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Bioequivalence regulation in emerging countries: Example of Moroccan regulations on immediate release formulations and comparison with international guidelines

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ABSTRACT

The purpose of this study was to analyze Moroccan regulations on bioequivalence studies and compare them with some international guidelines. It emerged that, as most common guidelines, Moroccan regulations treated essential questions relating to the conduct of bioequivalence studies while remaining general. An effort to harmonize the Moroccan regulations as closely as possible with international guidelines such as European Medicines Agency and World Health Organization was made. The decree 2-12-198 on bioequivalence studies includes worldwide gold standards such as inclusion and exclusion criteria, study design, choice and number of subjects, conduct of the study, pharmacokinetic parameters, BE acceptance criteria, and biowaiver requirements. It specifically addresses issues such as pro-drug, metabolites, urinary samples, and endogenous substances. Specific precisions such as the case of the modified release forms, the replacement of subjects on the withdrawal, or drop-out of a volunteer are not covered by this general decree and should be part of new directives, in the future. For an emerging country, the integration of Biopharmaceutics Classification System biowaivers within the decree confirms the efforts being made by the Moroccan regulations to join the most advanced guidelines on the investigation of bioequivalence and to prepare the International Council on Harmonisation M9 adoption.

INTRODUCTION

Generic drugs are expected to be bioequivalent and thus interchangeable with the original product (WHO, 2016), as they exhibit the same efficacy and safety, for the same dose, and a similar form. In order to demonstrate this equivalence, it is necessary to perform a specific pharmacokinetic study that demonstrates the similarity of plasma profile, which is used as a surrogate of a clinical study and allows to bridge the efficacy and safety of the generic product to the reference product. This specific study is called bioequivalence study (WHO, 2016). As all clinical studies, bioequivalence study must be performed in accordance with good clinical practices and respect of persons participating in the study.

In the absence of an internationally harmonized guideline on bioequivalence studies, each country or regional organization has established its own regulations and guidelines (ASEAN, 2015; CDSCO, 2005; Chand *et al*., 2013; China, 2015; EMA, 2010; Galgatte *et al*., 2013; GCC, 2011; HC, 2012; 2016; Japan, 2012; SADC, 2015; US-FDA, 2003). Currently, in Africa, as on other continents, very few countries have imposed bioequivalence as an essential step in obtaining the marketing authorization for generic drugs. This situation may be related to the low rate of local drug production in these countries. The majority of drugs sold are therefore imported from well-established producers (Ngozwana *et al*., 2012; Paul *et al*., 2018).

In Morocco, the notion of mandatory bioequivalence studies for generic drug authorization was raised for the first time in 2006 with the publication of Law 17-04 named "drug and pharmacy code" and subsequently in 2012, with the publication of decree 2-12-198, which provides some information on

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bioequivalence studies. However, the conditions for performing bioequivalence studies and the criteria for acceptance have been consolidated in a ministerial decree. In addition, the legal arsenal for carrying out clinical trials of different phases has been expanded by the publication of law 28-13 on the protection of persons participating in biomedical research and law 09-08 on the protection of the personal data (Morocco, 2012).

The aim of this paper was to summarize and critically analyze the Moroccan regulation in the field of bioequivalence studies and to compare it with the different international approaches concerning immediate release solid oral forms.

MATERIAL AND METHODS

This analysis was done during the last quarter of 2018. We analyzed all Moroccan regulatory documents related to bioequivalence (laws, decrees, draft orders, circulars, and ministerial decisions). Then, we compared them with some international regulations and guidelines. We used directives and publications of the regulatory agencies of several countries and groups of countries or organizations: WHO (World Health Organization), EMA (European Medicines Agency), US-FDA (United States Food and Drug Administration), ASEAN (Association of South East Asian Nations), India (Central Drugs Standard Control Organization/CDSCO), GCC (Gulf Cooperation Council), SADC (Southern African Development Community), Health Canada, Australia, China (Centre for Drug Evaluation / CFDA), Saudi Food and Drug Authority (SFDA), and Japan.

The Moroccan national regulations on bioequivalence studies were critically analyzed and compared to the others regarding the following elements: study design, choice and number of subjects, conduct of the study, pharmacokinetic parameters to be evaluated, bioanalytical methods, acceptance criteria, highly variable drugs and narrow therapeutic index drugs, and the criteria for biowaiver.

RESULTS

The main issues addressed when comparing Moroccan regulations with international guidelines are summarized in Table 1.

Study design

As basic design: Single-dose and non- replicate crossover studies are recommended. Under certain circumstances, provided the study design and the statistical analysis are scientifically sound, other well-established models can be considered: parallel design for active ingredients with very long half-lives and replicated crossover design for highly variable drugs (ASEAN, 2015; CDSCO, 2005; EMA, 2010; GCC, 2011; Haidar *et al*., 2008; HC, 2012; Japan, 2012; Midha *et al*., 2005; SADC, 2015; Tothfalusi *et al*., 2009; US-FDA, 2003). There is also the possibility in some countries to perform studies in two stages that require a statistical adjustment (adjusted confidence interval CI to avoid alpha risk inflation) and a specific analysis. This two-stage approach is not commonly used in comparison to the classical replicated crossover designs.

Dose: single or multiple

Moroccan recommendations are identical to those of other countries: single fasted administration is the standard. In some specific case, like in Europe and GCC, the realization of a multiple-dose study, for an immediate release form, is acceptable if a single dose study cannot provide enough information or cannot be performed (EMA, 2010; GCC, 2011). These are: (i) if bioanalysis problems related to the low limit of quantification exists, a multiple-dose study is performed in healthy volunteers (ii) if the study cannot be performed in healthy volunteers for safety reasons and in cases where single-dose study is not possible in patients, the bioequivalence study is then a multiple-dose study carried out in patients. For Health Canada, the same dose of each product should be used, preferably as single dosage form units (HC, 2012). According to ASEAN, CDSCO, and SADC, single-dose studies are recommended (ASEAN, 2015; CDSCO, 2005; SADC, 2015).

Subject selection

In Morocco as in all other countries, to reduce variability unrelated to product differences, bioequivalence studies should be conducted in healthy volunteers unless the drug has safety concerns (e.g., anti-cancer drugs, potent CNS drugs, etc.). Subjects are chosen based on criteria such as age and body mass index (BMI). Volunteers should generally be between 18 and 55 years of age and a BMI of 18.5–25 or 30 kg/m^2. It is recommended to include subjects of both sexes if possible.

Inclusions of female subjects

Morocco, EMA, Health Canada, ASEAN, GCC, and SADC consider the risk to women of childbearing age when conducting bioequivalence studies (ASEAN, 2015; EMA, 2010; HC, 2012; GCC, 2011; SADC, 2015) but do not prohibit their participation if there is no risk (for example efficacious contraception). In addition to the previous recommendations, CDSCO adds that women taking contraceptives should normally not be included (CDSCO, 2005). US-FDA does not give specific guidance on precautions to be taken during the inclusion of female subjects in studies (US-FDA, 2003). For some drugs dedicated to only one sex, the corresponding sex will be used (for example, female hormonal contraception will be tested in women).

Phenotyping and/or genotyping

According to Moroccan regulations, phenotyping and or genotyping of subjects can be studied for safety reasons or for pharmacokinetic reasons. These recommendations are identical to those of EMA, GCC, and ASEAN (ASEAN, 2015; EMA, 2010; GCC, 2011). US-FDA and Health Canada do not provide any information on phenotyping (HC, 2012; US-FDA, 2003). According to CDSCO, SADC phenotyping and/or genotyping of subjects should be considered for exploratory bioavailability studies and all studies using parallel group design (CDSCO, 2005; SADC, 2015).

Number of subjects

The number of subjects to be included in the bioequivalence study should be based on a calculation of the appropriate sample size. Like US-FDA, Health Canada, Australia, ASEAN, and WHO, Moroccan regulations specify that the number of evaluable subjects in a bioequivalence study should not be less than 12 (EMA, 2010; HC, 2012; US-FDA, 2003; WHO, 2016). For the GCC, a number

of 24 healthy volunteers are needed; a number less than 24 can be accepted (with a minimum of 18) when it is statistically justified (GCC, 2011). For CDSCO, the minimum number of subjects should not be less than 16 unless it is justified for ethical reasons (CDSCO, 2005). In case of large variability, in order to reduce the number of subjects, replicate cross-over studies are recommended (EMA and US-FDA) (EMA, 2010; US-FDA, 2003).

Conduct of bioequivalence study

In Morocco, the study should be standardized for fluid intake, diet, and exercise to minimize the variability of all factors except the test products. The regulations agree on an administration of the drug product with a standardized volume of water, which is in general between 150 and 250 ml. In case of product that can be taken without water (oral disintegrating tablet for example), the administration of water with the drug is prohibited. For immediate-release solid oral forms, studies are conducted on an empty stomach unless they are required to be taken during a meal in the Summary of Product Characteristics. For fasting study, a sufficient fasting state is required, usually greater than 8 hours. Fasting is considered to provide discriminatory conditions. Similar recommendations are present in many countries.

Table 1. Summary of Moroccan regulations compared to international guidelines.

Country/ organization	Study design	Conduct of the study			Sampling and Wash-out period (WP)	BCS Biowaiver
		Fluid intake	Posture and physical activity	Replacement of subject		
Morocco (Morocco, 2012)	- Randomized crossover study - Risk to women of childbearing age should be considered - Number of subject >12	Should be standardized: 150–250 ml of water	Unspecified	Unspecified	- ≥ 3= –4 samples during the terminal log-linear phase - WP ≥ 5 ($T_{1/2}$)	- Class I and III - IR solid oral pharmaceutical forms with systemic action - Highest dose soluble at pH within 1.2–6.8 in 250 ml or less of solvent
Europe (EMA, 2010)	- Randomized crossover study - risk to women of childbearing age should be considered - Number of subject >12	Standardized volume of fluid: at least 150 ml	May need to be standardized	It is not acceptable to have a protocol which specifies the existence of 'spare' subjects for replacements.	- ≥ 3–4 samples during the terminal log-linear phase - WP ≥ 5 ($T_{1/2}$)	- Class I and III - IR solid oral dosage forms - Highest single dose soluble at pH within 1 to 6.8 in 250 ml of buffers
USA (US-FDA, 2003; US-FDA, 2018)	- Randomized crossover study - No specifications on the inclusion of female subjects - Number of subject >12	240 ml of water unless the study is a food-effect BA and BE study	Unspecified	Unspecified	- ≥ 3–4 samples during the terminal log-linear phase - 12 to 18 samples per subject per dose - WP≥ 5 x $T_{1/2}$	- Class I and III - IR solid oral dosage forms - Highest dose strength soluble at pH within 1 to 6.8 in 250 ml 250 mL or less of aqueous media
Canada (HC, 2012; HC, 2016)	Idem EMA	standardized volume of water: 150–250 ml	- should be standardized - subjects should not be allowed to recline until at least two hours after drug ingestion.	A fixed number of subjects, in addition to the number estimated by the sample size calculation, should be recruited into the study.	- ≥ 3–4 samples during the terminal log-linear phase - Minimum 12 samples per subject per dose - WP ≥ 10 × $T_{1/2}$	Idem EMA
ASEAN, SADC (ASEAN, 2015; SADC, 2015)	Idem EMA	- ASEAN : Idem EMA - SADC: constant volume of fluid: usually 150 -200 ml	should be standardized	Idem EMA	Idem EMA	- Class I - immediate-release - highest single dose soluble at pH within 1 to 6.8 in 250 ml of buffers
GCC (GCC, 2011)	- Idem EMA - Number of subject >18	Idem EMA	should be standardized	Idem EMA	Idem EMA	- Class I - immediate-release - highest dose strength of the drug soluble at pH within 1.2 to 6.8 in 250 ml or less of aqueous media
CDSCO (CDSCO, 2005)	- Idem EMA - Number of subject >16	should be standardized	should be standardized	Acceptable provided the substitute follows the same protocol	- ≥ 4 samples during the terminal phase - WP: Adequate	- Not specified - Highest dose strength soluble at pH within 1 to 7.5 in 250 ml of aqueous media

IR: Immediate-release, WP: Wash-out period.

For immediate-release forms, there are types such as microemulsions and solid dispersions for which studies require two conditions: fasting and fed (US-FDA, EMA, and GCC) (EMA, 2010; GCC, 2011; US-FDA, 2003). In this case, it is acceptable to perform two crossover studies of two distinct periods or a four-period crossover study. There are no Moroccan recommendations regarding these forms. For fed studies, a hyperlipidic and hypercaloric diet is recommended (800 to 1,000 Kcal of which 50% from fat).

For concomitant use of other medications, only contraceptives are permitted by EMA and GCC, whereas CDSCO excludes contraceptive use. Most regulations do not address the subject (contraception). Moroccan regulations foresee the possibility of concomitant drug administration to a subject when this is unavoidable, such as during the occurrence of adverse events or to all subjects for safety reasons, provided the possible effects on the results of the study are analyzed (e.g., naloxone in case of study on opiate derivatives) like for example in the EMA guideline.

Posture and physical activity

Like EMA and US-FDA, Morocco does not provide specific instructions on posture or physical activity. According to Health Canada, subjects should not be allowed to recline until at least 2 hours after drug ingestion. Physical activity and posture should be standardized as much as possible to limit effects on gastrointestinal blood flow and motility (HC, 2012). For CDSCO, it is important to standardize post-dosing postures as well as physical activities (CDSCO, 2005). According to ASEAN, GCC, and SADC, posture and physical activity should be standardized because the bioavailability of an active fraction of a dosage form may be dependent on gastrointestinal transit times and regional blood flows (ASEAN, 2015; GCC, 2011; SADC, 2015).

Sampling

In general, the plasma concentration at the time of administration till the last concentration observed at time t [$AUC_{(0-t)}$] should cover at least 80% of the area under the curve of plasma concentration extrapolated to infinity [$AUC_{(0-\infty)}$]. In case of immediate release form, EMA specifies that the AUC can be truncated at 72 hours. The terminal elimination half-life should be calculated with a number of points greater than or equal to 3 or 4 according to the guidelines (EMA, 2010). US-FDA and China recommend that 12 to 18 samples at least should be collected for most drugs (US-FDA, 2003). The C_{max} must not be the first sampling point.

The washout period should be sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification or 5% of C_{max} in all subjects at the beginning of the second period. This duration is generally estimated at least five times the mean terminal half-life of the drug. This is to allow the body to eliminate practically the entire dose previously administered and to avoid having an overlap of plasma concentrations of the active ingredient in both periods.

Bioanalytical methods

The validation principles and procedures to be followed are listed but not detailed or referenced in Moroccan regulations unlike in Europe, USA, or Canada (EMA, 2011; HC, 2012; US-FDA, 2018).

Enantiomer and isomers

The quantification of the isomer (s) with enantio-selective methods is recommended if their pharmacokinetic behaviors are different or in case of particular toxicity.

Parent compound or metabolites

The assessment of bioequivalence should be based on the concentration of the parent compound or in the case where this is impossible, on the concentration of its metabolite(s). For inactive pro-drugs, demonstration of bioequivalence for the parent compound is recommended. However, for some pro-drugs with low plasma concentrations and rapidly metabolized, bioequivalence study with the parent compound is difficult to demonstrate. In this situation, it is acceptable to demonstrate bioequivalence with the main active metabolite without measuring the parent compound, provided all available data are available to justify that the exposure to the metabolite will reflect that of the parent compound and that the formation of this metabolite is not saturable at therapeutic doses. These recommendations are unanimous about this subject.

The use of urinary data

It is acceptable to use the cumulative quantities of the active ingredient in the urine to determine the degree of exposure in the case where it is impossible to measure accurately the plasma concentration profile of this active ingredient as a function of time. EMA, US-FDA, and GCC also allow the use of urinary data, with the above-mentioned limitations, in the establishment of bioequivalence (EMA, 2010; GCC, 2011; US-FDA, 2003) subject to the accurate determination of the rate of initial elimination (which can characterize C_{max}) in addition to the cumulative quantities.

Endogenous substances

According to Moroccan regulations, one should proceed either to subtract the average of the individual endogenous concentrations or subtract the individual AUCs of the endogenous substance so that the calculated pharmacokinetic parameters refer only to the additional concentrations provided by the administered drug. Similarly, according to EMA, calculation of pharmacokinetic parameters should be performed using baseline correction (EMA, 2010). In case of non-linear baseline (circadian cycle), subtraction of blood levels corresponding to the absence of drug administration should be made. In this case, a three-arm crossover study is performed: no drug versus reference treatment versus test treatment. The recommendations of the GCC are identical to those of EMA (GCC, 2011). In rare cases where substantial increases from baseline endogenous levels are observed, a baseline correction may not be needed (Dissanayake, 2010; EMA, 2010). CDSCO requires that, when validating the bioanalytical method, specificity and selectivity data should be generated to demonstrate that the assay does not interfere with endogenous compounds (CDSCO, 2005). In order to distinguish added drug from endogenous baseline, it is possible for Europe to overdose the subjects providing the absence of health risk.

Pharmacokinetic parameters, statistical analysis, criteria, and limit of acceptance

With a single-dose study, the main parameters are C_{max}, AUC (0–*t*) and AUC (0–∞) or AUC (0–72 hours). The analysis starts with an ANOVA on log-transformed parameters. The model of ANOVA includes sequence, subject (sequence), period, and treatments as effect; Morocco as EMA preferred a fixed model while US-FDA is using a mixed random model. The 90% CI of the ratio test/reference is calculated based on the residual variance and must be included within the predefined limits. The limit of acceptance of test/reference ratio of pharmacokinetic parameters is 80.00% to 125.00% rounded to two decimal places. The regulatory authorities with the exception of SADC (SADC, 2015), which sets a wider range for C_{max} (75.00%–133.00%), globally accept these limits. The criteria for accepting the pharmacokinetic parameters are detailed in Table 2.

For narrow therapeutic index drugs, the 90% CI is reduced to 90.00%–111.00% for C_{max} and AUC. In case of a replicated design for highly variable drug, the limits of CI can be broadened for C_{max} based on the intra subject coefficient of variation CV of the sole reference formulation starting at 30% up to a maximum corresponding to 50% of variability (80.00%–125.00% at 30% to 69.84%–143.19% for ≥50%) (EMA, 2010; Morocco, 2012). Rules of enlargement are different between EMA, HC, and US-FDA.

Complementary *in vitro* data to be provided

Dissolution and content data should be provided for batches tested *in vivo*, in the quality control medium, and in the three pHs: 1.2, 4.5, and 6.8 (and pH 3–5 in Japan due to achlorhydric patients). At least two batches of reference product must be tested. If the content differs by more than 5% between the test drug and the reference, an explanation must be given and the AUC and C_{max} parameters must be corrected by the contents before statistical analysis. In case of different results between *in vitro* and *in vivo*, *in vivo* prevails. However, the discrepancy must be explained.

Waiver of *in vivo* bioequivalence studies (Biowaiver)

According to the pharmaceutical forms

International regulations are unanimous regarding biowaivers of solutions, at time of administration, intended for parenteral, oral, or local use. These drugs have active ingredients at the same molar concentrations and excipients that are substantially similar qualitatively and quantitatively. Moroccan regulations adopt the same rules.

According to the different dosage strengths of a drug

In Morocco, for different strengths of a drug of the same formulation whose pharmacokinetics is linear in the therapeutic range, the qualitative composition is the same, manufactured by the same producer on the same site and at least the highest strength of which has undergone a bioequivalence study are dispensed from bioequivalence studies provided the dissolution curves are similar. In case of non-similarity of the composition, several bioequivalence studies are required. These recommendations are similar to the majority of international guidelines with some clarifications (for example, EMA does not grant biowaiver for the same production site).

A pharmacokinetic is considered linear by EMA if the differences in the AUC/dose are less than 25% between the different doses. In case of linear pharmacokinetics in the therapeutic range, the highest strength is recommended for bioequivalence studies. If this higher strength could lead to side effects that compromise subject safety, a lower dosage may be used. In the case of non-linear pharmacokinetics, two possibilities exist: either under linearity, the lowest and the highest strengths must be tested or in over linearity, the highest strength must be used.

According to the biopharmaceutical classification system (BCS)

This classification is based on the aqueous solubility at three pHs: 1.2, 4.5, and 6.8 of the highest therapeutic dose per intake in immediate release and intestinal permeability of the active ingredient. For non-narrow therapeutic index drugs, the equivalence between the generic drug and the reference drug takes into account comparative composition including active pharmaceutical ingredient and makes use of dissolution studies *in vitro* at the three pH values cited above in controlled and strict condition (for example, USP Type I at 100 rpm or Type II at 50 rpm) and in quality control method. Like EMA and Health Canada, Morocco grants exemptions for BCS class I and III drugs while China, ASEAN, and Saudi Arabia grant them just for class I (ASEAN, 2015; HC, 2012; 2014; SFDA, 2012). US-FDA directive broadens the exemption from Class I to Class III. Japan does not adopt this classification system for the time being. It has to be noticed that International Council on Harmonisation (ICH) M9 (including Japan) is on step 2 draft and is forecasted to be adopted in 2019. This ICH M9 provides clear indication on composition rules, dissolution processes to support bioequivalence surrogate.

In vivo–in vitro correlation (IVIVC)

The standard definition of IVIVC is recognized in Morocco as a predictive mathematical model describing the relationship between an *in vitro* property of an oral pharmaceutical form and a relevant *in vivo* response (plasma concentration of the active ingredient or the quantity of the active ingredient absorbed). In this case, derogations may be granted for changes in formulae, manufacturing processes, production sites, etc. To waive *in vivo* bioequivalence studies, IVIVC studies should be Level A studies that establish a close relationship (i.e., point-to-point) between the *in vitro* dissolution rate and the *in vivo* entry rate (absorption).

DISCUSSION

We reviewed the Moroccan requirements for bioequivalence studies and we found that they are globally similar to EMA and WHO guidelines. However, these requirements are always likely to be improved.

First, the definition and choice of the reference product against which the generic drug is tested should be further clarified. The reference product is the one whose marketing authorization file is complete including full part 4 and 5 and is marketed in Morocco. In USA, a list of reference products is published that not being the case in other countries.

Secondly, although Moroccan regulations cover the majority of pharmaceutical forms, recommendations for performing bioequivalence studies are focused on immediate release dosage forms. It would, therefore, be preferable to issue

Table 2. Pharmacokinetic Parameters and Acceptance Criteria for immediate release formulations.

Country/organization	Pharmacokinetic parameters (Single dose)	Acceptance criteria (special cases of drugs)			
		Narrow therapeutic index drugs		Highly variable drug products (HVDP): use of replicated design to enlarge CI	
		C_{max}%	AUC $_{(0-t)}$%	C_{max}%	AUC $_{(0-t)}$%
Morocco (Morocco, 2012)	AUC $_{(0-t)}$, AUC $_{(0-\infty)}$, Residual area, C_{max}, Reported and discussed: Residual area, T_{max} and $t_{½}$ T_{max} and $t_{½}$	90.00–111.11	90.00–111.11	80.00–125.00 with the possibility to widen this interval to 69.84–143.19 for C_{max} with intra-subject CV > 30% (reference drug)	80.00–125.00
Europe (EMA, 2010)	AUC $_{(0-t)}$, AUC $_{(0-\infty)}$, C_{max}, Reported and discussed: Residual area, T_{max} and $t_{½}$	90.00–111.11	90.00–111.11	90% CI within : 80.00–125.00 and can be widened to a maximum of 69.84–143.19 for C_{max} with a replicated design and intra-subject CV on reference drug > 30% GMR within 80.00–125.00 (*Product specific recommendations exists)	80.00–125.00
USA (US-FDA, 2003; US-FDA, 2018)	AUC $_{(0-t)}$, AUC $_{(0-\infty)}$, C_{max}, Reported and discussed: Residual area, T_{max}	80.00–125.00 Otherwise specify in product specific guidance	80.00–125.00 Otherwise specify in product specific guidance	80.00–125.00 Wider range up to 75–134 for intra-subject variability ≥ 30% and with the use of the Reference-scaled average bioequivalence - RSABE approach (*Product specific recommendations exists)	
Canada (HC, 2012; HC, 2016)	AUC $_{(0-t)}$, AUC $_{(0-\infty)}$, C_{max}, Reported and discussed: AUC$_T$ / AUC$_{(0-\infty)}$, T_{max}, λ and $t_{1/2}$	80.00–125.00			
Japan (Japan, 2012)	AUC$_{(0-t)}$, – AUC $_{(0-\infty)}$, Reported and discussed: AUC$_\infty$, t_{max}, MRT, kel	90% CI within 80.00–125.00; or, GMRs within 90.00–111.11 with the following conditions: a. the total sample size of the initial bioequivalence study is not less than 20 (n = 10/ group) or pooled sample size of the initial and add-on subject studies is not less than 30, and b. dissolution rates of test and reference products are evaluated to be similar.	90.00–112.00	90% CI of the relative mean AUC of the test to reference product should be within the following limits: 80.0%-125.0%, if sWR ≤0.294 (i.e., CV ≤30.0%); [exp(-0.76sWR) × 100.0%]-[exp(0.76sWR) × 100.0%] if 0.294 <sWR ≤0.534 (i.e., 30.0% <CV ≤57.40%); or, 66.7%-150.0%, if sWR >0.534 (i.e., CV >57.4%). The relative mean (GMR) AUC and C_{max} within 80.0% and 125.0% inclusive.	80.00–125.00
China (China, 2015)	AUC$_{(0-t)}$, AUC$_{(0-\infty)}$, C_{max}, Reported and discussed: T_{max}, λz and $t_{1/2}$	90.00–111.11	90.00–111.11	Limit of 90% CI widened to 69.84–143.19 with intra-subject variability> 30%	80.00–125.00
ASEAN, SADC (ASEAN, 2015; SADC, 2015)	AUC$_{(0-t)}$, AUC$_{(0-\infty)}$, C_{max}	90.00–111.11	90.00–111.11	90% CI within: 80.00–125.00 ; Can be widened to a maximum of 69,84–143,19 after a replicated design and intra-subject variability> 30% GMR within 80.00–125.00	80.00–125.00
Saudi Arabia /GCC (GCC, 2011)	AUC$_{(0-t)}$ and C_{max}	90.00–111.11		90% CI within: 80.00–125.00; can be widened to 75.00–133.00 GMR within 80.00–125.00	80.00–125.00
CDSCO (CDSCO, 2005)	AUC$_{(0-t)}$, AUC$_{(0-\infty)}$, C_{max}	A wider acceptance range may be acceptable if it is based on sound clinical justification	90.00–111.11	The regulator should be consulted	regardless of variability

CI: confidence interval, CV: Coefficient of variation, GMR: geometric mean ratio.

specific recommendations on modified-release dosage forms or to provide requirements in a separate document.

Moroccan regulations do not provide specific recommendations on variables to be taken into account in calculating the sample size of volunteers who should participate in the bioequivalence study. The method used should consider the design of the study and the expected intra-subject variance associated with the primary characteristic to be studied (CDSCO, 2005) or all the required pharmacokinetic parameters (HC, 2012). This variance is estimated from a pilot study or data from the literature. The other variables considered are the significance level of 5%, the expected deviation from the reference drug and the required power (80%–90%) (Chow and Wang, 2001; Chow *et al*., 2011; US-FDA, 2001), the expected ratio between test and reference (usually, 95–105.5 except in some cases), and the limits of the CI (80.00–125.00) if the product is not a narrow therapeutic index drug.

The exclusion of the subject is not discussed in the current Moroccan regulation. Good clinical practice requires that this should be done no later than the end of the clinical phase before the start of the bioanalysis to avoid any bias. In addition, the Moroccan regulations do not address the replacement of subjects after exclusions or abandonment, the consideration of outlier values and on the action to be taken in case of vomiting of the study drug. On this issue, opinions are divided: unlike Health Canada (HC, 2012) which recommends a fixed number of replacements before the study begins, and CDSCO (CDSCO, 2005) that allows replacement during the study, EMA (EMA, 2010) does not allow it. This aspect is quite important as the replacement of the subjects could lead to potential bias in the results (excluded a "bad" responder). Regarding vomiting, it is considered by EMA as a reason for excluding subject, and also by US-FDA (US-FDA, 2003) if only vomiting occurs at least twice before the median Tmax. EMA as US-FDA imposes to exclude a subject who does not have PK parameters (C_{max} or AUC) for any of the study periods, only subjects who have completed both periods can be taken into account.

Considering bioanalysis, reanalysis is only permitted in case of problems during the analysis and not for pharmacokinetic inadequacy of the results. Bioanalysis should be performed with strict adherence to guidelines (EMA, 2011; US-FDA, 2018), good laboratory practice, standard operating procedures, and specific regulatory requirements. The bioanalyst is free to choose between the different applicable methods provided they are validated and have a lower limit of quantification (must not exceed 5% of C_{max}) compatible with the studies. The validation of the analytical method will have to resort to EMA (EMA, 2011), US-FDA (US-FDA, 2018), and the ICH Q2. It has to be noticed that ICH M10 is on step 2 draft. This ICH M10 provide recommendations which are similar to the actual gold standard of EMA and FDA.

There are no specific recommendations for products in Morocco. It could be important for specific drugs that have potential public health concerns. It could also be interesting essential medicines to have a specific status considered necessary for the population and thus facilitate market access while ensuring quality, safety, and efficacy (e.g., antivirals, antiparasitic drugs, specific anti-cancer drugs).

As in other countries, question-and-answer documents could also be provided by the authorities to clarify issues such as statistical analysis, specific products, the use of surrogate markers, etc.

CONCLUSION

Moroccan regulations on bioequivalence studies were presented and evaluated. Some differences and specificities can be detected from one country to another. This regulation consolidates the health policy of the country, of its pharmaceutical industry and is similar to the actual gold standards. It has to be stressed that the bioequivalence studies must be performed against the reference product from the local market and could only be made once worldwide. The results of the bioequivalence studies are extrapolated to the local population and thus the recruitment must reflect this population and specificities in term of characteristics. This article included updated international guidelines.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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None.

DECLARATIONS

This article does not contain any studies with human or animal subjects performed by any of the authors.

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