dose that is administered

ICH M9, June 2018 draft: In case the CV% is too high, f2 calculation is considered not accurate and reliable and a conclusion on similarity in dissolution cannot be made.

Medium	pH	D/S Ratio (mL) D=153mg base	D/S Ratio(mL) D=600mg base
Water	6.4	< 24.60	< 96.49
*SGFsp	1.0	< 29.13	< 114.25
*SGFsp	1.2	< 23.06	< 90.70
Acetate buffer	4.5	< 22.55	< 88.45
§SIFsp	6.8	62.94	< 246.85
§SIFsp	7.0	1478	
§SIFsp	7.5	9243	

Dose solubility ratios for amodiaquine hydrochloride in aqueous buffer at 37 °C

Bio waivers

BCS- based bio- waivers

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Mini-Review

BCS Biowaivers: Similarities and Differences Among EMA, FDA, and WHO Requirements

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Abstract. The Biopharmaceutics Classification System (BCS), based on aqueous solubility and intestinal permeability, has enjoyed wide use since 1995 as a mechanism for waiving *in vivo* bioavailability and bioequivalence studies. In 2000, the US-FDA was the first regulatory agency to publish guidance for industry describing how to meet criteria for requesting a waiver of *in vivo* bioavailability and bioequivalence studies for highly soluble, highly permeable (BCS Class I) drugs. Subsequently, the World Health Organization (WHO) and European Medicines Agency (EMA) published guidelines recommending how to obtain BCS biowaivers for BCS Class III drugs (high solubility, low permeability), in addition to Class I drugs. In 2015, the US-FDA became better harmonized with the EMA and WHO following publication of two guidances for industry outlining criteria for obtaining BCS biowaivers for both Class I and Class III drugs. A detailed review and comparison of the BCS Class I and Class III criteria currently recommended by the US-FDA, EMA, and WHO revealed good convergence of the three agencies with respect to BCS biowaiver criteria. The comparison also suggested that, by applying the most conservative of the three jurisdictional approaches, it should be possible for a sponsor to design the same set of BCS biowaiver studies in preparing a submission for worldwide filing to satisfy US, European, and emerging market regulators. It is hoped that the availability of BCS Class I and Class III biowaivers in multiple jurisdictions will encourage more sponsors to request waivers of *in vivo* bioavailability/bioequivalence testing using the BCS approach.

KEY WORDS: bioavailability; bioequivalence; biopharmaceutics classification system; *in vitro* dissolution; regulatory guidance.

Table I. Similarities and Differences in Criteria for an Acceptable BCS-Based Biowaiver for the US-FDA, EMA, and WHO

Attribute/criteria	Parameter	US-FDA	EMA	WHO	Common positions
Type of BCS biowaiver considered by agency		I and III	I and III	I and III	I and III

The BCS Class I and Class III
criteria currently recommended by the US-FDA, EMA, and WHO revealed good convergence of the three agencies with respect to BCS bio-waiver criteria.

World Health Organization

GCC: Class I √
Class 3 ???

Japan: Not acceptable.

Executive Board of the Health Ministers' Council for GCC States

The GCC Guidelines for Bioequivalence

Version 2.4

Criteria for fast and complete dissolution; - Rate of dissolution

Class I: ≥85% 30 min **Class III: ≥85% 15 min**

"This challenged again my walnut-sized brain"

Appendix III: BCS-based Biowaiver

I. Introduction

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, *i.e.*, it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data.

Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index (see section 3.1.9). The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form. However, it is not applicable for sublingual, buccal, and modified release formulations. For orodispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded.

BCS-based biowaivers are intended to address the question of bioequivalence between specific test and reference products. The principles may be used to establish bioequivalence in applications for generic medicinal products, extensions of innovator products, variations that require bioequivalence testing, and between early clinical trial products and to-be-marketed products.

II. Summary Requirements

BCS-based biowaiver are applicable for an immediate release drug product if

- the drug substance has been proven to exhibit high solubility and complete absorption (BCS-class I; for details see section III) and
- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements (see section IV.1) and
- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred (see section IV.2).

Generally the risks of an inappropriate biowaiver decision should be more critically reviewed (e.g.

J Pharm Pharm Sci (www.cspsCanada.org) 21, 27 - 37, 2018

A Survey of the Regulatory Requirements for BCS-Based Biowaivers for Solid Oral Dosage Forms by Participating Regulators and Organisations of the International Generic Drug Regulators Programme

Joy van Oudtshoorn[1], Alfredo García-Arieta[2], Gustavo Mendes Lima Santos[3], Christopher Crane[4], Clare Rodrigues[5], Craig Simon[6], Ji Myoung Kim[7], Sang Aeh Park[7], Yusuke Okada[8], Ryosuke Kuribayashi[8], Chantal Pfäffli[9], Arno Nolting[9], Iván Omar Calderón Lojero[10], Zulema Rodríguez Martínez[10], Wen-Yi Hung[11], April C. Braddy[12], Nancy Arciniegas Leal[13], Diego Gutierrez Triana[13], Mitch Clarke[14], Peter Bachmann[15]

General aspects	Australia	Brazil	Canada	Colombia	European Union	New Zealand	Singapore	South Africa	South Korea	Switzerland	Taiwan	US	WHO	
Dosage form														
Oral solid IR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y
Capsules and tablets similar	Y	N	N	N	N	Y	N	Y	N	N	N	N		N
Modified release	N	N	N	N	N	N	N	N	N	N	N	N		N
Orodispersible tablets, if justified	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N		Y
Oral suspensions	Y	Y	N	N	Y	Y	Y	Y	N	Y	N	N[c]		
Additional strengths within dose range, not marketed by innovator	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	N		Y
Data for each product strength vs corresponding reference strength	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y		Y
Different salts if test and reference are both BCS Class I	Y	N	N	N	Y	Y	Y	Y	N	Y	N	N		N
Different esters, ethers, isomers, mixtures of isomers, complexes or derivatives	N	N	N	N	N	N	N	N	N	N	N	N		N

The new era (anomalies) of BE Product- specific Guidance

ELSEVIER

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

General Commentary

Past, Present, and Future of Bioequivalence: Improving Assessment and Extrapolation of Therapeutic Equivalence for Oral Drug Products

Rodrigo Cristofoletti [1,2], Malcolm Rowland [3], Lawrence J. Lesko [4], Henning Blume [5], Amin Rostami-Hodjegan [3,6], Jennifer B. Dressman [2,*]

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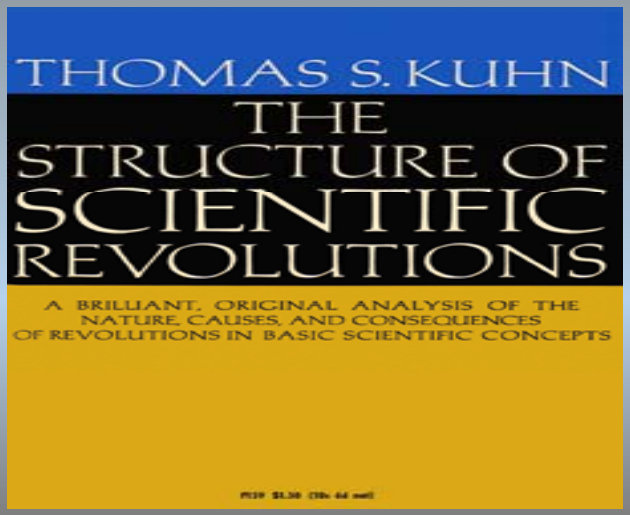
ABSTRACT

The growth in the utilization of systems thinking principles has created a paradigm shift in the regulatory sciences and drug product development. Instead of relying extensively on end product testing and one-size-fits-all regulatory criteria, this new paradigm has focused on building quality into the product by design and fostering the development of product-specific, clinically relevant specifications. In this context, this commentary describes the evolution of bioequivalence regulations up to the current day and



using the one size-fits-all approach (average BE), standard paradigm, to compare product performances and decide about therapeutic equivalence was reached, **deviations from the standard paradigm** (i.e., the so-called "anomalies" Thomas Kuhn)
have been accumulating, as demonstrated by the increasing numbers of drug products for which there are product specific recommendations for BE testing.

The new era of BE Product- specific Guidance

Imatinib

Contains Nonbinding Recommendations

Draft Guidance on Imatinib Mesylate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Imatinib Mesylate

Form/Route: Tablets/Oral

Recommended studies: 1 study

1. Type of study: Fed
   Design: Steady state, two-way crossover in vivo
   Strength: 400 mg
   Subjects: Patients already receiving a stable dose of imatinib tablets, 400 mg
   Additional Comments: Recruitment efforts should be targeted at patients for whom a titration away from the 400 mg dose is unlikely, such as patients with gastrointestinal stromal tumors and patients in their first three months of treatment for chronic myeloid leukemia (CML). Patients should be screened for hepatotoxicity prior to enrollment and the protocol should include procedures to monitor for heptotoxicity during the course of the study. Concomitant medication with drugs known to be inhibitors and/or inducers of CYP3A4 family should be a protocol exclusion criterion.

   A light breakfast can be used as the fed meal. The meal should be clearly identified in the study protocol, including calorie breakdown and composition.

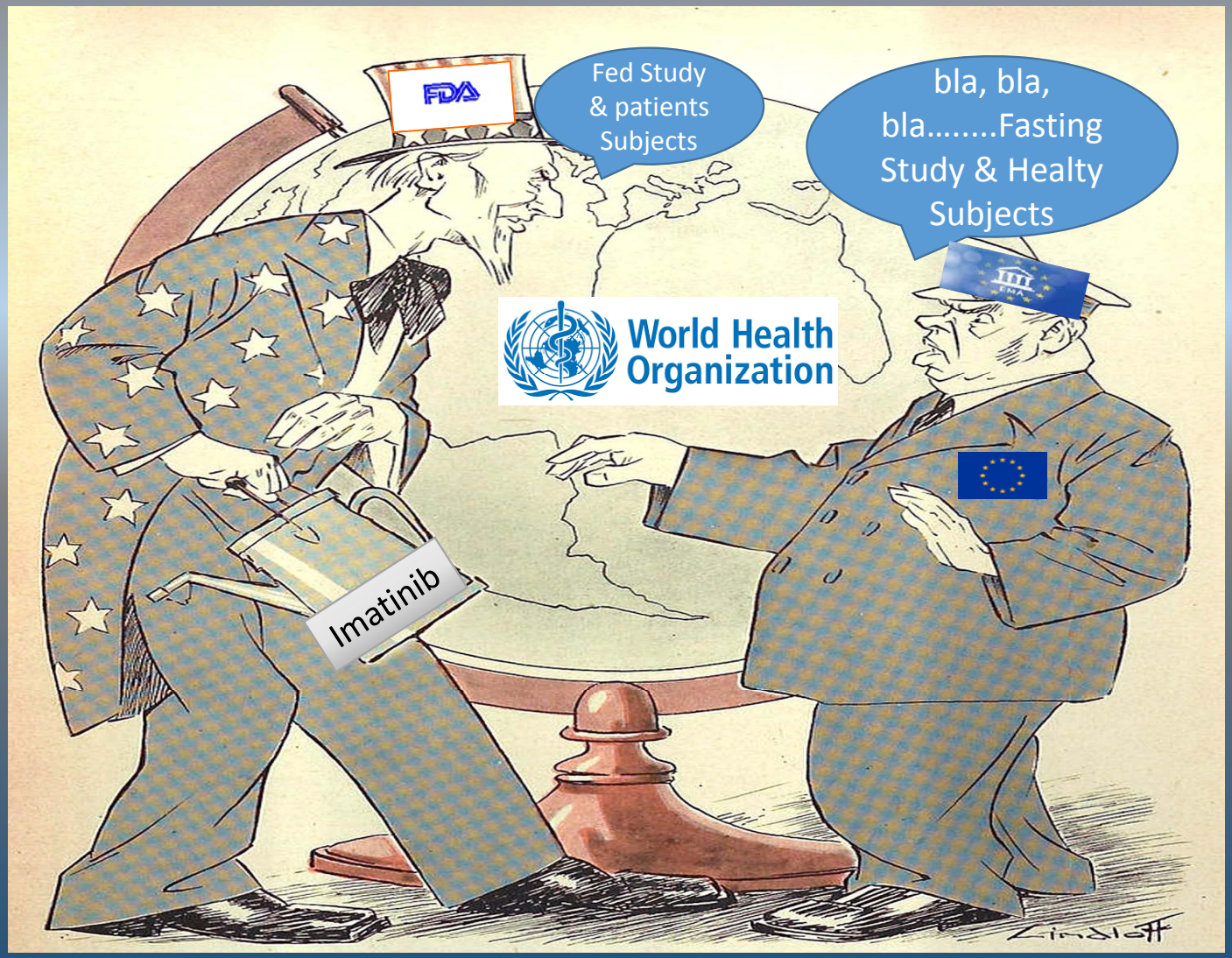
Imatinib hard capsules 50 and 100 mg, film-coated tablets 100 and 400 mg product-specific bioequivalence guidance

Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☐ **neither of the two** **Background:** imatinib is a compound with complete absorption, but the available data on solubility does not allow its BCS classification. If the Applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, imatinib could be classified as BCS class I drug and a BCS biowaiver could be applicable.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☐ **fasting** ☐ **fed** ☐ **both** ☒ **either fasting or fed** Either a fasting or a fed study is acceptable. The SmPC recommends intake in fed state to minimise the risk of gastrointestinal irritations. However, a single dose fasting study in healthy volunteers is feasible and preferred to increase the sensitivity to detect differences between products. A fed study is acceptable



Ooooops, I don’t have Product-specific Guidance's at all, What to do now?

FDA Issues 54 New and Revised Product-Specific Guidances

Posted 13 September 2018 | By Michael Mezher

The US Food and Drug Administration (FDA) on Thursday issued a batch of 54 new and revised product-specific draft guidances detailing its expectations for companies looking to develop generic versions of those products.

Among the documents are 42 new and 12 revised guidances providing specific recommendations for the studies FDA believes are necessary to demonstrate that the products are therapeutically equivalent to their reference listed drug (RLD).

Many of the product-specific guidances are for recently approved drugs, including AbbVie's Mavyret (glecaprevir and pibrentasvir), Gilead's Vosevi (sofosbuvir, velpatasvir and voxilaprevir), Novartis' Rydapt (midostaurin), Celgene's Idhifa (enasidenib) and Teva's Austedo (deutetrabenazine), all of which were approved by the agency in 2017.

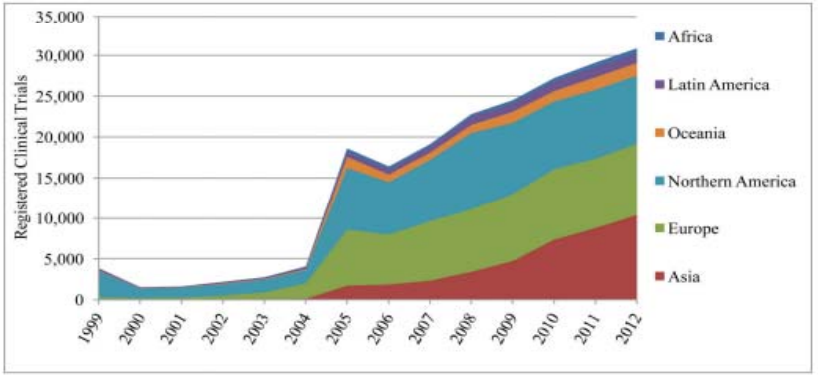
"With this new batch of guidance documents, we're not only providing recommendations for some new generic drugs, but the FDA is also modernizing some of its previously-issued guidance to make sure they reflect the most efficient path for developing generics," FDA Commissioner Scott Gottlieb said.

Of the 54 product-specific guidances, 18 (12 new and 6 revised) are for nonbiological complex drugs, 14 of which do not currently have any generic competitors.

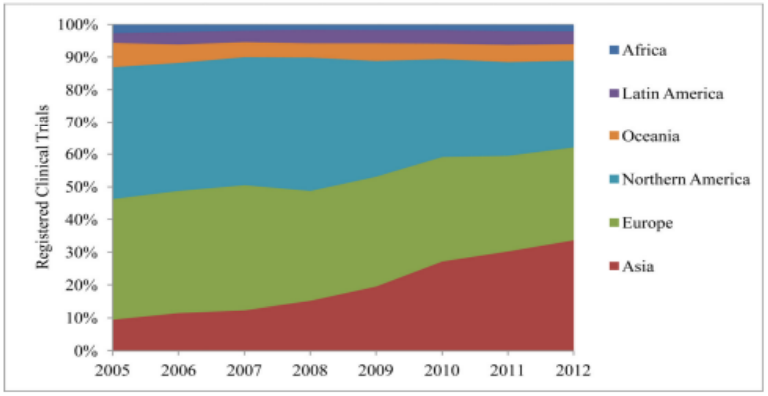
An important part of this process should be close communication by regulators internationally to ensure that drug (product)-specific BE requirements are harmonized across the globe.

Meaningful Study

A.



B.



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Global Migration of Clinical Trials in the Era of Trial Registration

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Trials move from high income countries to low- medium income, mostly in Asia, with all subsequent implications: Clinical, of public health, ethical, regulatory and economical.

Consequence's

Journal of Clinical Research & Bioethics

Patel, J Clin Res Bioeth 2017, 8:2
DOI: 10.4172/2155-9627.1000303

Reasearch Article OMICS International

Misconduct in Clinical Research in India: Perception of Clinical Research Professional in India

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Abstract

Misconduct in clinical research is an unfortunate reality and widespread. Researchers are expected to conduct research and report results honestly. However, that is not how clinical trials always get done. Good Clinical Practice (GCP) guideline is adopted internationally as a standard operating process for purpose of conducting, recording or reporting clinical trials. However, unavailability of international harmonized framework for misconduct management makes clinical research industry vulnerable to commit misconduct. Most of the cases of misconduct are probably not published. They are not recognized or covered up altogether. Misconduct and fraud can be due to any reasons and of various types. In all circumstances, any misconduct should be handled strictly and related regulations should be at place to prevent occurrences. Very few cases of scientific misconducts have been identified or reported in India. However, there is no evidence that all clinical trials conducted in India meet ethical standards and misconduct does not exist. Rather it is more likely that the scientific misconduct amongst researcher have not been systematically investigated. This article discusses the possible reasons for the occurrence of scientific misconduct and explores options, which can possibly help prevent such instances.

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FDA to Pharma Companies: Indian CRO's Clinical and Bioanalytical Studies are Unacceptable

Posted 20 April 2016

By Zachary Brennan

Another day, another issue with data integrity. This time, however, the US Food and Drug Administration (FDA) is taking the issue one step further and notifying sponsors of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) that clinical and bioanalytical studies conducted by Bangalore, India-based contract research organization (CRO) Semler Research are not acceptable as a result of data integrity concerns and need to be repeated.

Newsweek

INDIA'S FAKE DRUG TRIALS THREATEN WIDER TRADE DEAL

BY ROGER BATE AND DINESH THAKUR ON 1/24/16 AT 4:22 PM

47. The generic pharmaceutical industry in India, in conjunction with Indian clinical research organisations (CROs) have a long history of manipulating bioequivalence studies required by the American and European regulators. The Ranbaxy scandal, which first came to light in 2003, exposed the scale of fabrication and manipulation of bioequivalence studies being conducted in India. Recent investigations by the French regulator ANSM at GVK Bio, by the USFDA at Semler Research and the German regulator at Alkem Laboratories have exposed how Indian CROs continue to manipulate bioequivalence studies for their clients – mostly the Indian industry.

Harmonization of regulatory requirements is important

- **Objective of drug regulation: TO IMPROVE AND PROMOTE PUBLIC HEALTH**
- **Harmonization aimed to diminish duplicative efforts, creates "common language", can facilitate cooperation and access to medicines**
- **In case of harmonization of regulations the main objective should be:**
  - **MEASURABLE PUBLIC HEALTH GAINS**
- ***There may be other gains, but these should be in the centre***

The lack of expertise calibers of many NRAs (specially in developing nations)

Harmoni(z)ation or

Harmoni(s)ation ?

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