ADJUSTED INDIRECT TREATMENT COMPARISONS OF BIOEQUIVALENCE STUDIES

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ADJUSTED INDIRECT TREATMENT COMPARISONS OF BIOEQUIVALENCE STUDIES

Gecorrigeerde indirecte vergelijkingen van behandelingen in bioequivalentie studies

(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER 1

GENERAL INTRODUCTION

INTRODUCTION

Importance of generic medicines in public health

Improving access to affordable, quality medicines, particularly to the world's poorest, is part of the strategy to achieve the United Nations (UN) Sustainable Development Goals (SDGs) of reducing child mortality, improving maternal health and combating HIV and AIDS, malaria and other diseases [1]. However, the high price of medicines is a significant barrier for access to medicines, particularly in low-and middle-income countries (LMICs). Thus, use of generic medicines is essential because they significantly reduce the cost of medicines to both governments and the patients [2]. In fact, generic competition can lower the price of medicines by as much as 90% [3]. By definition, a generic medicine is a medicine produced without a license from the innovator company when the patent or other market exclusivity rights on the innovator product has expired [4].

Many countries implement generic prescribing and substitution policies to manage the increasing healthcare costs and to improve access to medicines. Generic prescribing is when a physician or a prescriber writes an order for a medicine or treatment using the international non-proprietary name (INN) for the drug and generic substitution is dispensing any available formulation of the same drug in the place of the prescribed branded formulation. In the Organisation for Economic Co-operation and Development (OECD) countries, generic prescribing is permitted in two-thirds and is mandatory in a few countries such as Estonia, Portugal, Spain and France [5]. Similarly, generic substitution occurs in the majority of the OECD countries and is mandatory in some countries such as Denmark, Finland, Spain, Sweden and Italy.

In many LMICs such generic substitution policies do not generally exist, but that does not mean that generics are not playing a critical role in national healthcare. The antiretroviral (ARV) market analysis in those settings for example, provides clarity on the impact of generics in management of HIV and AIDS and their importance in public health programmes. The introduction and wide spread use of generic ARVs and fixed dose combinations (FDCs) in the early 2000s enabled the scaling-up of access to antiretroviral therapy [2] from 0.5 million people on ARVs in 2003 to 15.8 million globally in 2015 [6]. The median price per patient per year of first-line antiretroviral

therapy was reduced from about US$10,000 to less than US$100 with the introduction of generic FDCs [2,7]. In contrast, the best possible price for potential third-line containing raltegravir, etravirine and darunavir/ritonavir is 15 times the current first-line therapy. There are neither generic equivalents, nor FDC formulations for raltegravir, etravirine and darunavir / ritonavir at this time.

In the United States (U.S.), the United Kingdom (U.K.), Germany, and New Zealand, generics accounted for more than 75% by volume, yet less than 60% of the value of pharmaceuticals sold in 2013 [5]. More specifically, in the U.S., which is the largest pharmaceuticals market, generics accounted for 84% by volume, and only 28% by value during the same period [5]. Similar to the high market share of generics in high-income countries, the market-share of generic ARVs increased from 39% in 2003 to 95% in 2008 by volume for the donor-funded programmes in LMICs [2]. In addition, in value terms, generics accounted for 78% of the US$ 463 million purchases by donor-funded programmes in 2008; a significant increase from the 29% share of the US$ 2.31 million purchases in 2003 [2]. Further, from 2000 to 2015, HIV-related deaths reduced by 24% [6], partly due to the increased access to ARVs in countries with high HIV and AIDS burden.

Regulatory requirements for approval of generic medicines

Approval of a generic medicine is based on the demonstration of interchangeability or therapeutic equivalence to the innovator through bioequivalence studies. Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose. Typically, the bioequivalence criterion is that, the 90% confidence interval of the ratio of the log-transformed geometric means of the test and reference for the maximum plasma concentration (C_{max}) and the area under the plasma concentration *versus* time plot (AUC) are within 80 – 125% limits [4,8]. These limits vary in some circumstances, e.g., using a reference scaling approach based on the within-subject variability of the reference to tighten the limits for narrow therapeutic index drugs, or widening the limits for highly variable drugs for C_{max} [4,8,9].

The requirement of bioequivalence studies for generics in lieu of clinical efficacy and safety studies was introduced in the U.S. in 1984

through The Drug Price Competition and Patent Term Restoration Act (Public Law 98-417), commonly known as the Hatch-Waxman Act [10], and it is now a widely accepted regulatory standard [4,8]. Bioequivalence is a cost- and time-efficient risk management approach enabling access to generic medicines with the same intended therapeutic benefits as the innovator products. It is important to note that the bioequivalence approach is also applicable to innovator products with respect to demonstration of therapeutic equivalence for the clinical batch and the to-be-marketed formulations, development of other dosage forms, e.g., capsules to tablets, and for scale-up and post approval changes.

Interchangeability of generic medicines

When two products are therapeutically equivalent, they can be interchanged in practice [11]. Interchangeability of generic medicines refers first to the prescribability of the drugs [12,13]. In other words, the prescriber can prescribe the generic medicine in place of the innovator product in a new patient as the bioequivalent generic product is assumed to have the same efficacy and safety profile as the innovator when used under the same conditions. Second, therapeutic equivalence is direct proof of switchability or substitution between the generic and the innovator product in patients already being treated with the innovator product [11,14]. In most cases, when the patent or market exclusivity rights of the innovator have expired, there are several generic medicines of the same drug approved and marketed. Studies show that four to five generic products of the same drug are necessary to create healthy competition that sufficiently lowers the prices of the generic medicines relative to that of the innovator product [15]. Hence, in these situations where multiple generics are available, it is common to switch patients between generics of the same drug in clinical practice.

Concerns regarding generic substitution or switching have been discussed extensively in literature since the introduction of bioequivalence requirement for the generic medicines in 1984 in the U.S. These concerns range from consumer perceptions of risks associated with generic medicines [16], to physicians concerns with generic substitution for specific drug classes, e.g., antiepileptics [17-20], immunosuppressants [21], cardiovascular drugs, psychotropics, and drugs with a narrow therapeutic index (NTI) [22,23]. In some jurisdictions where attempts have been made to address concerns,

narrow acceptance limits are used, while others impose restrictions on generic substitution for NTI drugs. In addition, other countries such as the U.S. provide data for products demonstrated to be interchangeable to assist healthcare professionals in generic prescribing and substitution [24,25]. Nonetheless, there is still need to address the concerns of generic substitution and switchability using empirical evidence, particularly for LMICs.

Indirect treatment comparisons

Direct comparisons within well-designed and well-conducted randomised controlled trials (RCT) is the gold standard for comparing health interventions. The usual practice to obtain marketing authorisation for new health interventions is to compare them to placebo, or the standard of care, but not with all available health interventions. Some interventions are developed simultaneously, thus it is not feasible to perform comparisons between them during this development phase to support marketing authorisations. Moreover, in some cases, there is a relatively large number of available interventions making direct comparison between them through RCTs impractical. Therefore, indirect comparisons are employed in these instances where multiple interventions exist and there is insufficient evidence to evaluate the relative effectiveness of the available interventions from direct comparisons (head-to-head comparisons)[26-28].

An indirect treatment comparison is defined as an evaluation of different health interventions using information from independent studies. This is useful when there are no data on direct comparison, or to provide supplementary evidence when the data from direct comparison are insufficient [29]. Indirect comparison can be categorised into naïve (unadjusted) indirect comparison, informal indirect comparison, and adjusted indirect comparison [28]. Naïve indirect comparison evaluates the data from the independent studies as if the data are from the same study ignoring the between-study variance. For this reason, evidence from naïve indirect comparison is equivalent to observational studies, prone to bias, and it may over or underestimate the treatment effect, thus this approach is not recommended for analysing data from RCTs [27-29]. In informal indirect comparison, the results from the independent studies are compared directly, and relative effects or statistical significance are not formally calculated [28]. Adjusted indirect treatment comparison

evaluates different treatments tested in independent studies modified based on the results of their direct comparison with a common control, partly preserving the power of RCTs [28] without the added cost of actual direct RCT comparison. However, adjusted indirect comparisons are less precise than the direct comparisons as reflected in wider confidence intervals [29]. Therefore, wherever possible direct comparisons should be performed.

Figure 1 illustrates the direct and indirect comparison of health interventions. Suppose there are 4 different treatments, A, B, C and D compared in 3 different trials. If treatment A was compared in a RCT with treatment B, treatment C in another RCT with treatment B, and treatment C with D in another RCT, adjusted indirect treatment comparison can be used to compare treatment A and C since both were tested in two independent trials with the common treatment B. Likewise, treatment B and D can be compared using adjusted indirect comparison since both were compared in direct comparison with common treatment C.

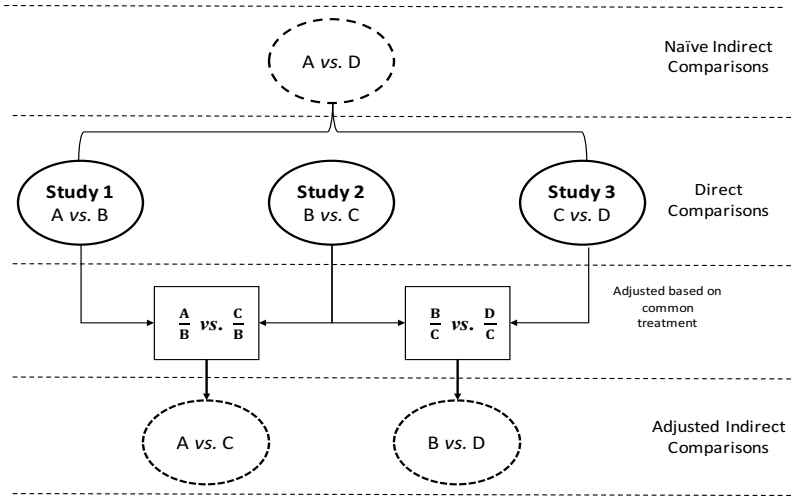

Figure 1: Adjusted indirect comparison versus naïve indirect comparisons. Adapted from F. Song (2009) [28]

A bioequivalence study comparing a generic and an innovator is a form of direct comparison. In an ideal world, one might wish to see each generic compared to every other generic through direct comparison in order to ensure interchangeability. Understandably,

this requirement for direct comparison through bioequivalence studies between generics is impracticable because the number of approved generic medicines increases over time following expiry of patents or market exclusivity arrangements and these generics are licensed often without knowledge of the other generics under development. For this reason, adjusted indirect treatment comparison is a useful approach to identify those generic products whose interchangeability can be guaranteed to support or ensure switchability in clinical practice without concerns for efficacy or safety due to the switching. This is done by comparing the different generic products that have been demonstrated to be bioequivalent with the same innovator or reference product.

Bioequivalence requirements and standards are not static, and continue to evolve over time, taking into account scientific and regulatory advances, consumers' and clinicians' concerns, while at the same time responding to the growing demands for faster and improved access to medicines. Adoption of risk based approaches reflect the dynamic nature of regulatory requirements e.g., acceptance of bioequivalence studies in lieu of clinical efficacy and safety studies, dissolution studies for waivers of *in-vivo* bioequivalence studies for additional strengths, for some drugs based on the Biopharmaceutics Classification System (BCS), or during post-approval changes, and the adoption of reference-scaling for the confidence intervals for highly variable drugs and for narrow therapeutic index drugs. Thus, reanalysis of dossier data, such as bioequivalence data, is considered one approach of regulatory science by which regulators and scientists can generate evidence to address public concerns regarding the robustness of regulatory decisions and products on the market [30]. For instance, the U.S. Food and Drug Administration (FDA) analysed bioequivalence data over a 12 year period to address growing public concerns with respect to bioequivalence standards as well as safety and efficacy concerns with generic substitution [11]. While regulatory decisions are open to scrutiny in high-income countries, there is little information from LMICs.

Status of medical regulatory systems in Africa: bioequivalence requirement in Africa

Africa is affected by a high disease burden, particularly infectious diseases such as HIV and AIDS, tuberculosis (TB) and malaria. It

carries the most severe burden of TB, with 281 cases per 100, 000 people in 2014, which is more than double the global average of 133 [31]. It is home to nearly 80% of TB cases among people living with HIV [31] and about 90% of malaria deaths occur on the continent [32]. Sub-Saharan Africa, in particular, bears 70% of the world's 36.9 million HIV positive people [6]. Attaining the UN SDGs targets on good health and well-being partly depends on increasing access to affordable, quality, essential medicines to the world's poorest [1]. In this respect, effective medicines regulatory systems are imperative, particularly in Sub-Saharan African countries in order to attain these SDGs targets.

The WHO recommends that national medicines regulatory authorities (NMRAs) should ensure that, before medical products are placed on their markets, they should conform to acceptable standards of safety, efficacy and quality, including demonstration of interchangeability for generics [4]. Regulatory authorities in Africa vary from non-existent systems to developed systems with respect to pre-marketing authorisations. Nonetheless, for most of the African countries, the requirement for the demonstration of interchangeability is either non-existent or not fully enforced. Likewise, most African pharmaceutical manufacturers are inexperienced in performing bioequivalence studies for their products and the capacity to perform these studies to the required regulatory standard is limited. Noting this situation and the global response to the HIV and AIDS epidemic, particularly in Sub-Saharan Africa, and the need for quality assurance of medical products that were being procured by multi-national agencies, the WHO prequalification (PQ) programme was established in 2001 as a quality assurance mechanism for products procured by the UN Agencies [33,34]. Since its onset, demonstration of interchangeability is one of its requirements for ensuring quality, safety and efficacy of prequalified generic medicines.

The WHO published its first bioequivalence guideline in 1996, however, to date, implementation of the WHO recommendations with respect to demonstration of interchangeability is currently unknown or not well documented in the Sub-Saharan Africa. While some countries as well as some regional economic communities (e.g., East African Community (EAC) and Southern African Development Community (SADC)) have national or regional bioequivalence guidelines, respectively, implementation of these is varied and not well documented.

Objectives of the research

The aim of the present research is to investigate if generic medicines that received regulatory approval based on a single bioequivalence study with the reference product can be considered switchable between them. Various approaches have been used or proposed for such a purpose, starting with Anderson and Hauck's probabilistic approach in 1996 [35], and Chow and Liu's [12] meta-analysis approach for bioequivalence studies in 1997 and so one of the objectives of this thesis is to describe the statistical methods that can be employed to conduct adjusted indirect treatment comparisons of generic medicinal products and to use them with the WHO prequalified products as case studies.

Although mechanisms such as the prequalification of medicines by the WHO may ensure prescribability through bioequivalence demonstration, generic substitution is considered a national responsibility that should be addressed at country level [36]. In addition, while pro-generic policies may exist in LMICs, demonstration of bioequivalence with the innovator is not mandatory or enforced in most of those settings. Therefore, in order to ensure switchability, it is necessary to ensure prescribability. This issue is guaranteed in high-income countries, but it is under-developed in LMICs. To this end, the research also analyses the approval of generic medicines in Sub-Saharan Africa by analysing the registration data from Zimbabwe and a collaborative medicine registration process involving SADC countries as a model to be followed by other developing countries.

The third objective of this thesis is to reflect on the main barrier for global harmonization with respect to generic medicines and their common availability, the use of a common comparator product globally.

Thesis outline

Chapter 2 describes four studies that explored the methodological issues and the applicability of adjusted indirect treatment comparisons in bioequivalence studies using the generic products prequalified by WHO for antimalarial, first-line antituberculosis, and first-line antiretroviral medicines. These three classes of medicines target the three main infectious diseases that affect LMICs, particularly Sub-Saharan Africa. The first study investigated the different approaches or methods for performing adjusted indirect

treatment comparisons for bioequivalence studies. Artemether / lumefantrine generics prequalified by WHO were used as a case model. In this study, we compared six methods that can be used to calculate the width of the confidence intervals for the comparison based on *z* distribution ($z_{0.9}$) or Student's *t* distribution ($t_{0.9,\ d.f.}$). Four methods that assumed small sample sizes with Student's *t* distribution are (a) the Chow and Liu meta-analysis method, [37] which assumes all studies had 2 x 2 cross-over designs and homogeneity of the variances in all studies, (b) homoscedastic method which assumes homogenous variances, (c) heteroscedastic method which assumes heterogeneous variances, and (d) the pragmatic approach which does not require the assumption of homogeneity of variances between studies with small sample sizes. The two methods which assumes large sample sizes with a standardised normal distribution ($z_{0.9}$) are (a) Chow and Shao meta-analysis method [38], and (b) the *z*-distribution method with no assumption of homogeneity of variances [39].

The second study investigated the influence of the point estimates and the study power on the ability to show bioequivalence between generics using adjusted indirect treatment comparisons. The next two studies present the application of adjusted indirect treatment comparisons to the first-line anti-tuberculosis medicines and first-line antiretroviral medicines prequalified by the WHO. These studies explored the utility of the recommended approaches from the previous two studies in investigating the bioequivalence between generics, as well as the value of additional constraints on bioequivalence requirements with respect to the point estimates in the original studies.

Chapter 3 describes two studies that put the results obtained in Chapter 2 into context in which the WHO prequalified products are mainly intended to be used, i.e., Sub-Saharan African countries with the highest disease burden of HIV and AIDS, TB and malaria. In addition, this chapter attempts to provide answers on whether the adjusted indirect treatment comparison results for WHO prequalified generics could be extrapolated in those settings. The first study describes the performance of the medicines registration system in Zimbabwe, a low-income country in Southern Africa with a functional medicines regulatory system as a case model. The second study looks at a collaborative medicines registration process among four Southern African countries as a model to ensure not only the quality but also

interchangeability of generic medicines in these countries. In these two studies, a critical analysis of the requirements for, and demonstration of interchangeability is presented.

Chapter 4 on regulatory perspectives presents a commentary on the selection of the comparator products in bioequivalence studies in the context of global harmonization. Performing an adjusted indirect treatment comparison requires the use of a common reference for the results to be valid. There is considerable progress with respect to harmonization of the conduct of bioequivalence studies, however, there are still disparities with respect to requirements for reference products for bioequivalence studies that affect not only the harmonization but also interchangeability between generics of different markets. This study reviewed and discussed the current requirements in specific jurisdictions, including the WHO guidelines for comparator products with the focus on the requirements for the reference products and proposed options for a harmonized global reference product.

Chapter 5 is a general discussion of the papers presented in this thesis. The discussion addresses benefits and limitations, including methodological issues of the adjusted indirect treatment comparisons. In addition, the approaches to medicines registration in Sub-Saharan Africa that assure quality, safety and efficacy of medicines comparable with WHO PQ standards are described. The discussion concludes with specific regulatory policy recommendations for assuring generic prescribability and switchability.

Methods

This thesis uses quantitative and qualitative approaches in the papers that are presented herein. The papers described in Chapter 2 on adjusted indirect comparisons use computational methods for the quantitative data analysis, while the papers in Chapter 3 employ mainly qualitative methods, including theory-directed approach for the analysis of the collaborative initiative in medicines registration. Chapter 4 is a review offering perspective on regulatory policy with respect to global harmonization of comparator products for bioequivalence studies.

Methods in indirect comparisons

Several methods are available for performing indirect comparisons: (1) naïve or unadjusted indirect comparisons, (2) modelling

approaches based on the individual patient data (meta-regression), (3) mixed treatment comparisons based on Bayesian statistics (logistic regression) [27,40]. (4) statistical methods using aggregate data, such as a simple weighted combination of separate estimates as suggested by Bucher et al [26] (adjusted indirect comparison). The naïve or unadjusted indirect comparison is prone to bias and is not recommended for analysing data from RCT, therefore, this method is not discussed any further.

In meta-regression analysis, the estimated difference between the groups (treatment effect) is modelled as a function of one or more study characteristics as the predictor variable. Estimated treatment effect in each study is weighted according to the inverse of its variance. A simple approach for meta-regression is weighted linear regression, and the residual heterogeneity is estimated using random effects. Meta-analysis can be performed using the fixed-effects to describe the residual heterogeneity. The key assumption for fixed effect meta-analysis is that the different trials estimated the same effect, for example, the effect of treatment A relative that of treatment B.

Regression methods such as logistic regression can be used to perform indirect comparisons using the generalised linear models and individual patient data. With regression modelling, one can adjust for other variables available for each study. While full individual patient data, which are required for logistic regression for indirect comparison, or the estimated treatment effect, its variance and covariates for each trial, which are necessary to perform meta-regression, are rarely publicly available, adjusted indirect comparison is performed using the summarised data available in published articles and approved product labelling. It is the simplest and most appropriate methodological approach when only two interventions are to be compared indirectly as it is the case for bioequivalence studies [41].

When using summarised data extracted from published data, first the data are extracted or calculated using appropriate summary statistics, e.g., confidence intervals, mean ratios, for each set of studies. For bioequivalence studies, the extracted data are study products, sample sizes, preferably in each sequence, confidence intervals, and study design (fasting or fed study, parallel or cross-over, single or multiple dose studies). The confidence intervals of the

bioequivalence studies are converted to log scale and used to estimate the point estimate and standard error of the treatment effects. Lastly, the data are combined to provide an overall comparison. The standard statistical result, i.e., the variance of the difference between the two independent estimates, is the sum of the two variances (variance is the square of the standard error), which is similar to a 2-sample *t*-test. Thus, using the illustration in Figure 1, if you have the 2 estimated effects for A *vs.* B and B *vs.* C as θ_{AB} and θ_{BC}, respectively, the effect of the comparison A *vs.* C is estimated as $\theta_{AC} = \theta_{AB} - \theta_{BC}$ and $var(\theta_{AC}) = var(\theta_{AB}) + var(\theta_{BC})$ [26]. The scale of the effect θ relates to the scale on which the data would be analysed such as risk difference, log risk ratio, log odds ratio for binary data, the means, mean difference, mean change for continuous data and log hazard ratio for time-to-event data. In bioequivalence studies, the pharmacokinetic outcome measure is continuous data, and the effect θ is the ratio of log-transformed geometric means of the treatments, e.g., A and B, (point estimate). The 90% confidence interval (CI) of the ratio of the log-transformed geometric means is the standard statistical result. Therefore, the 90% CI for the indirect comparison is $\theta_{AC} = \theta_{AC} \pm z/t \cdot \sqrt{var(\theta_{AC})}$, where z/t in this equation is the z value of standardised Normal distribution or the t value of the Student's t distribution that corresponds to the desired level of confidence (90% in case of bioequivalence studies) and the degrees of freedom in the case of the Student's t distribution.

Methods in analysis of the medicines registration approaches in Sub-Saharan Africa

The qualitative studies were meant to provide an in-depth and interpreted understanding of the registration process and the collaborative registration process in order to better understand the experience of the SADC countries when processing marketing authorisations. Atlas.ti (*version 7*), a computer aided qualitative data analysis software package was used as a data management and analysis tool for the literature review and the theoretical framework used to analyse the success factors and sustainability of the collaborative medicine registration process.

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CHAPTER 2

ADJUSTED INDIRECT TREATMENT COMPARISON OF GENERIC PRODUCTS PREQUALIFIED BY THE WORLD HEALTH ORGANIZATION

CHAPTER 2.1

Statistical approaches to indirectly compare bioequivalence between generics: a comparison of methodologies employing artemether / lumefantrine 20/120 mg tablets as prequalified by WHO

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ABSTRACT

Purpose: The objective of this study was to compare different methods of adjusted indirect comparisons that can be used to investigate the relative bioavailability of different generic products. To achieve this goal, generic artemether/lumefantrine 20/120mg tablets that have been prequalified by World Health Organization (WHO) were selected as model products for study.

Methods: Data from three bioequivalence studies conducted independently that compared three generics with the same reference product were used to indirectly determine the relative bioavailability between the generics themselves.

Results: The different methods of indirect comparison examined in this study provide consistent results. Methods based on the assumption of a large sample size give slightly narrower 90% confidence intervals. Therefore, the use of methods based on the *t*-test is recommended. Given the precision of the area under the time-concentration curve (AUC) data, it is possible to conclude that the extent of exposure of artemether and lumefantrine is bioequivalent between the generics studied. However, given the precision of the drug peak concentration (C_{max}) data, it is not possible to demonstrate equivalence within the conventional acceptance range for all comparisons; it is possible to conclude bioequivalence within the widened acceptance range 75-133%.

Conclusion: From a clinical viewpoint, not only are these prequalified generics bioequivalent and interchangeable with the reference product (Coartem, Novartis), but also the existing indirect evidence makes it possible to conclude that these WHO prequalified products are bioequivalent between themselves with respect to AUC. The lack of the necessary precision to demonstrate bioequivalence between generics with respect to C_{max} within the conventional acceptance range does not preclude considering them as interchangeable, if necessary, since C_{max} is considered of less clinical relevance for the relevant therapy.

INTRODUCTION

Generic (multisource) drugs significantly lower the cost of treatment, thereby increasing the availability of efficacious drugs, especially in developing countries where cost is a major barrier to treatment access. Typically, generic products are approved by regulatory authorities on the basis of bioequivalence with the innovator product [1-3]. However, generic products are never compared between themselves directly, although in practice patients may be switched from one generic to another. In order to estimate the relative bioavailability between generic products, it is therefore necessary to perform indirect comparisons. The same question may arise when the innovator company develops several dosage forms that are compared with the initial one (e.g., an orodispersible tablet and an oral solution are proven to be bioequivalent to the immediate release tablet, but whether the orodispersible tablet is bioequivalent to the oral solution is not tested directly) or when the generic company modifies the formulation or manufacturing process significantly and a new bioequivalence study *versus* the reference product is performed. In this latter case, the bioequivalence of the existing and the new generic product is not tested.

To address this issue, in 1997 Chow and Liu [4] proposed a meta-analysis based on the assumption that the intra- subject and inter-subject variability in all the bioequivalence studies between the generics under comparison and the reference product was the same and that all the studies had the same 2×2 cross-over design. However, before the studies could be combined to obtain a combined standard error (SE) for the estimation of the indirect 90 % confidence interval (CI) for the ratio test/reference of the pharmacokinetic parameters [area under the time–concentration curve (AUC) and peak drug concentration C_{max})], a test of homogeneity of the distribution of reference product data in all studies was required. In order to avoid these strict assumptions, which possibly may only be fulfilled for those drugs without bioavailability problems where the formulation effect is negligible, Chow and Shao [5] proposed a method based on the meta-analysis of the reference product data of all the individual studies, which can be assumed to come from the same population. This method increases the statistical power, especially when the number of studies is large and the inter-subject variability is not too large, since a large inter-subject variability results in a large variability

between study data sets. This assumption is even less realistic since intra-subject variability is rarely larger than inter-subject variability, especially when studies with different subject populations, centers, sampling times, and bioanalytical methods are combined. Simultaneously, in 1997 Butcher et al. [6] described a methodology for adjusted indirect treatment comparison when treatments are not generics but competing interventions in order to overcome the limitations of unadjusted indirect comparisons, which are biased as they ignore the randomization within the individual trials. In the adjusted indirect comparison, the comparison of the interventions of interest is adjusted by the results of their direct comparison with a common control group (i.e., the reference product in case of bioequivalence studies), and there is no assumption of homogeneity [7]. As all bioequivalence study results are expressed as the percentage of the ratio test/reference, the inter-study comparisons are always adjusted. The point estimate of a bioequivalence study is the difference between generic A and reference product) in the log scale $(d_{A-R} = A - R)$. Therefore, the difference between the point estimates of two bioequivalence studies gives the adjusted difference between generic A and generic B in the log scale $[\, d_{A-B} = d_{A-R} - d_{B-R} = (A - R) - (B - R) = A - B]$. Therefore, there is no need to authorisation the raw data to correct for study differences in absolute values, as performed by Maliepaard et al. [8] (i.e., adjust the absolute values of the plasma concentration – time data of each subject in each individual study in order to obtain comparable values of the reference product between studies), whose analysis gave inconsistent results. For example, although for gabapentine 400 mg G1/R gave a point estimate 103.0 and G3/R gave a point estimate 101.0, the point estimate for the comparison G1/G3 was 93.58. In contrast, the width of the 90 % CI, which depends on the SE of the pair-wise comparisons, can be calculated with different methods, and the correctness of the estimated SE will depend on strict but unverifiable assumptions [7].

The objective of our study was to compare the different methods of adjusted indirect treatment comparisons that can be used to investigate the relative bioavailability of different generic products. The fixed dose combination of artemether/ lumefantrine was identified as an appropriate model for exploring these comparisons since the potential for a formulation effect related to differences in manufacturing procedures or composition is increased due to the low

solubility and complicated bioavailability characteristics of this combination. To achieve this goal, we selected generic artemether/lumefantrine 20/120 mg tablets that have been prequalified by the World Health Organization (WHO)[1] as model products for the study.

MATERIALS AND METHODS

Identification of studies

Data from bioequivalence studies comparing fixed dose combination artemether/lumefantrine 20/120 mg tablets in adult healthy volunteers submitted to the WHO Prequalification of Medicines Programme (PQP) were considered in the analysis. The inclusion criteria for accepting bioavailability/bioequivalence (BA/BE) studies were: bioequivalence studies con- ducted in healthy volunteers comparing a single dose of fixed dose combination (FDC) tablets of artemether/ lumefantrine 20/120 mg tablets using artemether/lumefantrine 20/ 120 mg tablets (Coartem®/Riamet®) from Novartis Pharma (Basel, Switzerland) as the reference (comparator) product. The design of these three studies was similar: single dose, 2×2 cross-over design in the fasting state. The number of subjects that completed the study and were considered for statistical calculations were 55, 64 and 58, respectively.

[1] The WHO (World Health Organization) Prequalification of Medicines Programme was launched in 2001, in partnership with UNAIDS, UNICEF and UNFPA, with support from the World Bank. Its focus was evaluation of medicines for treatment of HIV/AIDS, malaria and tuberculosis. Products in other therapeutic categories are now also assessed. The Programme reviews product dossiers, mainly for generic products, according to stringent, internationally accepted criteria, including data on product quality and bioequivalence, and inspects the corresponding manufacturing sites, to assess compliance with good manufacturing practices (GMP). It also inspects contract research organizations (CROs), to verify compliance of the bioequivalence studies with good clinical practice (GCP) and good laboratory practices (GLP).

Statistical methods

To calculation the 90% CI of the adjusted indirect comparison, it is necessary to first define the point estimate (P.E.), the uncertainty factor based on the standardized normal distribution or Student's *t*-test distribution $Z_{0.9}/t_{0.9,df}$, and the SE of the difference (SE_{A-B} *or* SE_d) between generics in the log scale $90\%\ \mathrm{CI} = \mathrm{P.E} \pm z/t * \mathrm{SE_d}$).

The point estimate of the indirect comparison is adjusted as explained above [$d_{A-B} = d_{A-R} - d_{B-R} = (A-R) - (B-R) = A - B$], where A and B are the pharmacokinetic parameters of interest of product A and B, respectively. Even in the method proposed by Chow and Shao [5], the difference between test and reference in individual studies is estimated based on the results within each study instead of the mean response of the reference in all studies, which is not comparable due to inter-study differences. This combination as proposed by Chow and Shao would have been similar to the naïve or unadjusted indirect comparison, which is biased as explained above.

In bioequivalence, the following approaches to calculate the width of the confidence interval have been identified:

1) Z distribution method: This method assumes a large sample size with a distribution that follows the standardized normal distribution ($z_{0.9}$) and does not require any assumption regarding the homogeneity of variances ($SE_d^2 = SE_A^2 + SE_B^2$) [9]. This method is usually used for efficacy studies, but unrealistic for small sized bioequivalence studies.

2) Homoscedastic method: This method assumes small sample sizes with homogeneous variances whose difference follows Student's *t*-test distribution ($t_{0.9,d.f.}$), where the variability of the pair of studies under comparison is weighted to obtain a common estimation of variability $SD_{pooled}^2 = \frac{(n_1-1)SD_1^2+(n_2-1)SD_2^2}{n_1+n_2-2}$ where the degrees of freedom are (n_1+ n_2-2), where n_1 and n_2 are the number of subjects in study 1 for generic A and study 2 for generic B, respectively, SD is the standard deviation, and the subscript 1 or 2 indicates the study number. The SD of each study is calculated by $SD = \frac{2*SE_{(d)}}{\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}}$, where n_1 and n_2 represents the number of subjects in sequence 1 and sequence 2, respectively, since these are direct comparisons with cross-over designs. Once the SD_{pooled} is calculated, the SE_d for the indirect comparison is calculated by $SE_{(d)} = SD_{pooled}\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}$, where the

subscript 1 or 2 indicates the study number, since it is no longer a cross-over comparison, but an inter-study indirect comparison.

3) Heteroscedastic method: This method assumes small samples sizes ($t_{0.9,d.f.}$) with heterogeneous variances which relaxes the underlying assumptions for the variance estimations ($SE_d = SE_A^2 + SE_B^2$). It must be noted that a test which fails to reject the null hypothesis of homogeneous variances should not be considered as proof of homogenous variances, especially when the number of studies under comparison is low. However, the heteroscedastic approach requires the calculation of the degrees of freedom according to Welch[10], $d.f. = \frac{\left(\frac{SD_1^2}{n_1}+\frac{SD_2^2}{n_2}\right)^2}{\frac{\left(\frac{SD_1^2}{n_1}\right)^2}{n_1-1}+\frac{\left(\frac{SD_2^2}{n_2}\right)^2}{n_{2-1}}}$, in order to solve the Behrens-Fisher problem.

4) Pragmatic Method: This method does not require the assumption of homogeneity of variances ($SE_d = SE_A^2 + SE_B^2$), since it is unlikely verifiable, between studies with small sample sizes that follow Student's *t*-test distribution ($t_{0.9,d.f.}$), whose degrees of freedom are approximated for simplicity as if the variances were homogeneous (n_1+ n_2-2).

In addition, the meta-analysis approaches proposed by Chow and Liu[4] and Chow and Shao [5] are also employed for comparative purposes. However, only the method proposed by Chow and Shao for large sample sizes is tested since the method proposed for small sample sizes requires the use of the raw individual subject data, which is generally not available, and is computationally complex.

Comparison of Chow and Liu's method [4] with methods based on a *t*-test distribution will serve to investigate the role of a different method for variability calculation based on a combined variability for all pairs of comparisons. Comparison of Chow and Shao's method for large samples with the Z-distribution method will serve to compare not only the different method for variability estimation, but also two methods based on the Z-distribution and the four methods based on the Student's *t* distribution.

The abovementioned calculations were performed in MS Excel 2003 (Microsoft, Redwood, WA).

RESULTS

Three generic FDC products and one innovator FDC product containing artemether/ lumefantrine 20/120mg were prequalified by the WHO between 2004 and 2011. The three generic FDCs were evaluated in BE studies comparing them with the same WHO approved comparator product Coartem® (artemether 20mg + lumefantrine 120mg FDC tablet, Novartis). The BE data used in this study is publicly available in WHO public assessment reports (WHOPAR) at http://apps.who.int/prequal/ (http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/MA052part6v1.pdf, http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/MA062part6v1.pdf, and http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/MA064part6v2.pdf, respectively). The three studies enrolled a total of 177 adult male subjects and administered the same dose of four tablets of artemether 20 +lumefantrine 120mg for test and reference products as single doses in individual randomized, two-period, two-treatment, two-sequence, crossover studies conducted under non-fasting conditions.

Figure 1 shows the point estimates and 90% CI for the ratios of C_{max}, AUC_{0-t}, and $AUC_{infinity}$ for artemether for the three prequalified generic formulations when compared with same comparator product, Coartem®. Figure 2 shows the point estimates and 90%CI for the ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for lumefantrine for the three prequalified generic formulations when compared with same comparator product, Coartem®. There were three potential pairs of generic products tested at the same dose.

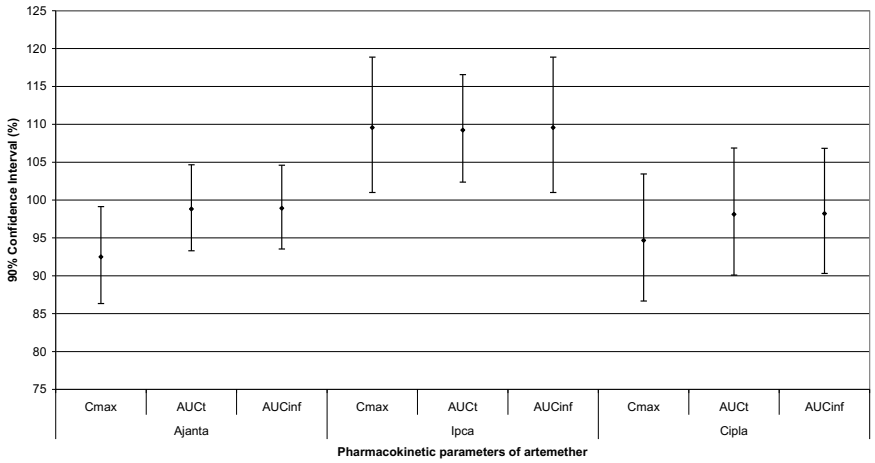

Figure 1:90% confidence intervals of the pharmacokinetic parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) of artemether in fixed dose combination generics of artemether / lumefantrine versus the artemether / lumefantrine comparator product (Coartem, Novartis).

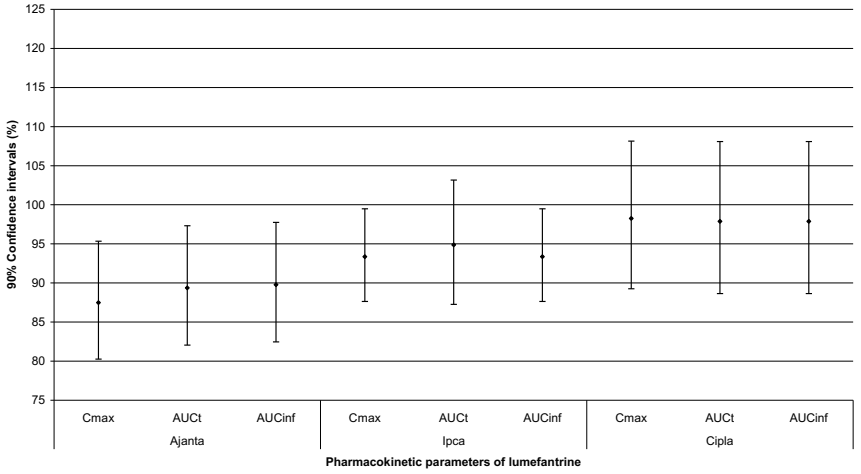

Figure 2:90% confidence intervals of the pharmacokinetic parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) of lumefantrine in fixed dose combination generics of artemether / lumefantrine versus the artemether / lumefantrine comparator product (Coartem, Novartis).

The indirectly determined point estimates and 90 % CIs for the comparisons between generics and direct comparisons with reference product for artemether and lumefantrine are presented in Tables 1

and 2, respectively. In the bioequivalence study performed by Cipla (Mumbai, India) for lumefantrine, an AUC truncated at 72 hours was reported. For artemether, the adjusted indirect comparison between generics shows that the products satisfy the conventional bioequivalence criterion of the 90 % CIs falling within 80– 125 % for the AUC, and even one comparison was able to satisfy the same criterion with respect to the C_{max}. Two comparisons resulted in 90 % CIs for the C_{max} that fall slightly outside the conventional 80–125 % criterion.

For lumefantrine, the adjusted indirect comparison between generics shows that the products satisfy the conventional 80–125 % acceptance range for AUC, and two were able to satisfy the same criterion for the C_{max}. One comparison resulted in a 90 % CI for C_{max} that falls slightly outside this acceptance criterion. The conclusions are independent of the method of calculation of the indirect comparison, and the numerical differences between methods are minor.

Table 1: 90% CIs for C_{max} and AUC_{0-t} of artemether obtained by different methods of adjusted indirect comparisons of generic products of artemether and lumefantrine.

Method / C_{max}	1 vs. 2	1 vs. 3	2 vs. 3
Chow and Liu	75.31 – 94.66	86.90 – 109.84	103.38 – 129.52
t heteroscedastic	75.94 – 93.87	87.40 – 109.21	102.69 – 130.38
t homoscedastic	75.81 – 94.04	87.33 – 109.30	102.72 – 130.34
Pragmatic	75.95 – 93.86	87.40 – 109.30	102.70 – 130.37
Chow and Shao	77.79 – 91.64	89.64 – 106.48	105.51 – 126.90
Z distribution	77.80 – 91.63	89.64 – 106.48	105.52 – 126.89
Method / AUCt			
Chow and Liu	81.88 – 99.95	90.93 – 111.53	100.89 – 122.81
t heteroscedastic	83.01 – 98.59	90.93 – 111.52	100.07 – 123.82
t homoscedastic	82.91 – 98.71	90.84 – 111.63	100.20 – 123.66
Pragmatic	83.02 – 98.58	90.94 – 111.63	100.09 – 123.80
Chow and Shao	84.65 – 96.88	93.07 – 108.95	102.52 – 120.86
Z distribution	84.66 – 96.67	93.07 – 108.95	102.53 – 120.85

Table 2:90% CIs for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of lumefantrine obtained by different methods of adjusted indirect comparisons of generic products of artemether and lumefantrine.

Method \ Cmax	1 vs. 2	1 vs. 3	2 vs. 3
Chow and Liu	83.45 - 105.21	79.08 - 100.26	84.77 - 106.52
t heteroscedastic	84.27 - 104.19	78.36 - 101.19	84.76 - 106.53
t homoscedastic	84.44 - 103.98	78.32 - 101.23	84.95 - 106.30
Pragmatic	84.29 - 104.17	78.36 - 101.23	84.79 - 106.51
Chow and Shao	86.33 - 101.70	80.67 - 98.29	87.00 - 103.79
Z distribution	86.34 - 101.70	80.67 - 98.29	87.01 - 103.79
Method \ AUCt			
Chow and Liu	82.97 - 106.93	80.18 – 103.96	85.53 - 109.83
t heteroscedastic	83.67 - 106.04	80.19 – 103.94	5.22 - 110.23
t homoscedastic	83.64 - 106.03	80.14 - 104.00	85.30 - 110.13
Pragmatic	83.68 - 106.03	80.19 - 104.00	85.23 - 110.22
Chow and Shao	85.95 - 103.23	82.59 – 100.91	87.75 – 107.06
Z distribution	85.96 - 103.22	82.59 - 100.92	87.75 - 107.05

DISCUSSION

In this study we compared different approaches for calculating adjusted indirect comparisons to investigate the relative bioavailability of generic products. Based on our results, we conclude that, although the differences in results between the methods were minor, the homoscedastic method is recommended when performing adjusted indirect comparisons of bioequivalence studies—unless a clear difference in variances is observed in the data. Indeed, this mathematical approach will be useful to obtain comparative information on generic versions of a given reference (innovator) product.

Further, the comparisons conducted revealed that the WHO-prequalified generic artemether/lumefantrine products used as models are not only bioequivalent with the reference product (Coartem; Novartis) in terms of the AUC and C_{max}, but they are also bioequivalent between themselves with respect to the AUC. Although some of the comparisons for C_{max} fell outside the traditional acceptance range, this result would, in part, be attributable to the reduced precision of the adjusted indirect comparison for C_{max}. These results suggest that these different generic products can be inter-changed safely without any safety or efficacy concerns.

Direct comparisons of treatments should be sought [6,7], but as direct comparisons between generic products are unavailable, indirect

comparisons can estimate the magnitude of the treatment differences across studies with some limitations.

When performing indirect comparisons, several methods are available: (1) naïve or unadjusted indirect comparisons, which are biased, (2) adjusted indirect comparisons, (3) meta-regression analysis, and (4) mixed treatment comparisons based on Bayesian statistics [11]. If only two interventions are to be compared indirectly, the adjusted indirect comparison seems to be the most appropriate methodological approach in terms of the validity of the data and the limited methodological effort [11]. In the case of bioequivalence studies where only two products are under comparison each time (i.e., no mixed or network of comparisons), there is no need to employ more complex statistical techniques. In addition, the adjusted indirect comparison is the simplest form of meta-regression [7] when there is only one trial available for the options under comparison (i.e., no heterogeneity to model by regression). In this case indirect comparisons are performed without meta-analysis [11]. Consequently, the previous stages of meta-analysis (i.e., collection or calculation of summary statistics for each of a set of studies, followed by the weighted combination of these statistics to provide an overall estimate) [7] are not required. As such, the indirect treatment comparison meta- analysis becomes simply an adjusted indirect comparison. However, if several studies were available, a meta-analysis [12] to summarize the relative bioavailability of generic *versus* reference could be performed as a previous step to the indirect comparison.

The major limitation of adjusted indirect comparisons of bioequivalence studies is that the uncertainty or standard error of the indirect comparison is larger than the largest standard error of the studies under comparison, in brief $SE_d^2 = SE_A^2 + SE_B^2$. This makes indirect comparison twice less effective than direct comparison according to Bucher et al. [6], requires 4-fold more data according to Song et al. [7], and/or the SE of the indirect estimate is expected to be about 1.41 larger than that of the direct estimate [7]. Consequently, the inability to show bioequivalence by means of indirect comparisons does not mean that the products are not equivalent, but simply there is not enough statistical power [13] to make this conclusion, because the individual studies were designed only to show equivalence with the reference product and not to be used in indirect comparisons. Therefore, failure to show equivalence should not be interpreted as

that the generics actually differ by the magnitude of the boundary of the 90% confidence interval most distant from unity [9], as an excuse to discredit generic substitution [14].

On the contrary, when bioequivalence is shown despite the lack of necessary statistical power we can consider not only that the products are bioequivalent but also quite similar. As soon as one of the generics has a point estimate slightly deviating from the ratio of 1, the probability of showing equivalence with the reference product decreases. Further, the probability of showing bioequivalence with other generics via indirect comparison is notably lower, taking into account that the sample size of the bioequivalence studies is calculated with the assumption that there is no difference or a difference of <5% with the reference product.

In conclusion, the demonstration of bioequivalence in AUC for the indirect comparison of artemether and lumefantrine AUC_{0-t} is indicative of a great similarity between the prequalified products. The failure to show equivalence for C_{max} in some comparisons is considered insignificant clinically since C_{max} is less therapeutically relevant and the 90% CI is always contained within the 75-133% that was used on some occasions in the European Union. In addition, it is noteworthy that in Canada, the C_{max} acceptance criterion for generics containing uncomplicated drugs is based on the point estimate only. In all indirect comparisons with the prequalified artemether / lumefantrine generics, the point estimate of C_{max} is included in the 80-125% acceptance range. Therefore, it would not be inappropriate to consider all of these products interchangeable for treatment of *Plasmodium falciparum*-related malaria.

Of course the assumption that gives validity to adjusted indirect comparisons, i.e., the variation in the observed results for patients treated with the common comparator will account for differences between studies in terms of methodology (e.g., bioanalytical methods, sampling times), subjects' baseline characteristics (e.g., metabolic status, race, sex, dose), among other [7] and is critical as the studies should be estimating the same effect. There should be no important differences between the trials under comparison in aspects that could influence (bias) the estimated formulation effect. That is, there should be no confounding of the comparison by trial characteristics. Therefore, it is not possible to combine or compare studies with different study designs/objectives since the formulation

effect cannot be expected to be the same between differing designs. For example, multiple dose studies or studies employing a metabolite as the analyte cannot be compared with single dose study data or parent as analyte data because the former study approaches are less sensitive than the latter to detect differences between formulations. Further, studies involving the collection of differing biological fluids, such as plasma *versus* urine or differences in fasted *versus* fed conditions, cannot be compared because of differences in the potential impact of these designs on formulation differences and dis- parities in their sensitivity to detect differences between formulations. However, in our opinion, conventional 2×2 designs and replicate design are combinable.

The adjusted indirect comparison is unbiased, even if both control and treatment groups differ in baseline characteristics, as long as the magnitude of the treatment effect is constant across differences in the populations' baseline characteristics. In bioequivalence studies it is recognized worldwide that differences between formulations do not generally depend on factors such as sex or race of the healthy volunteers. It is also taken for granted that there is no subject-by-formulation interaction or, in other words, the magnitude of the formulation differences does not depend on the covariates defining subgroups of patients (e.g., if patients' sensitive to the laxative effect of sorbitol or allergic to lactose would exhibit a reduced bioavailability).

Other limitations that may affect adjusted indirect comparisons of efficacy trials do not seem to affect those of bioequivalence studies because of the general consistency in the basic study design for these studies. For example, differences in disease state are not a concern since bioequivalence studies usually recruit healthy volunteers and this method controls for differences in baseline characteristics between treatment groups [6]. Further examples of design characteristics that are addressed amongst bioequivalence studies include the following: (1) outcome measures for bioequivalence studies [6] are consistently the same pharmacokinetic parameters [6], (2) differences in methodology, such as bioanalytical techniques [6], are corrected by the use of the same reference product in different bioequivalence studies, and (3) temporal bias [15] due to a change in baseline risk and opportunity bias [15] is related to a preference for participating in one of the studies. Similarly, in contrast to efficacy trials, it does not seem likely that indirect bioavailability

comparisons are less biased than direct bioavailability comparisons [16].

The results provided by the different methods of calculation (Tables 1 and 2) are consistent and can be divided in two groups. The methods based on the standardized normal distribution (Chow and Shao method for large sample sizes [5] and the method employed by Krauss et al. [9) provide narrower confidence intervals since the width of the confidence interval is calculated with a factor that is narrower ($z_{0.9}$=1.28) than the t value corresponding to the degrees of freedom of the combined analysis of the bioequivalence studies because the sample size of the bioequivalence studies is not large enough to make these values agree. Therefore, these methods cannot be recommended because the results are somewhat conservative (i.e., two or three units narrower).

The meta-analysis described by Chow and Shao [5] is based on the assumption that the absolute value of the pharmacokinetic parameters of the reference product, which is the same in all bioequivalence studies, is the same. This assumption is unlikely taking into account that the studies are performed in different sites with different populations and that plasma concentrations are authorisation with different bioanalytical methods. Therefore, absolute values may not be directly comparable in absolute terms, but only in relative terms.

The method described by Chow and Liu [4] has been employed on occasion [17,18], although it is based on strict assumptions that may not be fulfilled and that are not verifiable (i.e., the same intra-subject and inter-subject variability in all studies). In fact, the statistical test to investigate the heterogeneity of the reference product in all studies detected a significant difference in lumefantrine AUC and C_{max} (data not shown), probably due to the differences in the study population or bioanalytical method. In addition, in some cases it was the least powerful test since it gave the widest 90 % CI. Consequently, this method is not recommended, even if the results obtained are numerically similar to those based on conventional *t* tests, which are not based on the calculation of a common intra-subject and inter-subject variability from all studies.

Methods based on the *t* test differ in the assumption of homogeneous variances between studies (homoscedastic/heteroscedastic). The differences in the results

obtained with these two methods are minor (decimal units), and they do not appear to follow any trend; rather, they depend on data under pair-wise comparison (sample size and variability of each study). The method based on a combination of both (SE calculation of the heteroscedastic method and degrees of freedom of the homoscedastic method), which is the simplest numerical calculation, gives results similar to those obtained with the heteroscedastic approach, showing that the contribution of the different method of calculation of the degrees of freedom is negligible. In contrast, when compared with the method employed by Krauss et al., which uses the same method of calculation for the SE and differs in the use of the $z_{0.9}$ instead of the t value, the difference is notable (2 – 3units).

In conclusion, the homoscedastic method is recommended when performing adjusted indirect comparisons of bioequivalence studies—unless a clear difference in variances is observed in the data, which is unlikely. The artemether and lumefantrine 20/120 mg tablets currently on the WHO List of Prequalified Products are not only bioequivalent with the reference product (Coartem; Novartis) in terms of AUC and C_{max}, but we have demonstrated that they are also bioequivalent between themselves with respect to the AUC. The reduced precision of the adjusted indirect comparison for C_{max} indicates that the differences between generics are reasonably acceptable. For public health programs, these results suggest that these different generic products can be interchanged safely without any safety or efficacy concerns.

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CHAPTER 2.2

Influence of point estimates and study power of bioequivalence studies on establishing bioequivalence between generics by adjusted indirect comparisons

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ABSTRACT

Purpose: Adjusted indirect comparisons can be used to investigate bioequivalence between generic products that are bio- equivalent with a common reference product. In previous work with generic tuberculosis medicines prequalified by the WHO, it was observed that although indirect comparisons are an effective approach for confirming the interchangeability of generics, the approach is subject to less precision than direct comparisons. The objective of this investigation was to explore this by examining the influence of point estimates and power of bioequivalence studies *versus* the reference on the ability to show equivalence in indirect comparisons.

Methods: Power was considered as a determining factor instead of variability and sample size, because sample size is calculated based on variability and desired power. Scenarios were computed combining a range of point estimate differences (0–14 %) and statistical power of the studies (50–99.99 %).

Results: The indirect comparisons could conclude equivalence between generics only when (a) point estimate differences between generics were low (≤5.5 %) for any sufficiently powered study (>80 %), or (b) the differences were large (but less than 14 %) and both bioequivalence studies were overpowered (e.g., 10 % difference and power ≥95 %).

Conclusions: In summary, the ability to demonstrate inter-changeability between generics is dependent not only on the real differences between the products but also on the design of the original generic *vs*. reference bioequivalence studies being combined, as earmarked by their respective power.

INTRODUCTION

Regulatory authorities approve generic medicines based on their bioequivalence (BE) with the reference product [1-3]. Bioequivalent products are considered interchangeable with the reference product for their prescription in new patients (prescribability) and for switching patients that are already under treatment (switchability) [4]. However, in real clinical practice, patients are also switched between generics that have not been compared directly with each other.

Even if the comparison between generic products is theoretically desirable, it is impossible because generic products do not reach the market simultaneously and an increasing number of comparisons would be required for each new product coming to the market. It would be arbitrary to require only a single BE study *versus* the reference product for the first generic that applies for a marketing authorisation and to require "n" BE studies to the n^{th} generic application (one study *versus* the reference product and n-1 studies *versus* the n-1 generics that have been authorized previously). Moreover, to deny authorisation to a product that meets bioequivalence standards against the reference product but fails to meet those standards *vs.* another generic product is a difficult regulatory decision to make.

As all generic products are usually compared to the innovator/originator product, adjusted indirect comparisons can be employed to obtain an estimation of the differences that exist between the generics. Different methods to perform indirect comparisons have been described and compared previously by Gwaza et al. [5] based on artemether and lumefantrine generics prequalified by the World Health Organization (WHO) [6].

The precision of the indirect comparisons is lower than that of direct comparisons [7,8] and, consequently, if the BE studies were designed to just have enough power (e.g. 80 or 90%) to show equivalence with the reference product, the indirect comparisons may not have the necessary power to show equivalence between generics. This was observed in Gwaza et al. [9] by comparing a diverse group of prequalified first line tuberculosis (TB) medicines in order to explore the utility of the recommended approach for conducting adjusted indirect comparisons. On one hand, the study found that the TB

products being compared could be interchanged as necessary without significant concern regarding possible shifts in the quality of therapy. On the other hand, the outcomes of the indirect comparison suggested that assurances regarding interchangeability of two generic products are reduced when either the point estimate ratios in the original studies are shifted from unity (1.0) by more than 5%, or when the variability in those studies is large.

The objective of this study was to investigate the influence of point estimate, and variability of the main pharmacokinetic parameters (C_{max} and AUC) and the sample size in the original studies on the ability to demonstrate BE between generics in the adjusted indirect comparisons. However, instead of sample size and variability [8,10], statistical power should be employed in the computation of different scenarios because the sample size of the study is not free, but it is dependent on the variability and the desired statistical power. The standard error of the bioequivalence studies is the same when the variability is large or small if the sample size is calculated to obtain the desired statistical power. Therefore, the statistical power is the most relevant parameter for consideration.

MATERIAL AND METHODS

Computed scenarios

Combining 57 possible differences between point estimates from 0 to 14% in 0.25% increments and 16 possible study powers 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 99, 99.25, 99.50, 99.75, 99.80 and 99.99%, 14,592 scenarios were computed although some scenarios were repetitive (e.g., where the first study has 80% power and the second has 90% power is the same scenario as where the first study has 90% power and the second one has 80% power).

Study powers lower than 50% were not considered since 80% is the minimum intended study power employed in real practice and additional subjects are always employed to compensate for dropout subjects and withdrawals. Differences in point estimates larger than 14% were not evaluated because such differences are not able to show BE between generics even with statistical power of 99.99% in both studies.

Statistical analysis of indirect estimates

The 90% CI for the indirect treatment comparisons for each computed scenario was calculated as described previously [5] and brief description of the method is provided as online resource 1.

The number of subjects in each study was calculated according to the formula based on the standardized Normal distribution approximation as described by Julious [11] $N = \frac{2S_W^2(Z_{1-\beta}+Z_{1-\alpha})^2}{(Ln(\mu_T/\mu_R)-Ln\,(1.25))^2}$, where s_w^2 is calculated as $s_w^2 = Ln(1+(CV/100)^2)$. The ratio between the mean of the test and the reference is assumed to be 1.0526 (i.e. 5% difference), the desired power (1-β) is defined in the computed scenario, the variability in each study was fixed at 25%, and the consumer risk (α) corresponds to 0.1 for the 90% level of confidence.

Computations and data analysis were done using Microsoft Excel 2011 for Mac. Version 14.3.5.

Verification of the expected value of the calculations

Indirect comparisons between aciclovir generics that had been authorized in Spain were calculated to confirm expected results. The power of these studies was calculated based on the final study sample size and the observed intra-subject variability rearranging the previous equation employed for sample size calculation in order to estimate $Z_{1-\beta}$ (assuming differences between the formulation) and then calculating the corresponding 1-ß value.

RESULTS

Figure 1 illustrates the differences between generics that will result in a failure to show equivalence within the conventional acceptance range (80-125%), given the different study powers for the original BE studies where the generics were compared to the reference product.

Online resource 2 and 3 show the lower boundary of the 90% CI of the adjusted indirect comparisons when the difference between generics is 5% and 10%, respectively. The latter scenario deserves special attention because the specifications for assay are usually ±5% [12]. Therefore, two batches of the reference product can differ up to 10%. This difference can be even larger in certain drugs [13,14]. In the case of a 10% difference and the usual 80% power for the original BE studies, Online resource 3 shows that the lower boundary of the

90% CI of the adjusted indirect comparison is 76.39. Therefore, adjusted indirect comparisons will result in a failure to show equivalence between these two batches of the reference product that meet specifications, even if the power is 95% in both studies.

Table 1 illustrates the power of the second BE study necessary to show equivalence for a given difference between generics and the power of the first BE study.

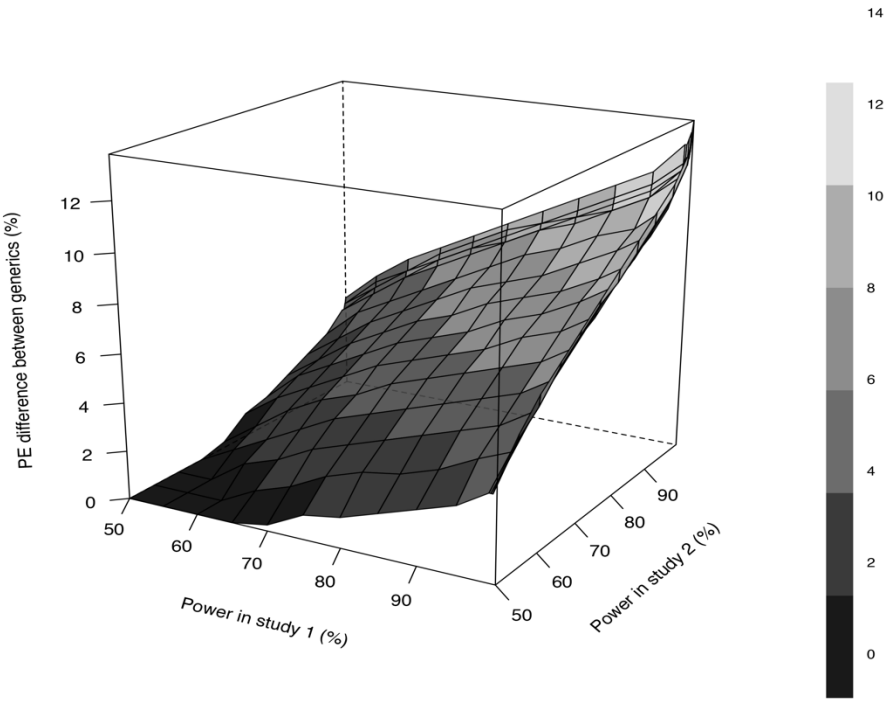

Figure 1: Surface plot of the point 14 estimate of the difference between generics that will result in a failure to show equivalence within the conventional acceptance range (80–125%) for the different study powers of the original studies where the generic was compared to the reference product. Point estimate differences above or on the surface of the plot will result in a failure to demonstrate BE at the respective study powers.

For any wider acceptance range (e.g. ±25%), the difference between generics that will still result in equivalence within this new acceptance range can be calculated from the results obtained in Table 1 by adding the additional width with respect to the conventional acceptance range (i.e. 5%) to the difference between generics.

Table 1: Power required in a study 2 to demonstrate equivalence given power in study 1 and the given difference in point estimates between generics

Statistical Power of Study 1 (%)

Difference between point estimate of generics	50.00	55.00	60.00	65.00	70.00	75.00	80.00	85.00	90.00	95.00	99.00	99.25	99.50	99.75	99.80	99.99
0.0	70.00	65.00	60.00	55.00	50.00											
0.5	75.00	65.00	60.00	55.00	55.00	50.00										
1.0	80.00	70.00	65.00	60.00	55.00	55.00	50.00									
1.5	85.00	75.00	70.00	65.00	60.00	55.00	55.00	50.00								
2.0	90.00	80.00	70.00	65.00	60.00	60.00	55.00	55.00	50.00							
2.5	95.00	85.00	75.00	70.00	65.00	60.00	60.00	55.00	55.00	50.00						
3.0	99.00	90.00	80.00	75.00	70.00	65.00	60.00	60.00	55.00	55.00	50.00					
3.5	99.75	95.00	85.00	80.00	75.00	70.00	65.00	60.00	60.00	55.00	55.00	55.00	55.00	50.00		
4.0		99.00	90.00	85.00	75.00	70.00	70.00	65.00	60.00	60.00	55.00	55.00	55.00	55.00	55.00	55.00
4.5		99.50	95.00	90.00	80.00	75.00	70.00	70.00	65.00	60.00	60.00	60.00	55.00	55.00	55.00	55.00
5.0		99.99	99.00	95.00	85.00	80.00	75.00	70.00	70.00	65.00	60.00	60.00	60.00	60.00	60.00	55.00
5.5			99.50	99.00	90.00	85.00	80.00	75.00	70.00	70.00	65.00	65.00	60.00	60.00	60.00	60.00
6.0			99.99	99.00	95.00	90.00	85.00	80.00	75.00	70.00	65.00	65.00	65.00	65.00	65.00	60.00
6.5				99.75	99.00	95.00	90.00	85.00	80.00	75.00	70.00	70.00	70.00	65.00	65.00	65.00
7.0					99.25	99.00	95.00	90.00	85.00	80.00	75.00	70.00	70.00	70.00	70.00	70.00
7.5					99.99	99.00	95.00	95.00	90.00	80.00	75.00	75.00	75.00	75.00	75.00	70.00
8.0						99.80	99.00	95.00	90.00	85.00	80.00	80.00	80.00	80.00	75.00	75.00
8.5							99.50	99.00	95.00	90.00	85.00	85.00	80.00	80.00	80.00	80.00
9.0							99.99	99.25	99.00	95.00	90.00	85.00	85.00	85.00	85.00	80.00
9.5								99.99	99.00	99.00	90.00	90.00	90.00	90.00	90.00	85.00
10.0									99.75	99.00	95.00	95.00	95.00	90.00	90.00	90.00
10.5									99.99	99.50	99.00	99.00	95.00	95.00	95.00	90.00
11.0										99.99	99.00	99.00	99.00	99.00	99.00	95.00
11.5											99.50	99.25	99.00	99.00	99.00	99.00
12.0											99.99	99.80	99.75	99.50	99.25	90.00
12.5												99.99	99.99	99.99	99.99	99.25
13.0														99.99	99.99	99.75
13.5																99.99

The shaded grey area shows the nonequivalence within the conventional bioequivalence criteria of ±20% limit, for given statistical power in study 1 and difference in point estimate. The un-shaded area (white) shows equivalence within conventional ±20% acceptance limit for statistical power greater or equal to 50 in study 2.

The results of the original aciclovir BE studies from Spain are plotted in Figure 2. The results of the indirect comparisons conducted between those generics of aciclovir marketed in Spain are shown in Table 2, together with the power of the corresponding BE studies.

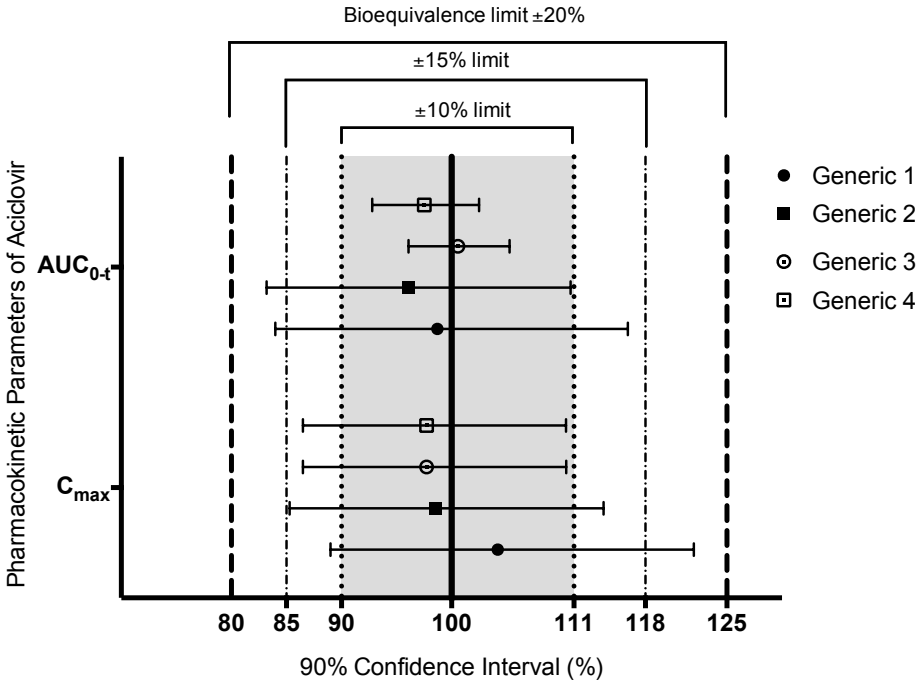

Figure 2: 90 % confidence interval Bioequivalence limit ±20% for the ratio test/reference of the pharmacokinetic parameters (C_{max}, AUC_{0-t}) of aciclovir generic formulations approved in Spain

Influence of point estimates and study power on substitution

Table 2: Verification of the expected value of the calculations based on point estimates difference and study powers on the bioequivalence conclusion of the adjusted indirect comparisons between generic products using aciclovir data on generic products

		Difference in point estimate	Study 1 power	Study 2 power	Adjusted Indirect Comparison Results	Expected Results (Based on Table 1)
C_{max}	1vs2	5.76	58.96	64.93	85.78 – 130.40 (Non BE)	Non BE
	1vs3	6.62	58.96	78.75	87.76 – 129.54 (Non BE)	Non BE
	1vs4	6.63	58.96	78.76	87.77 – 129.55 (Non BE)	Non BE
	2vs3	0.81	64.93	78.75	83.81 – 121.26 (BE)	BE
	2vs4	0.82	64.93	78.76	83.82 – 121.27 (BE)	BE
	3vs4	0.01	78.75	78.76	84.57 – 118.27 (BE)	BE
AUC	1vs2	2.81	57.28	65.40	83.21 – 127.03 (Non BE)	Non BE
	1vs3	1.86	57.28	100	83.11 – 115.89 (BE)	BE
	1vs4	1.21	57.28	100	85.61 – 119.65 (BE)	BE
	2vs3	4.54	65.40	100	82.23 – 110.81 (BE)	BE
	2vs4	1.55	65.40	100	84.71 – 114.41 (BE)	BE
	3vs4	3.13	100	100	96.58 – 110.12 (BE)	BE

DISCUSSION

The present study illustrates that demonstrating BE within the conventional acceptance range (80-125%) by means of adjusted indirect comparisons is only possible if the difference between point estimates is small and the original BE studies were well-powered (see Table 1). For example, if both original studies exhibited 80% power, the difference between generics cannot be larger than 5.5%. Consequently, it is unrealistic to expect that adjusted indirect comparisons will be able to show BE within the conventional acceptance range 80-125%. Therefore, due to the limited statistical power of indirect comparisons, we propose to define a slightly wider acceptance range (e.g. ±25%, i.e. 75 - 133%) for adjusted indirect comparisons, in order to be able to show equivalence between batches of the reference product, or between generic products, with this comparative approach. Products meeting the proposed acceptance criteria can be interchanged as necessary with little concern regarding possible shifts in the quality of therapy as observed by the patient or treating professional. As suggested previously [9], this work indicates that the best way to gain greater assurance of generic interchangeability, when necessary, is to place a constraint on the point estimates in the original generic *vs.* reference product bioequivalence studies.

Using aciclovir generics approved in Spain, our results demonstrate the utility of using statistical power in the original bioequivalence studies and the difference in point estimate alone (Table 1) to anticipate equivalence / non-equivalence between generics that have been compared against the same reference product (Table 2). Aciclovir studies included low powered scenarios e.g. for C_{max} and high powered scenarios e.g. for AUC. The model was able to anticipate the same outcome compared to performing the statistical calculations for adjusted indirect comparisons.

It is essential to understand that the power of the study is not the conventional power to show differences between treatments in superiority tests, but the power to show equivalence [11]. The validity of the bioequivalence conclusion is not questionable even in those cases where the power of the bioequivalence studies is not as high (e.g. 80%) as expected (e.g. when the observed variability or the rate of drop-outs are larger than expected). However, this post-hoc power

is influential on the ability to show bioequivalence between generics in adjusted indirect comparisons. In order to calculate the post-hoc power of the study, apart from the observed variability and the final sample size of the study, it is necessary to define not only the alpha value of the confidence interval (i.e. 10% for 90% CI) and the expected ratio between test and reference, which is usually assumed as 5%, but also the acceptance range, which is 80-125% for bioequivalence of conventional drugs. Furthermore, the method that we employed assumes equal allocation to each sequence and true point estimate not equal to 1.0. The formula provides a reasonable approximation when the point estimate is not equal to 1.0, especially when the point estimate is large relative to the interval limits (0.80 - 1.25) [11]. It should be noted that under different assumptions such as unequal allocation between sequences, no difference between the means or for different study designs, alternative formulas should be used for estimating the power of the original studies.

Demonstration of BE between generics can be of interest in certain situations. For drugs for chronic use and with a wide therapeutic range, demonstration of BE with the reference product within a ±20% acceptance range ensures "prescribability", and demonstrates direct "switchability" with the reference product. In addition, this is assumed to be sufficient evidence of switchability between generics products, since a slightly larger difference (e.g. ±25 - 30%) is still considered clinically equivalent. In these cases indirect comparison may be useful to quantitate the difference between generics, taking into account the limited precision, which can be compensated for with a slightly wider acceptance range (e.g. ±25 - 30%). Similarly, in the case of narrow therapeutic index drugs, an acceptance range of e.g. ±10% may be necessary to ensure "switchability" between generics within an e.g. ±20% range. In these cases, indirect comparisons become essential to quantify the potential differences in case of generic substitution. For drugs where such differences have clinical relevance, "switchability" between generic products should be avoided.

According to Table 1, demonstration of BE by means of indirect comparisons is only possible when the point estimates of the generics are not notably different (i.e. <14%). Further, BE is only likely with differences equal to or smaller than 5.5% if the studies are just sufficiently powered (i.e. 80%) to show equivalence, and with differences equal to or smaller than 8% if the studies were 90% powered. If generic products differ by 9.0%, the indirect comparison

will be able to show equivalence if the power of the studies is 95% and, if the difference is 10.5%, the studies have to be 99% powered.

Although bioequivalence studies with low statistical power only succeed when point estimates are close to unity and, consequently, point estimate differences between generics have to be small in the indirect comparisons, the low statistical power in the BE studies precludes the demonstration of equivalence in the indirect comparisons due to an excessive width of the 90% confidence interval. For instance, even if the difference between generics is zero, the indirect comparison is not able to show equivalence between generics if the original studies only had a 50% power.

Interestingly, if the power of the original studies were increased (e.g. from 80 to 95%) to have a greater probability of demonstrating equivalence between generics in the adjusted indirect comparisons, the point estimate difference between generic and reference product compatible with bioequivalence would increase and, subsequently, the point estimate difference between generics would also increase, which decreases the probability of showing equivalence between generics by adjusted indirect comparisons. In the extreme case, equivalence within the 20% acceptance range cannot be shown between generics that differ by 7% with respect to the reference product in different directions (i.e. a 14%-point estimate difference between generics) or between the batches at the edge of the specifications if these are ≥7% (e.g. 8% for carbamazepine according to USP [13], despite its narrow therapeutic index).

Previous investigations [8,15] have explored the probability of "inequivalence" between generics that have been shown to be bioequivalent with a common reference product. Anderson and Hauck (1996) showed that the proportion of the distributions outside of the acceptance range was not larger than 9.5%, when the difference between generics is assumed to be 5%, the intra-subject variability is low (10%) and the sample size is large (n=40) [15]. This scenario is unlikely, since products with low variability are never tested with 40 subjects because a lower sample size is enough to have sufficient power (80 or 90%) with consequent savings. Nonetheless, this may be the case when the sample size is estimated based on the most variable PK parameter (e.g. C_{max}) and the other one (e.g. AUC) is consequently overpowered. However, as C_{max} is usually the more variable parameter and the one with the largest differences in point

estimate, the simulated scenario seems to be representing AUC only. Adjusted indirect comparisons would be able to show equivalence between generics in such scenarios (i.e. difference between generics of only 5% and overpowered bioequivalence studies).

These authors explained that the higher the within-subject variability, the lower the power of the BE studies and thus, the less likely extreme values (i.e. values close to the acceptance boundaries 80-125%) will pass, which will allow small differences (e.g. 5%) between generics [15]. However, the contrary scenario was simulated i.e., low variability and high sample size, which increases the power to conclude equivalence. The higher the power of the trial, the more the post-trial distribution will include larger differences, in contrast to their assumption of differences not larger than 5%. The authors concluded that even with the "worse" scenario of 9.5% non-bioequivalent products, this low value provides reassurance of the BE of two generic products that have been shown to be bioequivalent to the same reference product. However, this does not seem to be the worst scenario, but a very favourable one, because point estimate differences between generics can be larger [5, 16].

Karalis et al. (2013) plotted the probability of accepting BE between generics as a function of their point estimates and concluded that although two generics are bioequivalent to the reference product, this does not ensure that they are bioequivalent to one another [8]. These results were obtained by Monte Carlo simulations where the sample size were fixed at 24 or 48 subjects and intra-subject variability were 20 or 40%, as if they were independent parameters, without taking into account that the sample size is calculated based on the intra-subject variability to obtain the required statistical power. Simulation of the effect of variability for a fixed sample size would seem to be inconsequential because when the variability of the drug under investigation is high, the sample size of the study is increased conveniently. Therefore, both factors, intra-subject variability and sample size, have to be handled in combination by means of the study power. These authors concluded that two products can be switched when the point estimates are close, the intra-subject variability is low and both BE studies were conducted with large number of subjects. These results are consistent with our results, in which indirect comparisons are able to show equivalence when the difference between point estimates is small and the BE studies are overpowered; this occurs when the sample size is large and the variability is

comparatively low. However, these authors focused on the scenario where generics can be switched because they are equivalent, whereas our focus is on when it is possible to demonstrate that generics are equivalent based on indirect comparisons.

In summary, the ability to show BE between generic products by means of indirect comparisons depends on the difference between the point estimates of the BE studies, which is the point estimate of the indirect comparison, and the power of the BE studies that are combined. The variability of the drug is not a relevant factor as long as the sample size is increased to obtain the desired statistical power (e.g. 80 or 90%) to be able to demonstrate equivalence with the reference product in the respective BE study. Therefore, this work supports the contention that if regulatory authorities wish to ensure generic interchangeability, and reduce the influence of study design on the outcome, the most effective approach would be to impose a point estimate constraint in the original bioequivalence studies.

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SUPPLEMENTARY MATERIAL

***Online resource 1**: Brief description of the method to calculate the 90% CI for the adjusted indirect comparisons for each computed scenario.*

Statistical analysis of indirect estimates

The CI of the indirect comparison between generics is calculated as: $\widehat{D}_{A,B} \pm t_{\alpha,df} \cdot SE_{(d)}$, where $\widehat{D_{A,B}}$ is the difference between point estimates of the BE studies, which were defined for each computed scenario (0-14%), $t_{\alpha,df}$ is the Student t-value that corresponds to the alpha of 10% in order to estimate CI with 90% confidence and the degrees of freedom of the combination of the BE studies.

The degrees of freedom were calculated as n_A+n_B-2 in those scenarios where the variability of both studies was the same, whereas in the case of scenarios with different variability they were calculated according to Welch [11], $d.f. = \frac{\left(\frac{SD_A^2}{n_A}+\frac{SD_B^2}{n_B}\right)^2}{\frac{\left(\frac{SD_A^2}{n_A}\right)^2}{n_A-1}+\frac{\left(\frac{SD_B^2}{n_B}\right)^2}{n_B-1}}$, where n_A and n_B are the number of subjects in study A for generic A and in study B for generic B, respectively, SD_A and SD_B are the standard deviations in each BE study (A and B).

The calculation of the $SE_{(d)}$ was performed without any assumption as $\left(SE_d^2 = SE_A^2 + SE_B^2\right)$in the case of heteroscedasticity and it was calculated as $SE_{(d)} = SD_{pooled}\sqrt{\frac{1}{n_A}+\frac{1}{n_B}}$, in the case of homoscedasticity. The combined standard deviation (SD_{pooled}) is derived from the equation $SD_{pooled}^2 = \frac{(n_1-1)SD_A^2+(n_2-1)SD_B^2}{n_A+n_B-2}$, where the degrees of freedom are ($n_A + n_B - 2$). The standard deviation (SD) of each individual study is calculated by $SD = \frac{2\cdot SE_{(d)}}{\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}}$, where n_1 and n_2 represents the number of subjects in sequence 1 and sequence 2, respectively for the crossover BE studies.

The standard error ($SE_{(d)}$) of each study was calculated according to $SE_{(d)} = \sqrt{\frac{2\,Ln(1+(CV/100)^2)}{n}}$, where n is the number of subjects in the BE study and CV is the coefficient of variation, which was fixed at 25% after verifying that the results are not altered since any change in

variability is compensated by the change in sample size required to keep the desired statistical power.

Online resource 2 *(Supplementary Table 1): The lower boundary of the 90% confidence interval of the adjusted indirect comparisons, for a given statistical power in the original bioequivalence studies when the difference between generics is fixed at 5%*

Statistical Power in Study 2

Statistical Power in study 1	50.00	55.00	60.00	65.00	70.00	75.00	80.00	85.00	90.00	95.00	99.00	99.25	99.50	99.75	99.80	99.99
50.00	74.02	74.68	75.25	75.74	76.18	76.59	76.96	77.32	77.69	78.10	78.61	78.67	78.74	78.84	78.87	79.13
55.00	74.68	75.37	75.96	76.48	76.94	77.37	77.76	78.14	78.53	78.97	79.51	79.58	79.65	79.76	79.79	80.07
60.00	75.25	75.96	76.58	77.12	77.60	78.04	78.46	78.86	79.27	79.73	80.31	80.37	80.46	80.57	80.61	80.91
65.00	75.74	76.48	77.12	77.68	78.18	78.64	79.07	79.49	79.92	80.41	81.02	81.09	81.18	81.30	81.34	81.66
70.00	76.18	76.94	77.60	78.18	78.70	79.18	79.63	80.07	80.52	81.03	81.68	81.75	81.84	81.98	82.01	82.35
75.00	76.59	77.37	78.04	78.64	79.18	79.68	80.15	80.60	81.07	81.61	82.29	82.37	82.47	82.61	82.65	83.01
80.00	76.96	77.76	78.46	79.07	79.63	80.15	80.63	81.11	81.60	82.17	82.88	82.96	83.07	83.22	83.26	83.64
85.00	77.32	78.14	78.86	79.49	80.07	80.60	81.11	81.61	82.12	82.72	83.47	83.56	83.67	83.82	83.87	84.28
90.00	77.69	78.53	79.27	79.92	80.52	81.07	81.60	82.12	82.66	83.29	84.08	84.18	84.30	84.47	84.51	84.95
95.00	78.10	78.97	79.73	80.41	81.03	81.61	82.17	82.72	83.29	83.95	84.81	84.91	85.04	85.22	85.27	85.75
99.00	78.61	79.51	80.31	81.02	81.68	82.29	82.88	83.47	84.08	84.81	85.76	85.87	86.02	86.22	86.28	86.82
99.25	78.67	79.58	80.37	81.09	81.75	82.37	82.96	83.56	84.18	84.91	85.87	85.99	86.13	86.34	86.40	86.96
99.50	78.74	79.65	80.46	81.18	81.84	82.47	83.07	83.67	84.30	85.04	86.02	86.13	86.28	86.50	86.56	87.12
99.75	78.84	79.76	80.57	81.30	81.98	82.61	83.22	83.82	84.47	85.22	86.22	86.34	86.50	86.72	86.78	87.36
99.80	78.87	79.79	80.61	81.34	82.01	82.65	83.26	83.87	84.51	85.27	86.28	86.40	86.56	86.78	86.84	87.43
99.99	79.13	80.07	80.91	81.66	82.35	83.01	83.64	84.28	84.95	85.75	86.82	86.96	87.12	87.36	87.43	88.07

The shaded grey area shows the adjusted indirect comparison within the conventional ±20% acceptance limit for given statistical power in study 1 and 2. The un-shaded area (white) shows when the comparison is outside the conventional ±20% acceptance limit.

Online resource 3 *(Supplementary Table 2): The lower boundary of the 90% confidence interval of the adjusted indirect comparisons, for a given statistical power in the original bioequivalence studies when the difference between generics is fixed at 10%*

Statistical Power in study 2

Statistical Power in study 1	50.00	55.00	60.00	65.00	70.00	75.00	80.00	85.00	90.00	95.00	99.00	99.25	99.50	99.75	99.80	99.99
50.00	70.12	70.75	71.29	71.76	72.17	72.55	72.91	73.25	73.60	73.99	74.47	74.53	74.60	74.69	74.72	74.97
55.00	70.75	71.40	71.96	72.45	72.89	73.29	73.67	74.03	74.40	74.81	75.33	75.39	75.46	75.57	75.60	75.86
60.00	71.29	71.96	72.54	73.06	73.51	73.93	74.33	74.71	75.10	75.54	76.08	76.14	76.22	76.33	76.37	76.65
65.00	71.76	72.45	73.06	73.59	74.06	74.50	74.91	75.31	75.72	76.18	76.76	76.82	76.91	77.03	77.06	77.36
70.00	72.17	72.89	73.51	74.06	74.56	75.01	75.44	75.86	76.28	76.77	77.38	77.45	77.54	77.66	77.70	78.02
75.00	72.55	73.29	73.93	74.50	75.01	75.48	75.93	76.36	76.81	77.32	77.96	78.03	78.13	78.26	78.30	78.64
80.00	72.91	73.67	74.33	74.91	75.44	75.93	76.39	76.84	77.31	77.84	78.52	78.60	78.70	78.84	78.88	79.24
85.00	73.25	74.03	74.71	75.31	75.86	76.36	76.84	77.31	77.80	78.36	79.07	79.16	79.26	79.41	79.45	79.84
90.00	73.60	74.40	75.10	75.72	76.28	76.81	77.31	77.80	78.31	78.90	79.66	79.75	79.86	80.02	80.06	80.48
95.00	73.99	74.81	75.54	76.18	76.77	77.32	77.84	78.36	78.90	79.53	80.35	80.44	80.56	80.74	80.79	81.24
99.00	74.47	75.33	76.08	76.76	77.38	77.96	78.52	79.07	79.66	80.35	81.25	81.35	81.49	81.68	81.74	82.26
99.25	74.53	75.39	76.14	76.82	77.45	78.03	78.60	79.16	79.75	80.44	81.35	81.46	81.60	81.80	81.85	82.38
99.50	74.60	75.46	76.22	76.91	77.54	78.13	78.70	79.26	79.86	80.56	81.49	81.60	81.74	81.94	82.00	82.54
99.75	74.69	75.57	76.33	77.03	77.66	78.26	78.84	79.41	80.02	80.74	81.68	81.80	81.94	82.15	82.21	82.76
99.80	74.72	75.60	76.37	77.06	77.70	78.30	78.88	79.45	80.06	80.79	81.74	81.85	82.00	82.21	82.27	82.83
99.99	74.97	75.86	76.65	77.36	78.02	78.64	79.24	79.84	80.48	81.24	82.26	82.38	82.54	82.76	82.83	83.44

The shaded grey area shows the adjusted indirect comparison within the conventional ±20% acceptance limit for given statistical power in study 1 and 2. The un-shaded area (white) shows when the comparison is outside the conventional ±20% acceptance limit.

CHAPTER 2.3

Adjusted indirect treatment comparison of the bioavailability of WHO-prequalified first-line generic antituberculosis medicines

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ABSTRACT

Approval of generic medicines is based on bioequivalence with the innovator product, but it is not unusual for generics to be interchanged between each other. This study investigated the differences in bioavailability between WHO-prequalified anti-tuberculosis generics by means of indirect comparisons to ensure interchangeability between these diverse generics. Data on 22 products containing isoniazid, rifampicin, pyrazinamide or ethambutol in single or fixed dose combination were included. The indirect comparison between generics shows that the differences, expressed as 90% confidence intervals, are always less than 30%. Furthermore, assurances regarding interchangeability of two generic products are reduced when either the point estimate ratios in the original studies are shifted from unity by more than 5% or when the width of the 90% confidence interval is large. From a bioequivalence perspective, not only are the generics bioequivalent with the reference, but also all these generics can be interchanged without safety / efficacy concern.

INTRODUCTION

Availability of good quality, safe, efficacious and affordable generic (multisource) medicines is important for public health programs, especially in countries with a high disease burden. One of the priorities of the World Health Organization (WHO) Prequalification of Medicines Programme is to improve the availability of quality generic medicines, especially for developing countries, by assuring medicines meet WHO standards for quality, safety and efficacy [1].

Tuberculosis (TB) is a global public health epidemic, especially in developing countries. According to the WHO Global Tuberculosis report, an estimated 8.7 million TB cases and 1.4 million deaths were reported in 2011 [2]. Ethambutol (ETH), isoniazid (INH), pyrazinamide (PZA) and rifampicin (RIF) are indicated for first-line treatment of tuberculosis as per WHO guidelines for TB treatment [3].

Approval of generic medicines by regulatory authorities is typically based on quality and demonstration of bioequivalence (BE) with the innovator or reference product [4–6]. Generic products are not compared directly between each other, although, it is not unusual for a TB patient to be switched between different generics during the course of treatment. This is because the demonstration of equivalence with the reference product within the conventional 80-125% acceptance range (*i.e.,* ±20%) is considered to be indirect evidence of similarity between generics, perhaps within a slightly wider acceptance range (e.g. ±25% or ±30%) [7], but still within a range considered to be clinically equivalent. To investigate their interchangeability, adjusted indirect comparisons can be performed to estimate the relative bioavailability (BA) between generic products that share a common reference product [8–13].

In a previous study we examined different methods of adjusted indirect comparisons that can be used to investigate the relative bioavailability of different generic products [10]. Generic artemether/lumefantrine 20/120 mg tablets that have been prequalified by the WHO were selected as case model products for study.

The aim of the present study was to determine the relative BA of generics; to investigate the interchangeability and therapeutic equivalence of the WHO prequalified single and fixed dose combination (FDC) generic products containing ETHC, INH, PZA, and

RIF using adjusted indirect comparisons; and to explore whether an additional criterion is necessary to ensure equivalence between generics.

METHODS

Identification of studies

Data from bioequivalence studies of products prequalified by the WHO comparing single-API formulations or FDC formulations (i.e., those containing more than one API) of ETH, INH, PZA, and RIF with their corresponding reference products in adult healthy volunteers were considered in the analysis. A total of 34 products containing ETH, INH, RIF, or PZA as single, dual, triple, or quadruple combinations were prequalified by the WHO between 2003 and 2012. Of these, 22 single or FDC generic products met the inclusion criterion for this study. Regarding the excluded products, one was suspended, one was a reference product, one was approved based on European Union approval, four were additional strengths in the same product line as strengths already included in the analysis, and five were based on BE studies using different reference products than those used for the other formulations.

The BE data used in this study are information that is publicly available in WHO Public Assessment Reports (http://apps.who.int/prequal/ default.htm).

The inclusion and exclusion criteria for accepting BA/BE studies were bioequivalence studies conducted in healthy volunteers submitted to and approved by the WHO prequalification program, products currently on the list of prequalified products (i.e., not suspended or withdrawn), and studies comparing a single dose or FDC of ETH, INH, PZA, or RIF using the WHO Prequalification of Medicines Programme–listed reference products for TB medicines: Myambutol (400-mg tablet, Riemser Arzneimittel AG, Germany), Isozid (100-mg tablet, Fatol Arzneimittel GmbH, Schiffweiler, Germany), Pyrazinamide (500-mg tablet, Novartis (Sandoz) Kempton Park, South Africa, or Lederle (Riemser Arzneimittel AG, Germany)), and Rimactane (150- mg, 300-mg tablet, Novartis or Sandoz Kempton Park, South Africa) as single-ingredient reference products and Rifamate or Rifinah (INH + RIF) from Sanofi Aventis (Midrand, South Africa) as FDC reference products. Products for which prequalification

was not based on in vivo comparative BA studies, such as solutions and syrups, were excluded from the current analysis. FDC products with other active ingredients not under investigation and that added additional strengths to product strengths already included in the analysis were also excluded from the analysis. For the products considered in the analysis, there were six products containing one active pharmaceutical ingredient only (one for ETH, three for PZA, and two for INH), three dual combinations of ETH/INH, six dual combinations of INH/RIF, two triple combinations of ETH/INH/RIF, one triple combination of INH/PZA/RIF, and four combinations of ETH/INH/RIF/PZA.

Statistical method for the indirect comparison between generic products

Because generic products have not been compared in vivo directly, bioequivalence between generics is estimated by means of indirect comparisons between pairs of generic products. The indirect comparison is based on the individual studies of each generic product *vs*. the reference product (studies A and B), as the reference product is the same in all studies. The indirect comparison is performed in relative terms (or percentages) because the values of the pharmacokinetic parameters of the reference product are considered 100% in all bioequivalence studies. Because the ratio between test and reference in original scale corresponds to difference between test and reference in logarithmic scale, the point estimate in logarithmic scale is calculated as as $(\bar{Y}_{TA} - \bar{Y}_{RA})$ in study A and $(\bar{Y}_{TB} - \bar{Y}_{RB})$ in study B as described elsewhere [10].

If we consider $\widehat{D}_{A,B}$, the point estimate of adjusted indirect comparison described as $\widehat{D}_{A,B} = (\bar{Y}_{TA} - \bar{Y}_{RA}) - (\bar{Y}_{TB} - \bar{Y}_{RB})$, where R_A and R_B are the same reference product, it can be concluded that $\widehat{D}_{A,B} = \bar{Y}_{TA} - \bar{Y}_{RA} - \bar{Y}_{TB} + \bar{Y}_{RB} = \bar{Y}_{TA} - \bar{Y}_{TB}$. Therefore, the difference between the point estimates of two bioequivalence studies gives the point estimate between generic products.

The width of the CI for the adjusted indirect comparisons was calculated using the recommended homoscedastic method as described elsewhere [10]. The homoscedastic method was selected for the indirect comparisons because a clear difference in variances is unlikely because variability depends mostly on the drug pharmacokinetics (e.g., absorption and clearance), with a limited

contribution from the dosage form in which it is contained. In addition, previous studies have shown that homoscedastic and heteroscedastic methods give almost identical results [10, 11]. This method uses the conventional t-test and assumes homogeneity of variances between the studies and small sample sizes. Brief, the combined SD of both bioequivalence studies is calculated from the variability of each individual study. First, the SD of each individual study is calculated by $SD = \frac{2 \cdot SE_{(d)}}{\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}}$, where n_1 and n_2 represents the number of subjects in sequence 1 and sequence 2, respectively for the crossover-bioequivalence studies. Second, the combined SD (SD_{pooled}) is calculated by $SD^2_{pooled} = \frac{(n_1-1)SD^2_A+(n_2-1)SD^2_B}{n_A+n_B-2}$, where the degrees of freedom are (n_A + n_B - 2), n_A and n_B are the number of subjects in study A for generic A and in study B for generic B, respectively, SD_A and SD_B are the SDs in each bioequivalence study (A and B). The $SE_{(d)}$ of the indirect comparison is then calculated as $SE_{(d)} = SD_{pooled}\sqrt{\frac{1}{n_A}+\frac{1}{n_B}}$, where n_A and n_B are the number of subjects in each bioequivalence study.

The CI of the indirect comparison between generics is then calculated as: $\widehat{D}_{A,B} \pm t_{\alpha,df} \cdot SE_{(d)}$, where $t_{\alpha,df}$ is the Student *t*-test value that corresponds to the alpha of 10% in order to estimate CI with 90% of confidence level and the degrees of freedom of the studies (i.e., n_A+n_B-2).

RESULTS

Figures 1, 2, 3 and 4 show the point estimates and 90% confidence intervals (CIs) for the ratios of peak concentrations (C_{max}) and area under the plasma concentration-time curve $(AUC)_{0\text{-}t}$ for PZA, ETH, INH, and RIF, respectively, for the prequalified generic formulations against formulations listed as reference products by the WHO. For all the studies, the 90% CIs for the ratios of C_{max} and $AUC_{0\text{-}t}$ were within the recommended standard of 80 – 125%.

The indirectly estimated 90% CIs for the comparisons between generics for PZA and ETH are presented in Table 1, and in Tables 2 and 3 for INH, and RIF, respectively.

The nine adjusted indirect comparisons between those pyrazinamide generics compared with Pyrazinamide Lederle and those

compared with Pyrazinamide Sandoz satisfy the conventional 80-125% acceptance range for all the pharmacokinetic parameters, except for one borderline case (79.90).

Similarly, the adjusted indirect comparisons between ETH generics satisfy the conventional bioequivalence criterion of 80-125% for AUC. Further, most adjusted indirect comparisons for ETH C_{max} satisfy the wider acceptance limits of 75 – 133% and, 6 out of 21 comparisons fall outside the 25% range, but inside the 30% range.

For the 78 adjusted indirect comparisons conducted between 13 generic INH products that had been compared with Isozid, the products satisfied the conventional criterion of 80 – 125% for AUC. The majority of comparisons (86%) satisfied the conventional criterion for C_{max}, except for 11 out of 78 comparisons, where the results come close to meeting the wider acceptance limit of 75-133% (±25%).

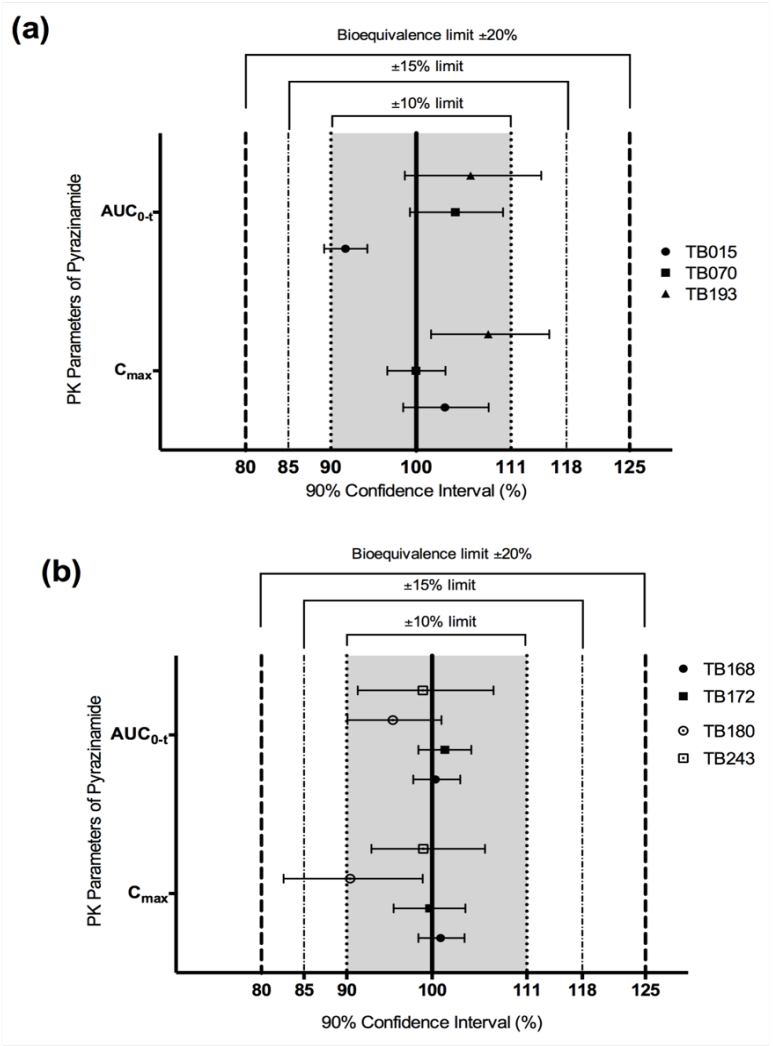

Figure 1. Geometric mean ratios of generic vs. WHO-approved reference with corresponding 90% confidence intervals of the pharmacokinetic parameters (Cmax, AUC0-t) in the original bioequivalence studies for pyrazinamide in single- and fixed-dose formulations with other anti-TB medicines. (a) Reference product is pyrazinamide – Lederle (Riemser Arzneimittel); (b) reference product is pyrazinamide from Sandoz (Novartis). Data points are the point estimates of the pharmacokinetic parameters, with 90% confidence intervals. The shaded region indicates the ±10% limit. The light dotted lines at 85% and 118% indicate ±15% limit. The heavy dotted lines at 80 and 125% indicate the standard 90% CI limit for bioequivalence. AUC, area under the plasma concentration-time curve; Cmax, peak plasma concentration; WHO, World Health Organization.

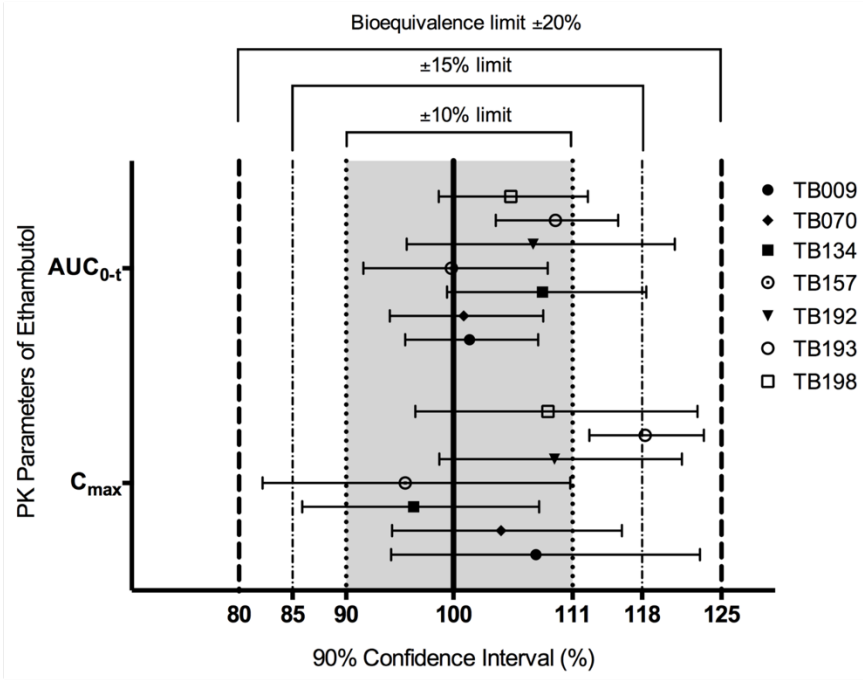

Figure 2. Geometric mean ratios of generic vs. WHO-approved reference (Myambutol (400-mg tablet, Riemser Arzneimittel) with corresponding 90% confidence intervals of the pharmacokinetic parameters (C_{max}, AUC_{0-t}) in the original bioequivalence studies for ethambutol in single- and fixed-dose formulations with other anti-TB medicines. Data points are the point estimates of the pharmacokinetic parameters, with 90% confidence intervals. The shaded region indicates the ±10% limit. The light dotted lines at 85% and 118% indicate ±15% limit. The heavy dotted lines at 80 and 125% indicate the standard 90% CI limit for bioequivalence. AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration; WHO, World Health Organization.

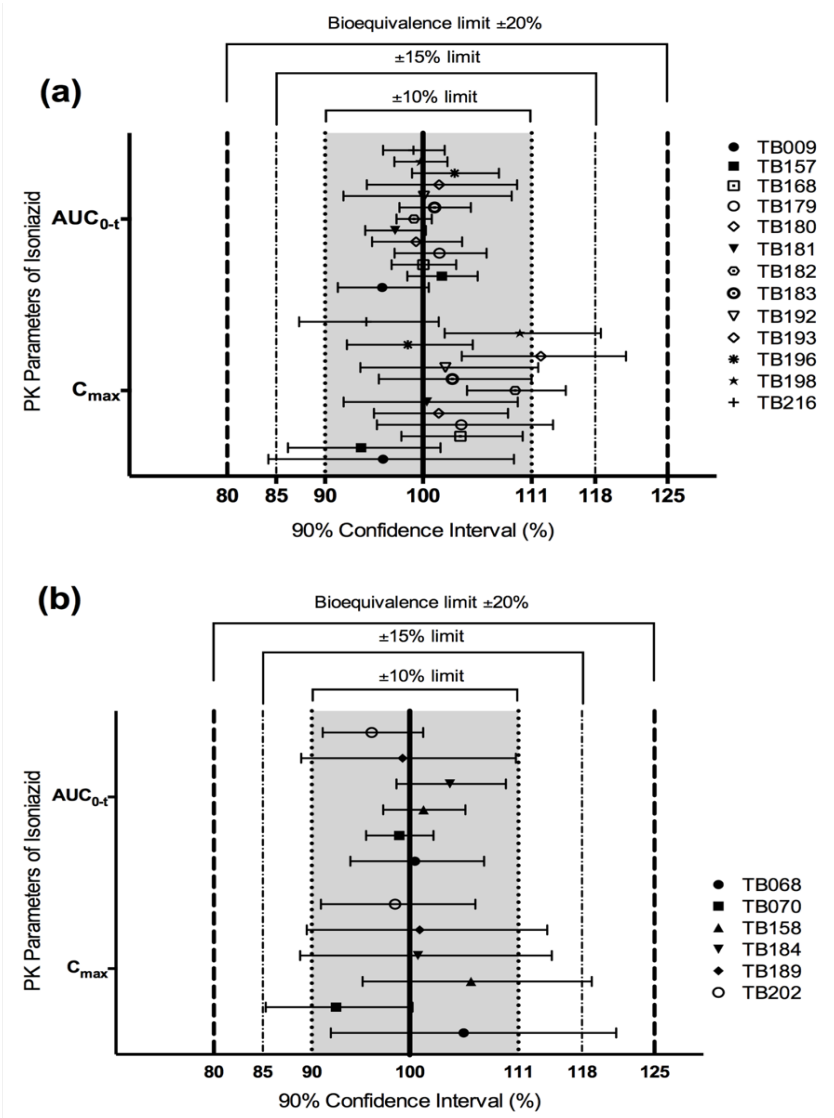

Figure 3. Geometric mean ratios of generic vs. WHO-approved reference with corresponding 90% confidence intervals of the pharmacokinetic parameters (C_{max}, AUC_{0-t},) in the original bioequivalence studies for isoniazid in single- and fixed-dose formulations with other anti-TB medicines. (a) Reference product is Isozid (Fatol Arzneimittel); (b) reference product is Rifinah (Sanofi-Aventis). Data points are the point estimates of the pharmacokinetic parameters, with 90% confidence intervals. The shaded region indicates the ±10% limit. The light dotted lines at 85% and 118% indicate ±15% limit. The heavy dotted lines at 80 and 125% indicate the standard 90% CI limit for bioequivalence. AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration; WHO, World Health Organization.

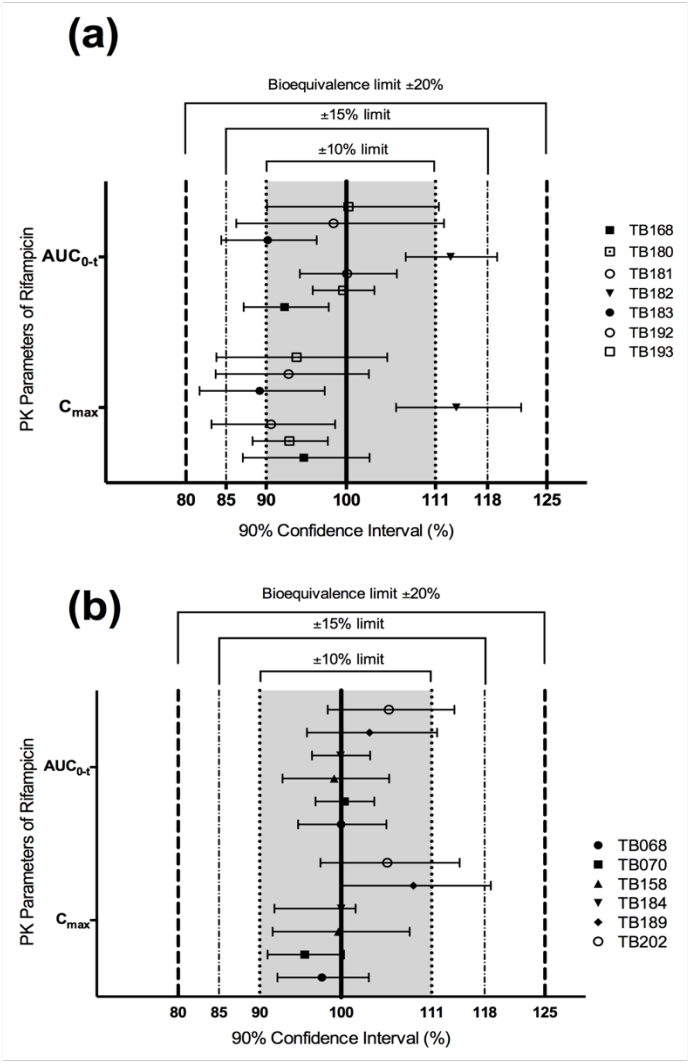

Figure 4. Geometric mean ratios of generic vs. WHO-approved reference with corresponding 90% confidence intervals of the pharmacokinetic parameters (C_{max}, AUC_{0-t}) in the original bioequivalence studies for rifampicin in single- and fixed-dose formulations with other anti-TB medicines (a) Reference product Rimactane from Sandoz (Novartis); (b) reference product – Rifinah from Sanofi–Aventis. Data points are the point estimates of the pharmacokinetic parameters, with 90% confidence intervals. The shaded region indicates the ±10% limit. The light dotted lines at 85% and 118% indicate ±15% limit. The heavy dotted lines at 80 and 125% indicate the standard 90% CI limit for bioequivalence. AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration; WHO, World Health Organization.

Table 1. 90% Confidence intervals for C_{max} and AUC_{0-t} obtained by adjusted indirect comparisons of bioequivalence studies of pyrazinamide and ethambutol generic products

Product	Reference	Indirect comparisons	90% Confidence interval	
			C_{max}	AUC_{0-t}
Pyrazinamide	Pyrazinamide - Lederle, Riemser Arzneimittel	1 *vs.* 2	97.48 – 109.68	82.82 – 92.85
		1 *vs.* 3	88.16 – 103.06	79.90* – 93.04
		2 *vs.* 3	85.90 – 98.92	89.90 – 107.53
	Pyrazinamide from Sandoz (Novartis)	4 *vs.* 5	95.99 – 107.23	94.91 – 103.42
		4 *vs.* 6	101.31 – 123.42	98.59 – 112.50
		4 *vs.* 7	94.83 – 109.17	93.52 – 110.38
		5 *vs.* 6	100.64 – 120.69	100.08 – 112.90
		5 *vs.* 7	93.17 – 107.95	95.28 – 110.38
		6 *vs.* 7	81.26 – 101.90	87.75 – 106.07
Ethambutol	Myambutol from Riemser Arzneimittel	1′ *vs.* 2′	87.62 – 121.20	93.68 – 107.82
		1′ *vs.* 3′	94.11 – 132.71*	86.62 – 101.37
		1′ *vs.* 4′	92.67 – 137.16	93.95 – 109.99
		1′ *vs.* 5′	83.59 – 115.77	85.60 – 104.24
		1′ *vs.* 6′	80.69 – 103.31	87.24 – 98.42
		1′ *vs.* 7′	82.65 – 118.39	90.03 – 103.07
		2′ *vs.* 3′	93.16 – 126.24*	85.77 – 101.34
		2′ *vs.* 4′	92.14 – 129.89*	93.04 – 109.96
		2′ *vs.* 5′	82.67 – 110.22	84.85 – 104.12
		2′ *vs.* 6′	79.26* – 99.04	86.28 – 98.52
		2′ *vs.* 7′	82.06 – 112.28	89.09 – 103.12
		3′ *vs.* 4′	83.90 - 121.29	99.08 – 118.78
		3′ *vs.* 5′	75.71* – 102.34	90.47 – 112.33
		3′ *vs.* 6′	73.24 – 91.14	91.73 – 106.61
		3′ *vs.* 7′	74.60 – 105.03	94.79 – 111.49
		4′ *vs.* 5′	73.32 – 103.84	83.38 – 103.56
		4′ *vs.* 6′	70.67 – 92.80	84.54 – 98.28
		4′ *vs.* 7′	72.72 – 105.87	87.36 – 102.79
		5′ *vs.* 6′	83.49 – 103.18	89.14 – 107.95
		5′ *vs.* 7′	86.09 – 117.44	192.22 – 112.76
		6′ *vs.* 7′	94.99 – 123.57	97.55 – 110.77

Values in bold indicate confidence intervals outside the 75 – 133% limit but inside 70 – 143% limit. Product numbers for pyrazinamide comparisons: 1, TB015; 2, TB070; 3, TB193; 4, TB168; 5, TB172; 6, TB180; 7, TB243. Product numbers for ethambutol comparisons: 1′, TB009; 2′, TB070; 3′, TB134; 4′, TB157; 5′, TB192; 6′, TB193; 7′, TB198. AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration.

*Confidence interval outside the 80-125% limit but inside 75-133% limit.

Table 2. 90% Confidence intervals for C_{max} and AUC_{0-t} of isoniazid obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing isoniazid in single- or fixed-dose combination with other anti-TB medicines

Reference	Indirect Comparisons	90% confidence interval	
		C_{max}	AUC_{0-t}
Isozid, Fatol Arzneimittel	1 *vs.* 2	88.04 – 119.15	88.66 – 99.70
	1 *vs.* 3	80.32 – 106.34	90.46 – 101.45
	1 *vs.* 4	79.22* - 107.60	88.27 – 100.62
	1 *vs.* 5	82.26 – 108.36	90.37 – 103.09
	1 *vs.* 6	82.18 – 111.10	93.34 – 104.26
	1 *vs.* 7	76.57* – 100.38	91.95 – 101.75
	1 *vs.* 8	80.37 – 107.95	89.28 – 100.48
	1 *vs.* 9	80.66 – 109.07	86.55 – 105.94
	1 *vs.* 10	74.50 – 98.41	85.72 – 103.72
	1 *vs.* 11	85.27 – 111.37	87.14 – 98.94
	1 *vs.* 12	76.19* – 100.01	91.35 – 101.08
	1 *vs.* 13	88.61 – 117.04	91.67 – 102.21
	2 *vs.* 3	81.64 – 99.73	97.19 – 106.82
	2 *vs.* 4	80.17 – 101.37	94.70 – 106.10
	2 *vs.* 5	83.10 – 102.26	96.82 – 108.86
	2 *vs.* 6	82.72 – 105.23	100.16 – 109.92
	2 *vs.* 7	78.00* - 93.94	98.96 – 106.95
	2 *vs.* 8	81.48 – 101.51	95.89 – 105.84
	2 *vs.* 9	81.18 – 103.31	92.46 – 112.16
	2 *vs.* 10	74.86 – 93.37	91.54 – 109.85
	2 *vs.* 11	85.92 – 105.38	93.29 – 104.52
	2 *vs.* 12	76.39* - 95.09	97.88 – 106.69
	2 *vs.* 13	88.94 – 111.16	98.21 – 107.90
	3 *vs.* 4	90.15 – 110.72	93.07 – 104.00
	3 *vs.* 5	93.41 – 111.73	95.13 – 106.72
	3 *vs.* 6	92.77 – 115.23	98.44 – 107.73
	3 *vs.* 7	88.12 – 102.13	97.32 – 104.76
	3 *vs.* 8	91.73 – 110.74	94.26 – 103.71
	3 *vs.* 9	91.05 – 113.14	90.80 – 110.01
	3 *vs.* 10	83.91 – 102.31	89.90 – 107.74
	3 *vs.* 11	96.45 – 115.29	91.65 – 102.48
	3 *vs.* 12	85.54 – 104.30	96.18 – 104.59
	3 *vs.* 13	99.65 – 121.86	96.50 – 105.77
	4 *vs.* 5	91.98 – 113.68	96.02 – 109.24
	4 *vs.* 6	91.58 – 116.95	99.41 – 110.22
	4 *vs.* 7	86.28 – 104.50	97.94 – 107.55

Reference	Indirect Comparisons	90% confidence interval	
		C_{max}	AUC_{0-t}
	4 *vs*. 8	90.16 – 112.87	94.90 – 106.43
	4 *vs*. 9	89.88 – 114.82	91.90 – 112.30
	4 *vs*. 10	82.89 – 103.76	91.01 – 109.96
	4 *vs*. 11	95.11 – 117.13	92.56 – 104.84
	4 *vs*. 12	84.60 – 105.65	97.04 – 107.10
	4 *vs*. 13	98.49 – 123.52	97.38 – 108.29
	5 *vs*. 6	90.74 – 112.88	96.72 – 108.00
	5 *vs*. 7	85.48 – 100.88	95.15 – 105.55
	5 *vs*. 8	89.03 – 109.32	92.30 – 104.33
	5 *vs*. 9	88.66 – 111.32	89.79 – 109.58
	5 *vs*. 10	82.05 – 100.25	89.25 – 106.90
	5 *vs*. 11	94.42 – 112.84	90.60 – 102.12
	5 *vs*. 12	83.93 – 101.85	94.78 – 104.54
	5 *vs*. 13	98.03 – 118.68	95.30 – 105.50
	6 *vs*. 7	82.78 – 101.69	94.43 – 101.81
	6 *vs*. 8	86.40 – 109.97	91.44 – 100.81
	6 *vs*. 9	86.37 – 111.57	88.39 – 106.56
	6 *vs*. 10	80.03 – 100.35	87.80 – 104.03
	6 *vs*. 11	92.00 – 113.05	89.37 – 99.10
	6 *vs*. 12	81.97 – 101.81	93.59 – 101.35
	6 *vs*. 13	95.73 – 118.65	94.07 – 102.32
	7 *vs*. 8	97.43 – 115.85	94.13 – 101.87
	7 *vs*. 9	96.51 – 118.61	90.22 – 108.59
	7 *vs*. 10	88.92 – 107.28	89.30 – 106.39
	7 *vs*. 11	102.29 – 120.80	91.25 – 100.97
	7 *vs*. 12	90.60 – 109.42	95.85 – 102.93
	7 *vs*. 13	105.57 – 127.81*	96.16 0 104.12
	8 *vs*. 9	89.63 – 113.14	91.75 – 111.36
	8 *vs*.10	82.64 – 102.27	90.84 – 109.06
	8 *vs*. 11	94.89 – 115.37	92.57 – 103.79
	8 *vs*. 12	84.30 – 104.19	97.11 – 105.95
	8 *vs*. 13	98.17 – 121.77	97.45 – 107.14
	9 vs 10	81.51 – 102.24	88.05 – 110.12
	9 *vs*. 11	93.38 – 115.60	88.50 – 106.25
	9 *vs*. 12	83.24 – 104.04	92.56 – 108.79
	9 *vs*. 13	96.89 – 121.66	92.90 – 110.00
	10 vs 11	103.19 – 125.53*	90.34 – 107.34
	10 *vs*. 12	91.99 – 112.97	94.42 – 109.98
	10 *vs*. 13	107.10 – 132.07*	94.79 – 111.18
	11 *vs*. 12	81.29 – 98.70	98.56 – 108.66
	11 *vs*. 13	94.67 – 115.35	98.96 – 109.82

Reference	Indirect Comparisons	90% confidence interval	
		C_{max}	AUC_{0-t}
	12 *vs.* 13	105.23 – 129.34*	96.69 – 104.95
Rifinah Sanofi-Aventis	1′ *vs.* 2′	97.44 – 133.58*	94.35 – 109.48
	1′ *vs.* 3′	83.54 – 118.06	91.07 – 107.94
	1′ *vs.* 4′	87.22 – 125.09*	89.50 – 114.60
	1′ *vs.* 5′	91.56 – 125.33*	95.87 – 114.14
	2′ *vs.* 3′	76.13* – 99.53	92.52 – 102.86
	2′ *vs.* 4′	79.31* – 105.68	89.63 – 110.79
	2′ *vs.* 5′	83.97 – 104.99	96.88 – 109.36
	3′ *vs.* 4′	89.60 – 123.47	90.34 – 115.50
	3′ *vs.* 5′	94.41 – 123.24	98.63 – 112.86
	4′ *vs.* 5′	88.90 – 118.30	91.48 – 116.63

Values in bold indicate confidence intervals outside the 75 – 133% limit but inside 70 – 143% limit. Product numbers (Rifinah (Sanofi-Aventis) as reference) : 1′, TB068 ; 2′, TB070 ; 3′, TB158 ; 4′, TB189 ; 5′, TB202. Product numbers (Isozid (Fatol Arzneimittel) as reference) : 1, TB009 ; 2, TB157 ; 3, TB168 ; 4, TB179 ; 5, TB180 ; 6, TB181 ; 7, TB182 ; 8, TB183 ; 9, TB192 ; 10, TB193 ; 11, TB196 ; 12, TB198 ; 13, TB216. AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration.

*Confidence interval outside the 80-125% limit but inside 75-133% limit.

In the generics that were compared with Rifinah the same trend can be observed in the indirect comparisons as that observed for INH. The 90% CIs of AUC_{0-t} consistently falls within 80-125% and the 90% CI of C_{max} was outside this range only in some indirect comparisons (5 out of 10).

Out of 21 adjusted indirect comparisons for 7 RIF-containing products, 15 satisfy the 80 – 125% criterion with respect to C_{max} and AUC and 6 comparisons for AUC and 6 comparisons for C_{max} did not.

For the generics that were compared with Rifinah, all RIF AUC indirect comparisons were within the 80-125% acceptance range. For $C_{max,}$ only one borderline case exhibited a lower boundary of the 90% CIS outside of the conventional 80-125% acceptance range (79.75%).

Table 3. 90% Confidence Interval for C_{max} and AUC_{0-t} of rifampicin obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing rifampicin in fixed dose combination with other anti-TB medicines

Reference	Indirect comparisons	90% Confidence interval	
		C_{max}	AUC_{0-t}
Rimactane from Sandoz (Novartis)	1 *vs.* 2	92.93 – 112.80	86.81 – 99.08
	1 *vs.* 3	92.94 – 117.55	84.98 – 100.22
	1 *vs.* 4	74.91 – 92.50	75.87* – 88.09
	1 *vs.* 5	94.36 – 119.49	94.04 – 111.57
	1 *vs.* 6	89.38 – 116.51	80.89 – 108.93
	1 *vs.* 7	87.13 – 116.87	80.81 – 105.00
	2 *vs.* 3	93.07 – 112.99	92.75 – 106.76
	2 *vs.* 4	75.24* – 88.64	82.91 – 93.73
	2 *vs.* 5	94.69 – 114.60	102.75 – 118.73
	2 *vs.* 6	89.49 – 112.02	88.50 – 115.76
	2 *vs.* 7	87.12 – 112.50	88.28 – 111.75
	3 *vs.* 4	71.39 – 88.84	81.88 – 95.84
	3 *vs.* 5	90.11 – 114.52	101.69 – 121.15
	3 *vs.* 6	85.67 – 111.27	88.27 – 117.21
	3 *vs.* 7	83.74 – 111.30	88.06 – 113.14
	4 *vs.* 5	114.44 – 142.19	115.52 – 135.89
	4 *vs.* 6	108.15 – 138.97	99.15 – 132.96*
	4 *vs.* 7	105.25 – 139.63	99.04 – 128.17*
	5 *vs.* 6	84.00 – 109.95	78.74* – 106.64
	5 *vs.* 7	82.43 – 109.57	79.10* – 102.23
	6 *vs.* 7	84.96 – 115.09	83.24 – 115.69
Rifinah from Sanofi –Aventis	1′ *vs.* 2′	94.87 – 110.06	93.45 – 106.12
	1′ *vs.* 3′	88.64 – 108.29	92.82 – 109.60
	1′ *vs.* 4′	81.16 – 99.11	88.24 – 105.81
	1′ *vs.* 5′	83.83 – 101.85	86.53 – 103.14
	2′ *vs.* 3′	87.11 – 105.54	94.55 – 108.49
	2′ *vs.* 4′	79.75* – 96.59	89.62 – 105.05
	2′ *vs.* 5′	82.39 – 99.24	87.94 – 102.32
	3′ *vs.* 4′	81.49 – 102.83	86.57 – 106.01
	3′ *vs.* 5′	84.14 – 105.72	84.95 – 103.26
	4′ *vs.* 5′	91.92 – 115.48	88.07 – 108.54

Values in bold indicate confidence intervals outside the 75 – 133% limit but inside 70 – 143% limit. Product numbers with Rifinah from Sanofi –Aventis as the reference: 1′, TB068; 2′, TB070; 3′, TB158; 4′, TB189; 5′, TB202. Product numbers with Rimactane from Sandoz (Novartis) as the reference; 1, TB168; 2, TB180; 3, TB181; 4, TB182; 5, TB183; 6, TB192; 7, TB193. AUC, area under the plasma concentration-time curve; C_{max}, peak plasma concentration.

DISCUSSION

The present work is an extension of our earlier work with WHO-prequalified artemether/lumefantrine generics [10]. This new study compares a diverse group of prequalified first-line TB medicines to explore the utility of the recommended approach for conducting adjusted indirect comparisons and suggests possible refinements to the methodology. The results of the present work produced two outcomes. First, the results show that these products can be interchanged as necessary without significant concern regarding possible shifts in the quality of therapy as experienced by the patient or observed by the treating professional. Second, the indirect comparison outcomes suggest that assurances regarding interchangeability of two generic products are reduced when either the point estimate ratios in the original studies are shifted from unity (1.0) by more than 5% or when the variability in those studies is large. This result could have important predictive value and could be used to consider further requirements for bioequivalence studies in situations when interchangeability of generics (switchability in addition to prescribability) is critical.

The landscape of medicinal products available for first-line treatment of TB is complex. The first-line TB medicines are available in mono-component, two-component, three-component, and four-component products of varying strength combinations. Considering this observation, this study endeavoured to make comparisons between all combinations of products with the expectation that different combinations of products may be used in the clinical setting based on product availability. As a result, a broad range of comparisons were conducted, including comparisons of very different products, for example, comparison of ETH BA of a 2-FDC compared to that of a 4-FDC, but these comparisons were undertaken to get a better overall understanding of the relative delivery of these first-line medicines from WHO-prequalified products.

Furthermore, because of the global nature of the WHO Prequalification of Medicines Programme, in some instances there are multiple products that could legitimately be considered accept- able reference products for generics, and therefore, for some invited products, more than one reference is listed (e.g., Pyrazinamide Lederle Tablets (Riemser Arzneimittel) and Pyrazinamide Tablets (Dava Pharms, Fort Lee, NJ)). In addition, innovator FDCs may also

be considered as valid references in some instances. This flexibility in reference products is, however, a limitation for this study because not all WHO-prequalified generic products were tested against the same reference and thus could not all be compared with each other through indirect comparisons. To compare generics with other generics by means of adjusted indirect comparisons, they have to have been compared with the same reference product. Consequently, for PZA, INH, and RIF, indirect treatment comparisons were performed in two groups, and some products could not be included in the analysis because they were the only ones that had been compared with a given reference.

The adjusted indirect comparison between generics (Tables 1–3) shows that the differences, expressed as 90% CIs, are less than 30% in all the cases (i.e., 70–143%). Although this represents a slightly larger range than that normally sought, it can be seen as an encouraging outcome, given that the results are based on unplanned indirect comparisons. In this regard, it is important to highlight that in Canada, an International Conference on Harmonisation–associated country with a long history of national use of generic medicines, the acceptance range of 80– 125% applies to the 90% CIs of the point estimate for the AUC, but only to the point estimate of the C_{max} ratio for uncomplicated drugs i.e., there is no requirement for the 90% CIs for C_{max}, only for the point estimate itself [14].

This draws attention to the occasional misunderstandings of the meaning of bioequivalence study results and the 90% CIs acceptance ranges. Some authors have stated that generic products can differ between themselves up to 45% [15] or between 40 and 50% [16], simply because the acceptance range for concluding bioequivalence is 80–125%. However, these arguments fail to consider that 80–125% is the acceptance range for a ratio between the pharmacokinetic parameters, AUC and C_{max} of test/ reference, and therefore 0.8 and 1.25 represent a ±20% difference because the comparison between test and reference is carried out as a ratio, and the inverse of 0.8 is 1.25. Other authors [17] prefer to claim that a patient who is treated with a generic that exhibits a 20% lower BA and is subsequently switched to a generic with a 20% higher BA is exposed to a 56% increase in dose because 125 is 156% of 80, again ignoring that 125% represents only a 20% increase in BA because test and reference are compared by means of ratios. It is important to highlight that such an event is extremely unlikely (<1%). If the generic product BA differs

20% from that of the reference product, the probability of showing bioequivalence in a study is only 5% (i.e., 0.05, because the conclusion of bioequivalence is based on the 90% CIs calculation). The same probability would be true for a product with a 20% difference in the other direction. Therefore, it is extremely unlikely that such a large difference between two generics will occur.

PZA, ETH, and INH are highly soluble drugs without BA problems [18–21], if formulated correctly to show in vitro dissolution profiles similar to those of the reference product and without critical excipients that may affect BA, which ensures a sufficiently similar point estimate in the bioequivalence studies. In addition, due to their low variability in AUC (interquartile ranges (IQRs) of the coefficient of variation (CV) observed in the studies are 7.14–15.20% for PZA, 14.39–17.46% for ETH, and 7.01–15.40% for INH), the indirect comparisons for AUC all satisfy the conventional bioequivalence criterion.

PZA C_{max}, which exhibits a low intra subject variability (IQR is 9.30–15.16% CV), exhibited enough precision to show equivalence in the indirect comparisons within the conventional 80– 125% acceptance range in all cases, except in one borderline case (79.90%). By contrast, the higher intrasubject variabilities for ETH C_{max} (IQR: 23.17–28.95% CV) and INH C_{max} (IQR: 15.21–30.93% CV) result in a lack of the necessary precision to conclude equivalence within the conventional acceptance range. However, as noted above, these ETH and INH indirect comparisons between generics would fulfill the criteria defined in Canada for direct comparisons. Furthermore, the precision was sufficient to show equivalence within a ±30% acceptance range.

Unlike the three active pharmaceutical ingredients discussed above, RIF is a low-solubility drug with high permeability (Biopharmaceutics Classification System class II drug), for which in vitro dissolution profiles are not able to predict in vivo bio- equivalence [21, 22]. Therefore, it is more likely that marked differences in the point estimates will be observed in bioequivalence studies, whereas for the other active pharmaceutical ingredients under investigation, the occasional deviating point estimate is more likely the result of random variability. This factor results in a higher failure rate when trying to demonstrate bioequivalence, and when showing equivalence, the 90% CIs may be displaced from the center of the acceptance range (Figure 4). These tendencies will have an impact on the indirect

comparison results, as is noted in the comparisons made for generics that have been tested against Rimactane. For those products, multiple comparisons failed to show equivalence for AUC within the conventional range because of deviations of 10% or more for point estimates for two products in the original studies, even though the intra subject variability is not high (IQR: 9.83–19.45% CV). For the same reasons, six adjusted indirect comparisons of RIF C_{max} failed to show equivalence within a 20% acceptance range. Importantly, however, the differences were never larger than 30%.

In contrast to the above, for those generics that were compared with Rifinah, all AUC indirect comparisons were within the 80–125% acceptance range. For C_{max}, only one borderline case exhibited a lower boundary of the 90% CIs outside of the conventional 80–125% acceptance range (79.75%). The positive results are obtained because all the point estimates from the bioequivalence studies are within the 10% limits, and only one 90% CIs for C_{max} is slightly outside of the 15% limit (Figure 4b), which is the one (no. 5, TB189) displaying the borderline result.

This article, despite the reduced precision of indirect comparisons relative to that seen with direct comparisons, demonstrates that in none of 154 comparisons did the difference between generics grow larger than 30%. For those generics containing PZA, ETH, or INH, the indirect comparisons fulfill in rounded figures the acceptance criterion defined in Canada for the approval of generics containing uncomplicated drugs. By contrast, in the case of RIF, a small number of indirect comparisons for AUC fail to show equivalence within the 20% acceptance range (less than 5% of all the performed comparisons). However, this does not indicate that the products are more than 20% different (as the null hypothesis is never demonstrated) but that the data are not able to show that they are less than 20% different. Hence, these failed comparisons are inconclusive. This result might be caused by the limited precision of indirect comparisons because the squared standard error used to estimate the width of the 90% CIs of the indirect comparison is the sum of the squared standard error of each of the two bioequivalence studies that are combined in the indirect comparison [23–25]. Finally, it is important to stress that patients switched between generics that have been shown to be bioequivalent with the reference product may experience a change in exposure slightly larger than the change caused when switched to or from the reference product, but in all

cases the patients continue to be exposed to drug levels that are safe and efficacious, as they are considered to be equivalent to, and produce a therapeutic effect equivalent to, those obtained under treatment with the reference product.

The inability to show equivalence within a 20% acceptance range in the adjusted indirect comparisons is due to two additive factors: variability and difference in point estimates in the original bioequivalence studies. Failures in ETH C_{max} occurred because most of the products (five of seven) had a 90% CIs for C_{max} exceeding the 15% range. For INH generics compared with Isozid, the failures in C_{max} are caused by products no. 1 (TB009), no. 10 (TB193), and no. 12 (TB198), whose 90% CIs for C_{max} are outside of the 15% range (Figure 3), and product no. 7's (TB182) point estimate is almost 10% different, like those of product nos. 10 (TB193) and 12 (TB198) (Figure 3). For those INH generics that were compared with Rifinah, the failures in C_{max} are due to product no. 1' (TB068), whose 90% CIs for C_{max} is outside of the 15% limit, and product no. 2' (TB070), whose point estimate shows close to a 10% difference (Figure 3).

For those RIF generics compared with Rimactane, six comparisons failed to show equivalence for AUC because the point estimate in the original study of product no. 4 (TB182) (Figure 4a) is outside of the 10% limit on the upper side, and the point estimate of product no. 5 (TB183) is borderline within the 10% limit on the lower side. Six adjusted indirect comparisons of RIF C_{max} fail to show equivalence within a 20% acceptance range because of product no. 4 (TB182), whose point estimate in the original study is outside of the 10% limit (Figure 4a).

Although product no. 5 (TB183) is also outside the 10% range, its comparisons are inside the limit because its deviation is in the same direction as the other point estimates. For those RIF generics that were compared with Rifinah, positive results are obtained because all the point estimates from the bioequivalence studies were within the 10% limits, and only one 90% CIs for C_{max} was slightly outside of the 15% limit (Figure 4b), which is the one (no. 4', TB189) displaying the borderline result. Although the present study relates directly to products prequalified within the WHO framework, the implications would be applicable to any regulatory framework that uses similar BE acceptance principles. Moreover, these results can be extrapolated to future batches because these generic products are subject to the

same quality standards and specifications as innovator products, so batch-to-batch variation is no more an issue here than it is when changing from comparator product batch to batch. If health authorities are interested in ensuring bioequivalence between generics within the conventional acceptance range that is currently used for direct comparisons between generics and reference products (±20%), additional requirements should be defined for the direct comparisons, for example, a point estimate constraint of ±10% and a narrower acceptance range of ±15% for the 90% CIs. These additional considerations would provide greater assurance of generic-to-generic bioequivalence in critical therapeutic situations, although they do not seem to be necessary in the case of the antituberculosis medicines examined in this work because, despite the complex array of first-line TB treatment products prequalified, only limited cases of generic-to-generic comparison exceed the 20% range, and none exceed the 30% range. In most cases, the failure to show equivalence within the 20% range is due to the imprecision of indirect comparisons, and only a few RIF cases appear to be caused by actual differences between products, differences that in no instance exceed the 30% acceptance range. Therefore, not only are the generics bioequivalent to the reference products, but also all prequalified products of these four anti-TB drugs seem to be interchangeable among themselves. For public health programs, these different generic products can be interchanged without concerns for safety and efficacy when bioequivalence has been demonstrated with the same reference product in the original bioequivalence studies.

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CHAPTER 2.4

Interchangeability between first line generic antiretroviral products prequalified by WHO using adjusted indirect comparisons

Submitted

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ABSTRACT

Objective: The scaling up of access to antiretroviral therapy, particularly in low- to middle-income countries, was facilitated by the introduction and widespread use of generic antiretroviral medicines and fixed dose combinations. Generic medicines are approved by regulatory authorities based on the demonstration of bioequivalence with the innovator or reference product, as well as meeting quality standards. In clinical practice, however, it is not unusual for generics to be interchanged between each other. This study investigated the differences in bioavailability between WHO-prequalified first-line antiretroviral generics by means of adjusted indirect comparisons to ensure interchangeability between these generics.

Methods: Data on 34 products containing emtricitabine, tenofovir disoproxil fumarate, lamivudine and efavirenz in single formulations or fixed dose combinations were included in the analysis. The 90% confidence interval for the adjusted indirect comparisons was calculated using the homoscedastic method that uses the conventional t test, and assumes homogeneity of variances between the studies and small sample sizes. The combined standard deviation of both bioequivalence studies was calculated from the variability of each individual study.

Results: The adjusted indirect comparisons between generics showed that the differences, expressed as 90% confidence intervals, are less than 30%. Confidence in the interchangeability of two generic products was reduced if the mean difference between the test and reference in the original studies is more than 10%.

Conclusion: From a bioequivalence perspective, the generic antiretroviral medicines prequalified by WHO are interchangeable with the reference, as well as between each other without safety or efficacy concerns.

INTRODUCTION

The HIV epidemic continues to be a major public health threat, especially in sub-Saharan Africa, which accounts for 70% of the 36.9 million people living with HIV globally in 2014 [1]. The goal of antiretroviral therapy (ART) is to ensure sustained and durable viral suppression, reduce morbidity and mortality, and improve the quality of life [2]. According to the World Health Organization (WHO) HIV treatment guidelines, the combination of tenofovir disoproxil fumarate, lamivudine or emtricitabine plus efavirenz is the recommended first-line ART for HIV treatment [2]. Globally, ART coverage increased from 2% of people living with HIV in 2000 to 40% in 2014 [3]. Nonetheless, according to the WHO, there are still 22 million people living with HIV globally that lack access to ART [1].

The scaling up of access to ART, especially in low- to middle-income countries, in the last 15 years was made possible through the introduction and widespread use of generic antiretroviral medicines and fixed dose combinations (FDCs) [4]. According to the WHO, a generic medicine is a pharmaceutical product that is usually intended to be interchangeable with an innovator product, manufactured without a license from the innovator company, and is marketed after the expiry date of the patent or other exclusivity rights [5]. Use of generic medicines and FDCs transformed treatment for HIV and AIDS by significantly reducing the pill burden, improving adherence, and lowering treatment costs [6, 7].

One of the priorities of the WHO Prequalification of Medicines Programme is to improve the availability of quality-assured medicines that meet WHO standards for quality, safety, and efficacy [8] because ensuring access to quality, safe, and efficacious medicines, including generic medicines, is important in public health programs, particularly in those settings where the regulatory systems are inadequate and the burden of disease is the highest. In addition to meeting the quality requirements, generic medicines are prequalified by WHO after demonstration of bioequivalence to the innovator product or an acceptable reference product [5, 9, 10]. Two pharmaceutical products containing the same active substance are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (maximum or peak plasma concentration (C_{max}) and time to reach peak concentrations (T_{max})) and extent of absorption (area under the plasma concentration *versus*

time plot (AUC)), after administration in the same molar dose under the same conditions, lie within acceptable predefined limits [5, 9].

Two products that are bioequivalent are considered therapeutically equivalent and can be interchanged, that is prescribable and switchable, in clinical practice. Furthermore, demonstration of bioequivalence of all the generics with the same reference product is also considered as indirect demonstration of switchability between all the generics [11]. Although in clinical settings generic-to-generic switching is widely practiced, the comparison between generics is not a regulatory requirement. Adjusted indirect comparisons have been proposed for those cases where assurance of equivalence between generics is considered essential such as for chronic treatments [12–15].

The objective of this study was to investigate the bioavailability and the interchangeability of the recommended first-line antiretroviral generics prequalified by WHO using adjusted indirect comparisons.

MATERIALS AND METHODS

Identification of products

Products containing emtricitabine, tenofovir disoproxil fumarate, lamivudine and/or efavirenz in single formulations or fixed dose combinations were identified from the list of prequalified products that is available on the WHO Prequalification Team Medicines (WHO PQT-m) website (www.who.int/prequal). Data from bioequivalence studies comparing the generic products with corresponding reference products in adult healthy volunteers were obtained from the WHO Public Assessment Reports (WHOPARs) that are available on the WHO prequalification website.

The inclusion criteria for accepting the bioequivalence studies for adjusted indirect comparison were: bioequivalence studies conducted in healthy volunteers and found acceptable as per WHO norms and standards, products currently prequalified (i.e., not withdrawn, or delisted), and studies conducted with the same reference product. Products for which prequalification was based on in vitro comparative dissolution studies such as waivers for in vivo bioequivalence studies for additional strengths or based on the Biopharmaceutics Classification System (BCS) were excluded from the analysis. Fixed

dose combination products with other active ingredients not under investigation were also excluded from the analysis.

Reference products in the WHO Prequalification Team Medicines

The acceptable reference products for emtricitabine, tenofovir, lamivudine and efavirenz in single formulation or FDCs for demonstrating bioequivalence are as follows:

- Emtriva® (emtricitabine) 200 mg capsule, Gilead Sciences
- Viread® (tenofovir disoproxil fumarate) 300 mg tablet, Gilead Sciences
- Epivir® (lamivudine) 150 mg and 300 mg tablet, GlaxoSmithKline
- Sustiva® (efavirenz) 100 mg and 200 mg capsule, 600 mg tablet Bristol-Myers Squibb
- Truvada® (tenofovir disoproxil fumarate/emtricitabine) 300/200 mg tablet, Gilead Sciences
- Atripla® (tenofovir disoproxil fumarate/efavirenz/emtricitabine) 300/600/200 mg tablet, Bristol-Myers Squibb and Gilead Sciences

Statistical method for the adjusted indirect comparison between generic products

The 90% confidence interval (CI) for the adjusted indirect comparison of each comparison was calculated as described by Gwaza et al [12]. Briefly, the width of the 90% CI for the adjusted indirect comparisons was calculated using the recommended homoscedastic method [12]. This method uses the conventional t test and assumes homogeneity of variances between the studies and small sample sizes. The combined standard deviation of both bioequivalence studies is calculated from the variability of each individual study.

Although ±20% acceptance range is used for direct comparisons, ±30% acceptance range is proposed for adjusted indirect comparisons [12, 14], due to the limited precision of indirect comparisons [16, 17].

RESULTS

Thirty-four products met the inclusion criteria and were included in the analysis. Twenty products were dual and triple combinations

reflecting the current recommendations and practice of using FDCs to lower treatment costs, pill burden and improve adherence. Figure 1 shows the formulations and frequency in single formulation and fixed dose combination included in the analysis. Tenofovir disoproxil fumarate appears as the key drug in the prequalified first-line ART with a total of 26 formulations compared to 14, 12 and 11 for emtricitabine, efavirenz and lamivudine, respectively. Moreover, tenofovir disoproxil fumarate appears in all the FDCs included in the analysis. The combinations also reflect the recommended choice of 2 nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) as part of the first-line treatment for HIV and AIDS [18].

Figures 2 shows the point estimates and 90% CI for the ratios of C_{max} and AUC_{0-t} for emtricitabine and efavirenz, while Figure 3 shows the data for lamivudine and efavirenz for the prequalified generic formulations against formulations listed as reference products by WHO [19]. Two mono-component products for emtricitabine are not included in the figures. The 90% CI for these 2 products were 85.6 – 94.8% for C_{max}, 91.3 – 97.5% for AUC_{0-t} (HA418), and 91.3 – 108.0% for C_{max}, and 101.0 – 107.9% for AUC_{0-t} (HA451). For all the studies, the 90% CI for the ratios of C_{max} and AUC_{0-t} was within the recommended standard of 80 – 125% with the exception of 2 products that were approved with wider limits for C_{max} for lamivudine (HA282) and efavirenz (HA306).

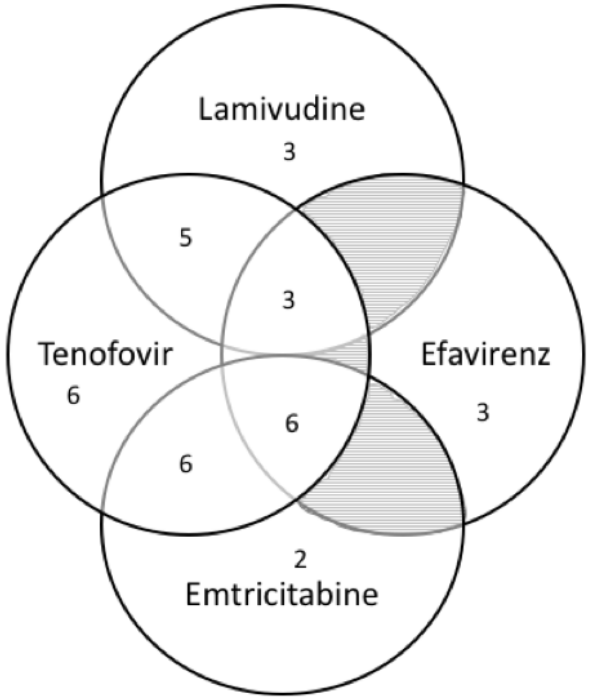

Figure 1: Number of formulations of efavirenz, emtricitabine, lamivudine and tenofovir included in the analysis. The shaded area indicates absence of prequalified products or products meeting the inclusion criteria.

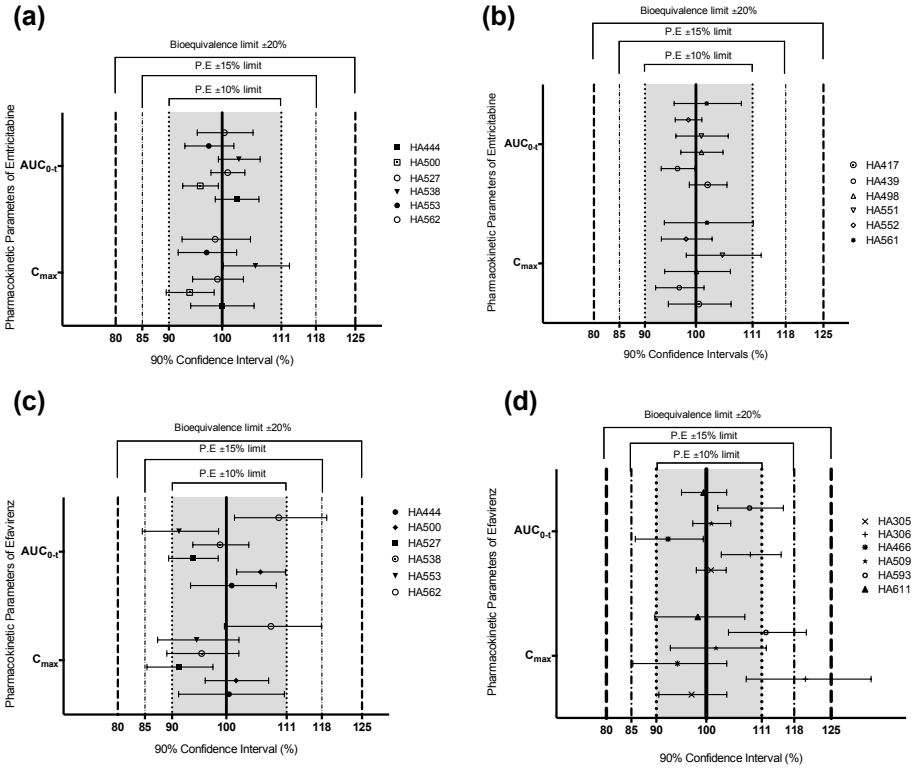

Figure 2: Geometric mean ratios of generic vs. WHO-approved reference with corresponding 90% confidence intervals (CIs) of the pharmacokinetic parameters (C_{max}, AUC_{0-t}) in the original bioequivalence studies for emtricitabine and efavirenz. Reference product for emtricitabine is (a) Atripla®, Gilead Sciences, and (b) Truvada ®, Gilead Sciences; reference product for efavirenz is (c) Atripla®, Gilead Sciences, and (d) Sustiva®, Bristol-Myers Squibb. Data points are the point estimates (PE) of the pharmacokinetic parameters, with 90% CI). The shaded region indicates the ±10% limit. The light dotted lines at 85% and 118% indicate ±15% limit. The heavy dotted lines at 80 and 125% indicate the standard 90% CIs limit for bioequivalence

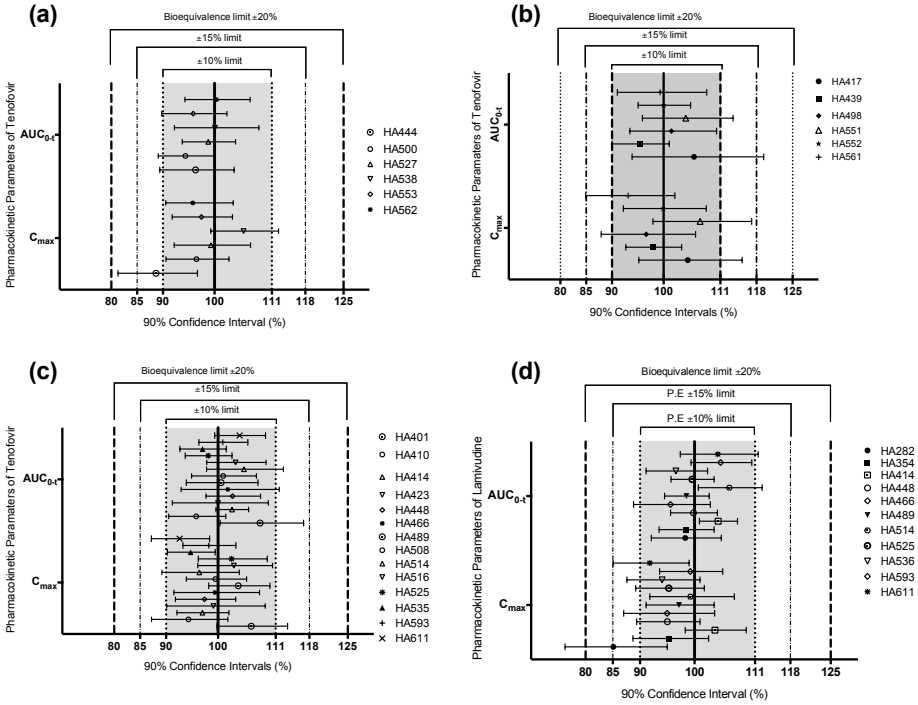

Figure 3: Geometric mean ratios of generic vs. WHO-approved reference with corresponding 90% confidence intervals (CIs) of the pharmacokinetic parameters (C_{max}, AUC_{0-t},) in the original bioequivalence studies for tenofovir disoproxil fumarate and lamivudine. Reference product for tenofovir is (a) Atripla®, Gilead Sciences, (b) Truvada®, Gilead Sciences, and (c) Viread®, Gilead Sciences; reference product for lamivudine is (d) Epivir® GlaxoSmithKline. Data points are the point estimates (PE) of the pharmacokinetic parameters, with 90% CIs. The shaded region indicates the ±10% limit. The light dotted lines at 85% and 118% indicate ±15% limit. The heavy dotted lines at 80 and 125% indicate the standard 90% CIs limit for bioequivalence

Adjusted indirect comparisons between generics

The distribution of the differences in bioavailability (AUC and C_{max}) between generics calculated by adjusted indirect comparisons is presented in Table 1. The indirectly estimated 90% CI for the comparisons between generics for emtricitabine, tenofovir disoproxil fumarate, lamivudine, and efavirenz are presented in Supplementary Files 1, 2, 3 and 4, respectively.

Table 1: Distribution of the differences in bioavailability (AUC and C_{max}) between generics calculated by adjusted indirect comparisons

Drug	Reference	# of Products	# of indirect comparisons	Difference between generics based on 90% confidence intervals calculated by adjusted indirect comparisons							
				≤ 20%		>20 - 25%		>25 - 30%		> 30%	
				C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Emtricitabine	Emtriva®	2	1	1	1	-	-	-	-	-	-
	Truvada®	6	15	15	15	-	-	-	-	-	-
	Atripla®	6	15	15	15	-	-	-	-	-	-
Tenofovir disoproxil fumarate	Viread®	14	91	90	91	1	-	-	-	-	-
	Truvada®	6	15	12	13	3	2	-	-	-	-
	Atripla®	6	15	15	13	-	2	-	-	-	-
Lamivudine	Epivir®	11	55	46	55	8[a]	-	1[a]	-	-	-
Efavirenz	Sustiva®	6	15	7	13	3	2	4[b]	-	1[b]	-
	Atripla®	6	15	12	12	3	2	-	1	-	-
TOTAL			237	213	228	18	8	5	1	1	0

[a]: These indirect comparisons are comparisons with HA282, prequalified with wider C_{max} limits for lamivudine

[b]: These indirect comparisons are comparisons with HA306, prequalified with wider C_{max} limits for efavirenz

All the 31 generic adjusted indirect comparisons for emtricitabine satisfy the conventional bioequivalence criterion of 80 – 125% for C_{max} and AUC_{0-t}, which corresponds to ±20%.

The 91 adjusted indirect comparisons between tenofovir generics with Viread® as reference in the original studies satisfy the conventional 80 – 125% acceptance range for all the pharmacokinetic parameters, except for one borderline case for C_{max} (105.28 – 125.35 %). Similarly, 15 adjusted indirect comparisons between tenofovir generics with Truvada® as reference in the original studies satisfy the conventional 80 – 125% acceptance range for most comparisons except 2 borderline cases for AUC_{0-t} (97.29 – 126.65% and 90.58 – 125.47%) and 3 cases for C_{max} (97.94 – 129.08%, 79.20 – 102.79% and 101.34 – 130.44%). The same trend was observed with Atripla® as a reference since the adjusted indirect comparisons for AUC_{0-t} and C_{max} was within acceptance range of 80 – 125% in all the 15 comparisons, except 2 cases for C_{max} (79.77 – 99.93% and 75.54 – 93.27%).

Similarly, the adjusted indirect comparisons between lamivudine generics satisfy the conventional bioequivalence criterion of 80 – 125% for AUC_{0-t} for all the 55 comparisons. Further, 46 comparisons satisfy the conventional limits for C_{max}, while 8 comparisons satisfy the wider acceptance limits of 75 – 133% and one was outside this ± 25% range, but inside the ± 30% range.

For efavirenz, in the generics that were compared with Atripla®, the 90% CI for C_{max} and AUC_{0-t} falls within 80 – 125% acceptance limits for the 15 comparisons except in 3 cases for C_{max} and AUC_{0-t}, but results were within ± 30% range. For the generics compared with Sustiva®, 8 comparisons were outside 80 – 125% for C_{max} but within ± 30% except one. Two comparisons were outside the conventional 80 – 125% for AUC_{0-t}, but within ± 30% range.

DISCUSSION

This work describing the adjusted indirect comparisons for first-line HIV medicines is an extension of previous work on use of adjusted indirect comparisons to investigate the bioequivalence between WHO prequalified generics for artemether/lumefantrine [12], and first-line anti-tuberculosis medicines [14]. This assessment demonstrates that first-line antiretroviral generics prequalified by WHO can be

interchanged without any safety and efficacy concerns in clinical settings. Notwithstanding that some comparisons were outside the conventional acceptance limits of ± 20% for direct comparisons, in part, due to the reduced precision of the adjusted indirect comparisons, there were no generic-generic comparisons outside a wider limit of ± 30% for the highly soluble drugs emtricitabine, tenofovir disoproxil fumarate, and lamivudine. For efavirenz, a poorly soluble drug, however, only one out of 30 generic-generic comparisons for C_{max} was outside ± 30%.

Failure to show equivalence within a ± 30% acceptance range in one out of thirty adjusted indirect comparisons should be interpreted as insignificant number since it is in less than 5% of the comparisons (3.33%). Furthermore, in clinical practice the difference in C_{max} at steady state between test and reference product is known to be much lower than the difference observed in the single dose bioequivalence study [20]. In fact, bioequivalence studies are conducted as single dose studies because a single dose study is the worst-case scenario where the difference in C_{max} are detected with higher sensitivity [5, 9, 10].

Generic prescribing and substitution policies are widely adopted in many countries. In these situations, the physician can prescribe using international non-proprietary (generic) names and the dispenser has discretion to dispense any available product containing the same drug, strength and dosage form. Demonstration of bioequivalence between the generic and the innovator ensures prescribability of the generic in place of the innovator for new patients. This applies for all generic products either for acute or chronic treatments. Furthermore, for chronic conditions such as HIV and AIDS, the dispenser may substitute the previously administered product with the available product (generic substitution or switching) based on availability, price, patients' preference or restrictions by third part insurers. In these cases, generics need not only to be prescribable, but also switchable between themselves.

If bioequivalence is demonstrated with the innovator or acceptable reference using the current regulatory limits of 80 – 125% for the 90% confidence intervals of the ratio test/reference for AUC and C_{max}, should clinicians and patients be concerned with generic-generic switching for antiretroviral medicines? If the same dose is administered without any dose titration, as it is with the products

under investigation, it should not matter if one generic or another one is administered. These investigated products are prescribable and switchable with the reference as bioequivalence was demonstrated with the reference within the conventional acceptance limits. However, regulatory authorities and clinicians have to be careful in some cases when it comes to substitution of the generics between themselves. While this is not critical for most drugs including the antiretrovirals investigated in this study, a point estimate constraint may be relevant for drugs with a narrow therapeutic index or for patients close to the border of its therapeutic window. In fact, narrow therapeutic drugs are usually assessed with a narrowed acceptance range (e.g., 90-111%) [5, 9, 10].

In the drugs under investigation we must take into account that the prevalence of central nervous system (CNS) adverse events for efavirenz increases with plasma concentrations above 4 μg/ml [21–24]. This is higher in specific populations, such as African population, with higher prevalence of CYP2B6 single nucleotide polymorphisms that result in reduced clearance. Therefore, these patients are likely to have higher plasma concentrations on the border of the therapeutic window with the standard dose of 600 mg once per day. Some authors [25, 26] have argued for therapeutic drug monitoring for efavirenz or dose adjustments based on genotyping to reduce the incidence of CNS adverse events. Thus, failure to show equivalence in indirect comparisons within wider limits of ± 30% may be of concern for efavirenz for which changes in C_{max} may result in increased incidence of adverse events when patients are switched between generics. Moreover, this confirms our previous recommendation that regulatory authorities may consider point estimate constraint of ±10% [14, 27], particularly when generic substitution is recommended by national governments.

The drugs under investigation emtricitabine, lamivudine and tenofovir disoproxil fumarate, are highly soluble drugs according to the BCS [28–30] without known bioavailability problems. If formulated correctly to show similar in vitro dissolution profiles to those of the reference product and without critical excipients that may affect bioavailability, generics of these products are likely to have very similar point estimates of the ratio test / reference of AUC and C_{max} in the bioequivalence studies. For emtricitabine, the point estimates were within ± 5% of the unity value (100%) in the direct comparisons in most studies and never in excess of 10%. In addition, it has a low

intra-subject variability in pharmacokinetics thus, the width of the confidence intervals is narrow in the direct comparisons. All the products considered for emtricitabine, except two, were formulated as FDCs. If the original studies are overpowered for emtricitabine because the sample size has been calculated to compensate for the more variable active pharmaceutical ingredients tenofovir and efavirenz co-formulated with emtricitabine, the reduced precision associated with indirect comparisons becomes inconsequential [27]. Therefore, indirect comparisons for emtricitabine were able to meet the acceptance criterion of 80 – 125% for C_{max} and AUC_{0-t} in all comparisons.

Tenofovir disoproxil fumarate is a BCS class III drug (highly soluble and poorly permeable), [28, 30] without bioavailability problems, thus the indirect comparisons were able to meet the acceptance criterion of 80 – 125% in all 121 comparisons for AUC_{0-t}, except two borderline cases. Two of the three cases that were outside the 80 – 125% for C_{max} were due to one product (HA444) for which the point estimate difference in direct comparisons was greater than 10%. Similar to tenofovir disoproxil fumarate, lamivudine is a BCS class III [28], though lamivudine C_{max} is problematic, its indirect comparisons were able to meet the acceptance criterion of 80 – 125% for AUC_{0-t} and C_{max} in all the comparisons, except comparisons with one product (HA282) for C_{max}. HA282 was prequalified with wider limits of 75 – 133% for C_{max} and the point estimate difference in the direct comparison was greater than 10%. Consequently, all the comparisons for C_{max} with this product satisfied this wider limit of 75 – 133%, except one indirect comparison. These wider limits were accepted at the time as it was concluded that the C_{max} for lamivudine was clinically irrelevant by the US FDA and met the Health Canada requirement of point estimate within the 80 – 125% limits for C_{max} [31].

Efavirenz is a lipophilic drug with low solubility in water and buffers across the physiological pH range of 1.2 to 6.8. It is classified as either BCS class II drug [32, 33] or as a BCS class II/IV drug [34]. Thus, efavirenz oral absorption is limited by both dissolution rate and solubility. In addition, variation in excipients or in the manufacturing process was reported to impact the rate and extent of efavirenz oral absorption and in vitro dissolution profiles are not able to predict in vivo bioequivalence [35]. Thus, marked point estimate differences are more likely to occur for efavirenz compared to the other drugs under investigation. This will impact on the outcome of the indirect

comparisons. Two products, HA593 and HA306, with point estimate difference greater than 10% and 14%, respectively, for efavirenz C_{max} in the original studies, accounted for 7 of the 8 indirect comparisons outside the 80 – 125% limit. HA306 was able to show bioequivalence with the reference in the original study, despite such large point estimate difference, because efavirenz has low intra-subject variability and the studies are usually overpowered. The results for HA306 are consistent with computations that have shown that adjusted indirect comparisons are unlikely to meet the 80 – 125% criterion even for overpowered studies when point estimate difference is greater than 14% [27].

The major limitation associated with adjusted indirect comparison is the reduced precision which makes them less effective as compared to direct comparisons [16, 17]. Therefore, on one hand, if bioequivalence between generics is shown with conventional limits of 80 – 125% in indirect comparisons, which was the case for more than 90% of the comparisons, we can consider the generics not only to be bioequivalent but also quite similar. On the other hand, the cases (10% for C_{max} and 4% for AUC) that failed to show equivalence within the 80 – 125% acceptance limits in indirect comparisons, does not indicate that the generics differ by more than 20% as the null hypothesis is never demonstrated, but that the data are inconclusive.

Although these results are based on data submitted at the time of prequalification, the results can be extrapolated to future batches because the generics are subjected to the same quality standards and specifications as the innovator products, and there are requirements on post approval changes to ensure that future batches perform to the same standard as the batch used in the bioequivalence studies (biobatch) throughout the product's life cycle. In some instances, a new bioequivalence study is required to support such post approval changes. A limitation of this study is that it only considers the studies submitted at the time of prequalification based on the available data in the WHOPARs and may not reflect results of new bioequivalence studies submitted to support such post approval changes. Further, this study relates to products prequalified by WHO and caution should be applied when extrapolating results to products approved by national authorities applying different bioequivalence acceptance principles. Nevertheless, the results obtained in this study are consistent with the outcomes reported elsewhere using data from other regulatory authorities [13, 36, 37].

In conclusion, this study provides confidence that prequalified generic antiretroviral medicines may be switched between them without any concerns for safety and efficacy if bioequivalence was demonstrated with the same reference product. In addition, most of the studied cases met the proposed limit of ±30% range for adjusted indirect comparisons due to the limited precision of indirect comparisons. Thus, interchangeability in practice should not be of concern in these cases except for poorly soluble drugs, with a narrow therapeutic index or for patients close to the border of the therapeutic window. Lastly, these results confirm our previous findings that approval of products with no constraint on the point estimate or mean difference between the test and the reference may result in failure to demonstrate equivalence in indirect comparisons as shown by the cases for lamivudine and efavirenz.

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Supplementary Files

Additional File 1. 90% Confidence interval for C_{max} and AUC_{0-t} of emtricitabine obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing emtricitabine in single or fixed dose combination with other anti-retroviral medicines

Reference	Indirect Comparisons	90% confidence interval	
		C_{max}	AUC_{0-t}
Emtriva® (emtricitabine) 200 mg capsule (Gilead Sciences).	HA418 *vs.* HA451	82.84 – 99.34	86.13 – 94.83
Truvada® (tenofovir disoproxil fumarate / emtricitabine) 300/200 mg tablets (Gilead Sciences).	HA417 *vs.* HA439	96.21 – 112.33	101.02 – 111.45
	HA417 *vs.* HA498	91.96 – 109.70	95.92 – 106.82
	HA417 *vs.* HA551	87.05 – 104.97	95.37 – 107.48
	HA417 *vs.* HA552	94.72 – 110.99	99.27 – 108.67
	HA417 *vs.* HA561	88.99 – 108.86	93.69 – 107.21
	HA439 *vs.* HA498	89.34 – 104.49	90.55– 100.51
	HA439 *vs.* HA551	84.74 – 99.78	90.04 – 101.11
	HA439 *vs.* HA552	91.99 – 105.74	93.71 – 102.24
	HA439 *vs.* HA561	86.50 – 103.62	88.43– 100.88
	HA498 *vs.* HA551	86.67 – 104.50	93.90 – 106.54
	HA498 *vs.* HA552	94.26 – 110.54	97.90 – 107.54
	HA498 *vs.* HA561	88.39 – 108.63	92.09– 106.45
	HA551 *vs.* HA552	98.75 – 116.50	97.39 – 108.05
	HA551 *vs.* HA561	92.37 – 114.77	91.30 – 107.32
	HA552 *vs.* HA561	87.55 – 105.25	90.69 – 102.67
Atripla®(tenofovir disoproxil fumarate / efavirenz / emtricitabine) 300/600/200 mg tablet (Bristol-Myers Squibb and Gilead Sciences).	HA444 *vs.* HA500	98.59– 114.76	101.52 – 113.03
	HA444 *vs.* HA527	93.46 – 108.66	96.71 – 106.87
	HA444 *vs.* HA538	86.56– 102.07	94.32– 105.16
	HA444 *vs.* HA553	94.87 – 111.56	99.11 – 112.01
	HA444 *vs.* HA562	92.77 – 110.38	95.95 – 109.05
	HA500 *vs.* HA527	88.31 – 101.62	90.32 – 99.74
	HA500 *vs.* HA538	81.95 – 95.29	88.18 – 98.02
	HA500 *vs.* HA553	89.79 – 104.17	92.90 – 104.14
	HA500 *vs.* HA562	87.85 – 103.03	89.91 – 101.42
	HA527 *vs.* HA538	86.58 – 100.50	93.32 – 102.83
	HA527 *vs.* HA553	94.88 – 109.85	98.01 – 109.58
	HA527 *vs.* HA562	92.85 – 108.62	94.94 – 106.63
	HA538 *vs.* HA553	101.00 – 118.59	99.63 – 112.34
	HA538 *vs.* HA562	98.78 – 117.33	96.47 – 109.35
	HA553 *vs.* HA562	90.39 – 107.05	90.59 – 104.05

AUC, area under the plasma concentration - time curve. C_{max}, peak plasma concentration ;

Additional File 2. 90% Confidence interval for C_{max} and AUC_{0-t} of tenofovir obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing tenofovir in single or fixed dose combination with other anti-retroviral medicines

Reference	Indirect Comparisons	90% confidence interval	
		C_{max}	AUC_{0-t}
Viread® (tenofovir disoproxil fumarate) 300 mg and 40 mg tablet (Gilead Sciences)	91 comparisons	all within 80 - 125%, except one, i.e. 105.28 - 125.35 %	all within 80 - 125%
Truvada® (tenofovir disoproxil fumarate / emtricitabine) 300/200 mg tablets (Gilead Sciences).	HA417 *vs*. HA439	95.89 – 119.20	97.29 – 126.65[a]
	HA417 *vs*. HA498	94.75 – 124.00	89.59 – 121.42
	HA417 *vs*. HA551	85.20 – 112.25	86.17 – 119.60
	HA417 *vs*. HA552	92.55 – 118.70	92.63 – 121.00
	HA417 *vs*. HA561	97.94 – 129.08[a]	90.58 – 125.47[a]
	HA439 *vs*. HA498	91.47 – 112.36	85.28 – 103.52
	HA439 *vs*. HA551	82.98 – 100.83	82.96 – 100.82
	HA439 *vs*. HA552	89.18 – 107.76	88.31 – 103.00
	HA439 *vs*. HA561	95.21 – 116.16	86.98 – 106.04
	HA498 *vs*. HA551	79.20[a] – 102.79	86.56 – 109.44
	HA498 *vs*. HA552	85.64 – 109.19	92.49 – 111.40
	HA498 *vs*. HA561	90.93 – 118.34	90.78 – 115.09
	HA551 *vs*. HA552	95.07 – 120.82	95.21 – 114.24
	HA551 *vs*. HA561	101.34 – 130.44[a]	93.24 – 118.28
	HA552 *vs*. HA561	95.04 – 121.09	91.72 – 110.56
Atripla®(tenofovir disoproxil fumarate/efavirenz/emtricitabine) 300/600/200 mg tablet (Bristol-Myers Squibb and Gilead Sciences).	HA444 *vs.* HA500	82.78 – 101.96	93.09 – 111.99
	HA444 *vs.* HA527	79.77[a] – 99.93	89.18 – 106.63
	HA444 *vs.* HA538	75.54[a] – 93.27	86.28 – 107.38
	HA444 *vs.* HA553	82.01 – 100.92	91.07 – 110.86
	HA444 *vs.* HA562	81.95 – 102.24	87.03 – 105.82
	HA500 *vs.* HA527	88.14 – 107.15	88.03 – 103.62
	HA500 *vs.* HA538	83.26 – 100.25	85.64 – 103.77
	HA500 *vs.* HA553	90.37 – 108.51	90.12 – 107.46
	HA500 *vs.* HA562	90.36 – 109.85	85.98 – 102.74
	HA527 *vs.* HA538	85.38 – 103.52	89.77 – 108.53
	HA527 *vs.* HA553	92.68 – 112.03	94.84 – 111.95
	HA527 *vs.* HA562	92.69 – 113.40	90.85 – 106.60
	HA538 *vs.* HA553	99.52 – 118.03	94.12 – 115.78
	HA538 *vs.* HA562	99.63 – 119.37	89.87 – 110.60
	HA553 *vs.* HA562	92.07 – 109.96	87.22 – 104.58

AUC, area under the plasma concentration - time curve; Cmax, peak plasma concentration.

[a]Confidence interval outside the 80 – 125% limit but inside 75 – 133% limit.

Additional File 3. 90% Confidence Interval for C_{max} and AUC_{0-t} of lamivudine obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing lamivudine in single and fixed dose combination with other anti-retroviral medicines

Reference	Indirect comparisons	90% Confidence interval	
		C_{max}	AUC_{0-t}
Epivir® (lamivudine) 150 and 300 mg tablets (GlaxoSmithKline)	HA282 *vs*. HA354	78.55[a] – 101.30	92.13 – 108.24
	HA282 *vs*. HA414	73.52[b] – 91.51	88.18 – 100.63
	HA282 *vs*. HA448	79.93[a] – 100.34	91.40 – 106.10
	HA282 *vs*. HA466	77.74[a] – 103.26	92.14 – 114.74
	HA282 *vs*. HA489	77.57[a] – 98.92	92.40 – 107.73
	HA282 *vs*. HA514	75.41[a] – 97.50	84.99 – 100.42
	HA282 *vs*. HA525	79.30[a] – 100.57	91.96 – 105.96
	HA282 *vs*. HA536	79.81[a] – 102.56	93.42 – 110.85
	HA282 *vs*. HA593	76.74[a] – 95.86	86.08 – 102.20
	HA282 *vs*. HA611	81.65 – 105.30	85.75 – 103.58
	HA354 *vs*. HA414	84.29 – 100.31	89.03 – 99.93
	HA354 *vs*. HA448	91.19 – 110.53	92.14 – 105.53
	HA354 *vs*. HA466	88.56 – 113.91	92.91 – 114.10
	HA354 *vs*. HA489	88.15 – 109.38	93.06 – 107.26
	HA354 *vs*. HA514	86.39 – 106.95	85.81 – 99.74
	HA354 *vs*. HA525	90.85 – 110.32	92.84 – 105.23
	HA354 *vs*. HA536	91.79 – 112.06	94.40 – 109.99
	HA354 *vs*. HA593	87.57 – 105.57	86.77 – 101.66
	HA354 *vs*. HA611	93.67 – 115.34	86.59 – 102.86
	HA414 *vs*. HA448	100.49 – 118.63	98.80 – 110.61
	HA414 *vs*. HA466	98.01 – 121.73	100.06 – 119.08
	HA414 *vs*. HA489	97.31 – 117.20	99.77 – 112.44
	HA414 *vs*. HA514	95.35 – 114.61	92.17 – 104.36
	HA414 *vs*. HA525	100.13 – 118.39	99.58 – 110.28
	HA414 *vs*. HA536	101.21 – 120.21	101.46 – 115.02
	HA414 *vs*. HA593	96.47 – 113.35	93.17 – 106.42
	HA414 *vs*. HA611	103.35 – 123.66	93.14 – 107.48
	HA448 *vs*. HA466	90.04 – 111.15	96.01 – 113.55
	HA448 *vs*. HA489	89.36 – 107.06	95.39 – 107.61
	HA448 *vs*. HA514	86.94 – 105.43	87.65 – 100.42
	HA448 *vs*. HA525	91.18 – 109.06	94.43 – 106.40
	HA448 *vs*. HA536	91.88 – 111.07	96.29 – 110.90
	HA448 *vs*. HA593	88.10 – 104.12	89.02 – 101.91
	HA448 *vs*. HA611	94.09 – 113.94	88.74 – 103.22
	HA466 *vs*. HA489	88.01 – 108.61	89.69 – 104.98
	HA466 *vs*. HA514	85.38 – 107.27	81.98 – 98.47
	HA466 *vs*. HA525	88.12 – 112.75	87.13 – 105.77
	HA466 *vs*. HA536	88.62 – 115.07	88.73 – 110.39
	HA466 *vs*. HA593	84.98 – 107.86	82.31 – 101.10
	HA466 *vs*. HA611	91.66 – 116.86	82.62 – 101.70
	HA489 *vs*. HA514	88.23 – 108.60	86.43 – 99.21
	HA489 *vs*. HA525	91.11 – 114.08	92.11 – 106.27
	HA489 *vs*. HA536	91.78 – 116.23	94.09 – 110.57
	HA489 *vs*. HA593	87.72 – 109.30	86.67 – 101.98
	HA489 *vs*. HA611	94.80 – 118.19	87.27 – 102.26
	HA514 *vs*. HA525	94.22 – 115.13	100.01 – 114.15
	HA514 *vs*. HA536	94.97 – 117.23	101.79 – 119.20
	HA514 *vs*. HA593	91.04 – 109.92	93.98 – 109.69
	HA514 *vs*. HA611	97.15 – 120.38	93.63 – 111.15
	HA525 *vs*. HA536	92.04 – 111.50	96.39 – 110.26
	HA525 *vs*. HA593	88.02 – 104.81	88.65 – 101.86

Reference	Indirect comparisons	90% Confidence interval	
		C_{max}	AUC_{0-t}
	HA525 *vs*. HA611	94.09 – 114.58	88.53 – 102.97
	HA536 *vs*. HA593	86.46 – 103.96	84.99 – 99.97
	HA536 *vs*. HA611	92.48 – 113.58	84.70 – 101.27
	HA593 *vs*. HA611	98.47 – 118.68	92.33 – 109.35

AUC, area under the plasma concentration - time curve; Cmax, peak plasma concentration. [a]Confidence interval outside the 80 – 125% limit but inside 75 – 133% limit; [b]confidence interval outside the 75 – 133% limit but inside 70 –143% limit.

Additional File 4. 90% Confidence interval for C_{max} and AUC_{0-t} of efavirenz obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing efavirenz in single or fixed dose combination with other anti-retroviral medicines

Reference	Indirect Comparisons	90% confidence interval	
		C_{max}	AUC_{0-t}
Sustiva® or Stocrin®(efavirenz) 100 mg and 200 mg capsule, 600 mg tablet (Bristol-Myers Squibb or Merck)	HA305 *vs.* HA306	71.63[b] – 91.57	87.27 – 98.60
	HA305 *vs.* HA466	91.23 – 116.29	100.93 – 118.40
	HA305 *vs.* HA509	84.75 – 106.96	95.19 – 104.90
	HA305 *vs.* HA593	78.63[a] – 95.58	86.80 – 99.43
	HA305 *vs.* HA611	88.32 – 110.42	96.43 – 106.84
	HA306 *vs.* HA466	110.31 –146.64[c]	107.46 – 129.24[a]
	HA306 *vs.* HA509	100.69 –137.26[b]	99.58 – 116.54
	HA306 *vs.* HA593	94.82 – 120.84	92.32 – 108.65
	HA306 *vs.* HA611	105.78 – 140.56[b]	101.63 – 117.81
	HA466 *vs.* HA509	79.23[a] – 107.83	82.16 – 101.71
	HA466 *vs.* HA593	74.67[b] – 94.86	77.37[a] – 93.34
	HA466 *vs.* HA611	83.29 – 110.35	84.37 – 102.18
	HA509 *vs.* HA593	80.96 – 102.41	85.01 – 101.68
	HA509 *vs.* HA611	90.97 – 118.27	95.56 – 107.97
	HA593 *vs.* HA611	101.87 –127.38[a]	100.67 – 118.57
Atripla®(tenofovir disoproxil fumarate/efavirenz/emtricitabine) 300/600/200 mg tablet (Bristol-Myers Squibb and Gilead Sciences)	HA444 *vs.* HA500	88.93– 109.59	87.62– 103.00
	HA444 *vs.* HA527	98.12 – 123.55	98.37 – 117.77
	HA444 *vs.* HA538	93.58 – 118.43	93.11– 112.11
	HA444 *vs.* HA553	93.95 – 120.24	99.29 – 123.30
	HA444 *vs.* HA562	81.74 – 105.46	82.57 – 102.70
	HA500 *vs.* HA527	102.11 – 121.82	106.19 – 120.88
	HA500 *vs.* HA538	97.45 – 116.70	100.59 – 114.99
	HA500 *vs.* HA553	97.93 – 118.37	107.49 – 126.19[a]
	HA500 *vs.* HA562	85.31 – 103.69	89.48 – 105.00
	HA527 *vs.* HA538	86.94 – 105.15	88.47 – 101.85
	HA527 *vs.* HA553	87.17 – 106.91	94.01 – 112.41
	HA527 *vs.* HA562	76.03[a] – 93.52	78.39[a] – 93.37
	HA538 *vs.* HA553	90.97 – 112.06	98.76 – 118.75
	HA538 *vs.* HA562	79.34[a] – 98.03	82.35 – 98.65
	HA553 *vs.* HA562	78.00[a] – 97.82	74.69[a] – 92.74

AUC, area under the plasma concentration - time curve; Cmax, peak plasma concentration.

[a] Confidence interval outside the 80 – 125% limit but inside 75 – 133% limit; [b] confidence interval outside the 75 – 133% limit but inside 70 – 143% limit; [c] confidence interval outside 70 – 143% limit.

CHAPTER 3

MARKETING AUTHORISATIONS IN SUB-SAHARAN AFRICA

CHAPTER 3.1

Registering drugs in low-income countries: a trend analysis for Zimbabwe from 2003 to 2015

Submitted

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ABSTRACT

We analysed Zimbabwe's marketing authorisation system as a case model for similar settings. Data were collected from legislation, policies, guidelines, procedures as well as register of medicines. The duration of regulatory review was used to measure the agency's performance. Zimbabwe has four regulatory routes, which include (1) full review, (2) abridged review, (3) verification, and (4) regional collaborative registration process. Eighteen full-time equivalent assessors perform the assessments while an external expert committee makes the decisions. The registration requirements are consistent with World Health Organization's guidelines. A total of 2,083 applications were received, and 1,002 products were approved between 2003 – 2015. It takes almost 24 months (without start/stop clock system) to have a product approved in Zimbabwe (overall median time was 710 days (IQR 422; 1065)). Zimbabwe has an established and functional marketing authorisation system, though it has low regulatory performance based on approval metrics when compared to well-resourced authorities.

INTRODUCTION

Improved access to affordable, quality, essential medicines to the world's poorest is a key component in attaining the United Nations Sustainable Development Goals (SDGs) of reducing child mortality, improving maternal health and combating HIV and AIDS, malaria and other diseases [1]. Effective medicines regulatory systems (MRS) are imperative for achieving the SDG targets on good health and well-being, however, regulatory systems in most Sub-Saharan African countries are perceived to be non-robust in comparison to well-resourced countries, which inadvertently may act as a barrier on access to quality essential and innovative medicines, and inadequate in protecting the public from harmful products.

The effectiveness of African regulatory systems is largely unknown as there is no objective information on their performance primarily due to lack of transparency [2]. In contrast, information on the performance and activities of regulatory authorities in high-income countries such as the International Council on Harmonization (ICH) member countries is widely available and regularly updated in the public domain, [3-7] including public scrutiny of their activities [8-12]. Globally, there is a growing trend and advocacy for regulatory authorities to be transparent. In this respect, accountability and transparency are components of good regulatory practice and good review management practices [13].

In order to address this issue, information on regulatory systems in low-and middle-income (LMICs) e.g., Sub-Saharan Africa, should be available. This information from LMICs, battling with high disease burden and poor access to medicines and with different regulatory approaches to ICH countries, would give insights into the regulatory systems in those settings and may be useful for evidence-based strategies to strengthen regulatory capacity in Sub-Saharan Africa and other regions with similar systems [12].

Zimbabwe is a low income country in the southern African region with an estimated population of 15.25 million people [14]. The Medicines and Allied Substances Control Act [Chapter 15:03] established the MRS in Zimbabwe in 1969 [15]. The Medicines Control Authority of Zimbabwe (MCAZ) is a body corporate since 1997 established as a successor to the Drugs Control Council and the Zimbabwe Regional Medicines Control Laboratory. Similar to other

Sub-Saharan African countries, the greatest public health threat is due to HIV and AIDS, tuberculosis, and malaria, which account for the significant disease burden in the country. The mandate of the Authority, among other regulatory functions, is issuing marketing authorisations of medicines, including vaccines, based on demonstration of safety, efficacy, quality, and availability in the public's interest.

The objective of the present study was to analyse the performance of Zimbabwe's marketing authorisation system for medicines as a case model. To this end, the duration of regulatory review was calculated, since this approval time metric is one simple measure for an objective assessment of a regulatory agency's performance [3,16].

METHODS

Data sources

Data on the human medicine registration procedure, requirements and the review process for marketing authorisations were obtained from the legislation, policies, guidelines, and procedures implemented by the Authority available on www.mcaz.co.zw. Quantitative data on approval metrics were determined from the register of approved human products, which is publicly available on the MCAZ website http://www.mcaz.co.zw/images/pdf/Human_medicines_register.pdf, and the register of received applications obtained from the MCAZ. Information prior to 2003 was incomplete, therefore the data on the above was collected for the period 2003 – 2015. Information on human resources and staffing levels was obtained from the Human Resources Department and the 2014 MCAZ Annual report, [17] respectively.

Analysis of the data

This was a descriptive study of the submission and approval of products over a thirteen-year period (2003 – 2015). Analysis of the registration requirements was categorised under the following: (1) GMP inspection requirements, (2) requirement for contract research organisations, (3) chemistry, manufacturing and control (CMC) requirements, (4) clinical efficacy and safety requirements, and (5) requirements for demonstration of interchangeability. Analysis of the human capacity in the Authority was based on assessment of staff numbers, highest level of qualifications, and regulatory or other

relevant experience.

Approval metrics

Products were categorised according to pharmacological classification [18]. These data were used to analyse the time to approval, inclusive of the applicants' time to respond to queries or provide further information. There was lack of information on start stop clock system to calculate and discount the time taken by the applicant to respond. The analysis included new active substances (NAS) and generic products. In this paper, NAS is defined as chemical, biological, or radiopharmaceutical substances not previously authorised in a pharmaceutical product in the country being studied, [16,19] whereas a generic product is defined as a pharmaceutical product, usually intended to be interchangeable with the innovator product, marketed after the expiry of patent, or market exclusivity rights [20].

Descriptive statistics were performed using Microsoft Excel 2016 for Mac version 15.19.1.

RESULTS

The MCAZ human medicines registration system

The MCAZ uses an external expert committee that meets once a month to make decisions on marketing authorisations on behalf of the Authority. Technical staff that are employed by the Authority act as the secretariat responsible for preparing assessment reports for each application. In 2014 the total income was USD 3.9 million, which is entirely from user fees. The current application fees for registration of a NAS is USD 3,000, while that for an imported generic is USD 2,500 and line extension USD 1,500. Application fees for locally manufactured products is USD 900.

Registration Pathways

There are four pathways for submission and review of applications for registration of medicines in Zimbabwe, these include (1) full review, (2) abridged review, (3) verification, and (4) work-sharing.

The abridged review process is applied for all NAS with prior approval in an ICH country. The abridged review is a partial assessment based on prior approval from a 'reference' agency for which public assessment and inspection reports or similar

documentation are available in the public domain. The abridged review focuses on differences in requirements or situational factors such as stability test conditions (climatic zones), labelling, ethnicity of study populations, influence of co-morbidities and nutritional status on drug efficacy, differences in field strains or serotypes of infectious agents and national policies.

Since June 2012, the World Health Organization (WHO) prequalified products are reviewed through the WHO Prequalification Collaborative Procedure, [21] which entails access to the WHO Prequalification Team –Medicines (PQT-m) assessment and inspection reports with consent of the manufacturer. In those cases, only verification that the prequalified product is the same as the product [21] intended for marketing in Zimbabwe is performed. The pre-requisite is cooperation with the reference agency and sharing of the assessment and inspection reports. At the end of 2015, nine products had been approved under the WHO PQ Collaborative procedure.

MCAZ is one of the four founding regulatory authorities of the ZAZIBONA (Zambia, Zimbabwe, Botswana, and Namibia) collaborative medicines registration process, which started in October 2013. By 2015, 23 products were approved under the ZAZIBONA process.

Approval metrics

In the period 2003 – 2015, a total of 2,083 applications were received, while 1,002 products were approved (48%). Figure 1 shows the trend of the number of applications received and approved per year. Table 1 shows the type (generic or NAS) and origin of the approved products. The majority of product applications (83%) were generic products while the rest (17%) were NAS. Products from India constituted the majority of the generic applications (72 %). There is significant focus on promoting African local production of essential medicines: these data, as a case model, shows African local products contribute 21.4 % of the approved generics and about 25.4 % of the total approved products.

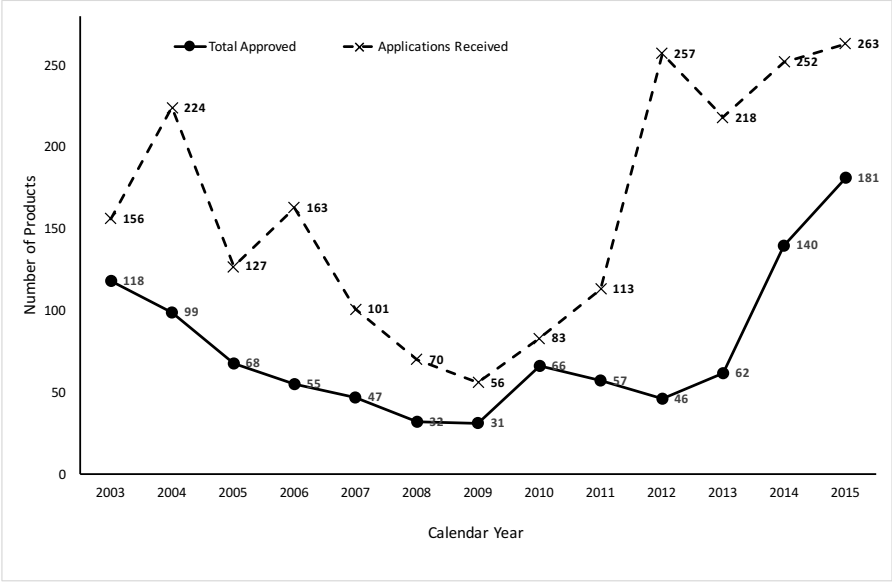

Figure 1: Number of application received per year and number of approved products per year from 2003 to 2015 in MCAZ. Note that the product applied on a given year may have been approved in another year. Therefore, for a given year the number of approved product does not correspond to the applications received in that year.

Table 1: Type of product and origin of approved products

Type of Product	Origin				
	Zimbabwe	Other African	Indian	Other	Total
NAS	-	77[a]	12	81	170
Generic	86	92[b]	602	52	832
Total	86	169	614	133	1,002

The country of origin refers to the country where the applicant is based (e.g., regional office of the innovator company), thus it may not represent the actual country of the manufacturer.

NAS: new active substance

[a] This figure is for South Africa only.

[b] Only two products were non-South African product (Egypt and Zambia).

The distribution of the pharmacological categories of the approved products is shown in Figure 2. Antiretrovirals, antituberculosis and antimalarials constituted 23% of the total approved products, consistent with the high infectious disease burden in Zimbabwe.

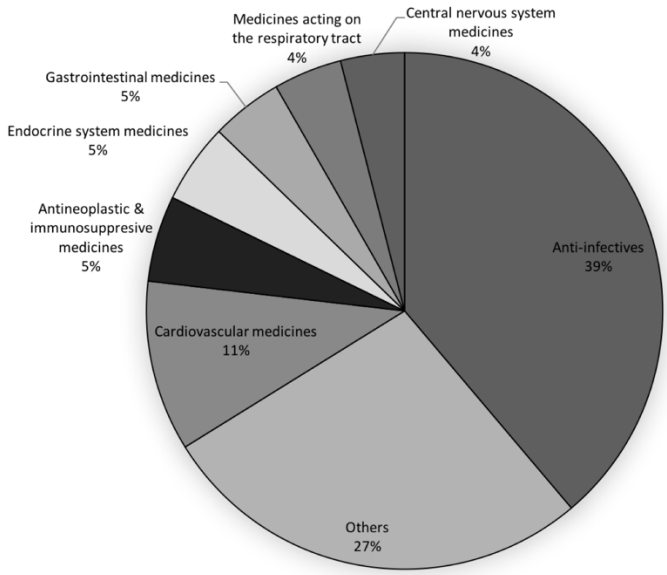

Figure 2: Pie chart representing the pharmacotherapeutic categories of the products approved in Zimbabwe since 2003 to 2015.

For the period 2003 to 2015, the overall median time for registration of all products (including the manufacturers' time to respond to queries) was 710 (interquartile range (IQR) 422; 1065) days. Figure 3 shows the median approval time by year from 2003 to 2015. From 2003, the median gradually increased from 516 days to a peak of 1,673 days in 2011, and decreased thereafter, reaching 585 days in 2014 and rose to 845 days in 2015.

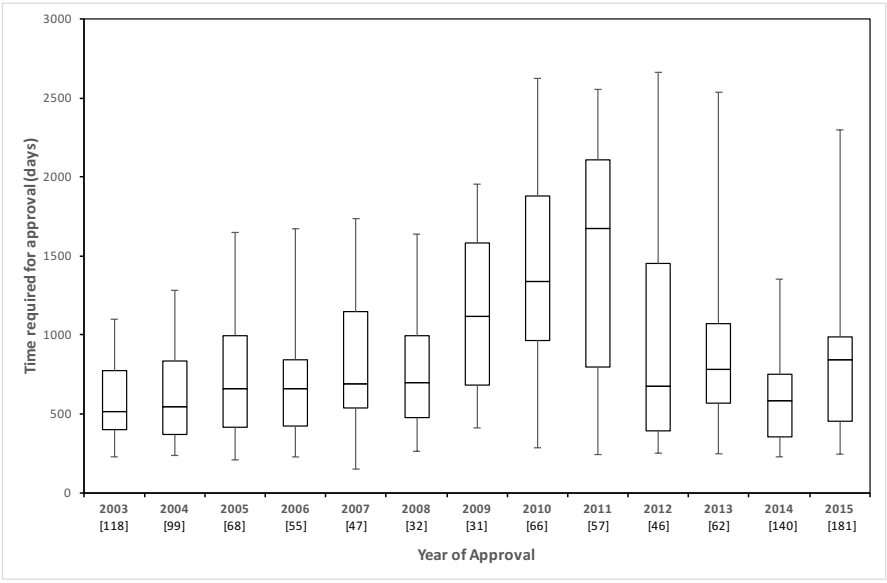

Figure 3: Box plot of time required for approval in Zimbabwe from 2003 to 2015. The number of approval is indicated in parenthesis under the year. The box plot represents the median (horizontal line), the IQR (upper and lower extremes of the box) and the 5% and 95% range (whiskers).

Human Capacity

The analysis on human resources was based on 2014 figures. The MCAZ staff was 100 people at December 2014, including technical and non-technical staff. The Evaluations and Registration Division is responsible for performing assessments for the marketing authorisations and constituted 20% of the total MCAZ staff with 20 full-time equivalent (FTE) staff of which 18 FTE were technical staff (assessors). In 2014, all the technical staff had an undergraduate degree in either pharmacy (15), veterinary (3) or basic sciences (2), while six of them had a graduate degree; 4 at masters' level and 2 with PhD. The median regulatory experience was 3 years (range 0.5 – 17 years). In that same year, the total number of applications received were 252, giving a ratio of 1 assessor per 14 dossiers / applications per year. The same assessor evaluates CMC data as well as bioequivalence data for generic applications. There was no staff turnover in the Division in 2014.

Good Manufacturing Practice Inspections

The Authority applies the WHO good manufacturing practice (GMP) requirements. Exemptions to GMP inspections is applied to applicants

from countries participating in the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S), or manufacturing sites in ICH countries, or in cases where the manufacturing sites had been inspected by PIC/S, ICH or WHO PQ inspectors for the finished pharmaceutical product. Presently, no GMP inspections are performed for active pharmaceutical ingredient (API) manufacturing site(s).

Inspections of contract research organizations (CROs)

In the period under review, no inspections of foreign contract research organizations performing bioequivalence studies for submission to Zimbabwe were performed; however, evidence of inspections by regulatory authorities from ICH countries, PIC/S participating countries or WHO is required.

Chemistry, manufacturing and controls (CMC) requirements

The technical elements in the MCAZ Registration Guideline are based on the Southern African Development Community (SADC) Registration Guidelines, which are consistent with WHO guidelines. Applicable stability requirements are for climatic zone IVb (30°C/75%RH) in line with SADC Guidelines on Stability Studies. Studies performed at zone IVa (30°C/65%RH) are also acceptable.

Clinical safety and efficacy requirements

Appropriate ICH guidelines should be used for requirements on submission of efficacy and safety data to support applications for registration of new (innovator) medicines.

Bioequivalence requirements for generic products

For generic medicines, bioequivalence data are required to demonstrate interchangeability with the innovator product. This requirement was introduced in 2006 following the approval of the SADC bioavailability / bioequivalence guidelines [22].

Typically, a single dose 2x2 crossover design is recommended for a bioequivalence study comparing a test and reference. The reference product for bioequivalence studies should be, in order of preference: (1) an innovator product, which is imported from a country with stringent regulatory authority, such ICH member countries, where it has been approved on the basis of clinical data demonstrating safety

and efficacy, (2) the WHO-recommended comparator product, if applicable, (3) nationally authorised innovator, (4) in any other case, a product selected as comparator should be comprehensively justified based extensive documented use in clinical trials reported in peer-reviewed scientific journals, long and unproblematic period of post-market surveillance. Foreign comparator products are acceptable and should be procured from an ICH country.

The acceptance limits are that the 90% confidence interval for the test/reference ratio for the area under the plasma concentration *versus* time plot AUC($_{0-t}$) and maximum plasma concentration (C_{max}) should lie within the acceptance interval of 80.00 – 125.00 %. Wider limits for C_{max} may be acceptable for highly variable drugs or tightened to 90.00 – 111.11% for AUC for narrow therapeutic index drugs. Where C_{max} is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. Requirements set in the bioanalytical method validation guidelines from the United States (US) Food and Drug Administration-(FDA) or European Medicines Agency (EMA) should be followed.

Waivers

Waiver of *in vivo* BE studies for immediate release oral solid dosage forms are accepted based on the Biopharmaceutics Classification System (BCS) for class I and III drugs, and for additional strengths. BCS class I drugs are highly soluble and highly permeable, and dissolution data in the physiological media in the pH range 1.2 to 6.8 is considered sufficient to ensure therapeutic equivalence if dissolution is similar and complete in 30 minutes. For BCS class III drugs, which are highly soluble and poorly permeable, the product should be very rapidly dissolving, i.e., release more than 85% within 15 minutes for test and reference in order to behave like a solution when they are emptied from the stomach and excipients should be qualitative the same and quantitatively the very similar to ensure that excipients do not affect absorption.

DISCUSSION

Data on the processes and performance of MRS in Sub-Saharan Africa is scarce, especially approval time metrics as a key indicator for regulatory performance [3,16]. It takes almost 24 months (including

manufacturers time to respond to queries) to have a product approved in Zimbabwe (overall median time for all products was 710 days), which is higher compared to 406 days (excluding the manufacturers time to respond to queries) for mature markets.[4] It is important to note that the data for the mature markets are for new active substances only, while that for Zimbabwe is for both new active substances and generic products. Ideally, comparison with other African countries or countries with similar regulatory systems would be more ideal, however, there were no data in literature to allow this comparison.

The registration system employed by the MCAZ separates the responsibility for preparing the technical reports from the decision making role between technical staff and external experts. On the contrary, other agencies such as the Medicines Control Council (MCC) South Africa, or the US-FDA uses different approaches. The MCC utilises the Council members who are external experts outside the Department of Health for preparing scientific reports and the Council is responsible for the final decision, whereas the US-FDA uses Scientific Advisory Committees for scientific opinion, for example for NAS; however, the FDA's Commissioner is responsible for the final decision [23]. For Ghana FDA, assessments are performed similarly to MCAZ, though the final decision is made by the Chief Executive Officer of the Authority on recommendation from a technical committee.

The Authority's income (USD 3.9 million) is low compared to other regulatory authorities, for example the Health Sciences Authority (HAS) of Singapore's operating income in the same period was USD 201 million, inclusive of USD 79 million in government grants [24]. However, it is important to note that Singapore is a high-income country compared to Zimbabwe. Further, the scope of regulation is significantly different between the two. MCAZ's mandate is only for medicines and medical devices, specifically condoms and gloves, whereas HSA scope includes medical devices, blood and blood products, allopathic and Chinese medicines, food, and cosmetics. No financial data could be found in literature on regulatory authorities in LMICs or Sub-Saharan Africa in particular, for comparison purposes, i.e., no publicly available annual reports with financial information. The Food and Drugs Authority of Ghana regularly publishes its annual reports, [25] however, the reports exclude financial data. The registration fees for NAS and generics in Ghana are slightly higher at

USD 5,400 and USD 3,600 respectively, compared to USD 3,000 and USD 2,500 for NAS and generics respectively in Zimbabwe.

In contrast to mature markets, Zimbabwe employs a different marketing authorisation system which is based on availability of, or sharing of information or assessment workload with other regulatory authorities. For instance, mature markets perform full review of new active substances, whereas in Zimbabwe registration in the country of origin is a prerequisite for NAS. There is a general lag-time between first authorisations in primary markets and subsequent submissions to LMICs. As a result, at the time of submission to Zimbabwe there is generally more information, including further reviews on the safety and efficacy of NAS in the primary markets post-approval, making review of the preclinical and pivotal phase III trial data redudant in those cases.

The majority of the applications received (> 80%) over the 13-year period were for generic products for which most have no prior reviews by stringent regulatory authorities, thus the MCAZ focuses its attention on performing full review of these generics including demonstration of interchangeability with the innovator product or an acceptable reference. The median time for approval of generic products was higher at 737 days compared to 585 days for NAS, due to a number of potential reasons: the quality of the dossier submission from the innovator companies is generally higher compared to generics in general, the differences in the extent of scientific assessment for an innovator and a generic, and prior approvals from stringent regulatory authorities. Nevertheless, these figures for the abridged review of NAS were higher when compared to emerging markets that applies a similar review system for NAS, i.e., relying on approvals of NAS in the primary markets, i.e., in the United States, Europe or Japan. For example, overal medial approval time across emerging markets for the period 2009 – 2013 was 381 days for the abridged route for NAS [4].

While in most cases, regulators use the benchmark performance of well-resourced regulatory authorities such as the US-FDA, EMA or Pharmaceuticals and Medical Devices Agency (PMDA) Japan, it may be prudent for Zimbabwe and countries with similar systems to consider benchmarking with each other, for example Ghana FDA, or the countries that employ similar systems such as HSA in Singapore. These countries have essentially similar registration pathways

(scientific assessment models); namely verification route, abridged review and full assessments [26]. Moreover, Zimbabwe has an additional scientific assessment model of work sharing or collaboration as part of regional harmonisation (ZAZIBONA process). This ZAZIBONA pathway is essentially similar to the decentralised process in the European Union, which has been adopted for the assessment of generic medicines by the International Generic Drug Regulators Programme (IGDRP) in a pilot with some countries [27].

Although approval time is a key metric for regulatory performance, there is need to balance faster approvals with the risk-benefit assessment [28]. More importantly, the job of regulators is not only to increase faster access to innovative therapies but also to balance this with adequate protection of public health from harmful products through thorough assessment of the risk-benefit analysis and quality of the products. Although, not all submitted products receive approvals from regulatory authorities, information on these negative outcomes is rarely published. Consequently, the key performance metric for regulatory authority is approval time, which ignore whether the regulatory authority performs thorough scientific assessments or just issues marketing authorisations with minimal reviews. Notwithstanding this, measuring the quality of the scientific assessment is subjective and presently there are no agreed indicators, other than the subjective indicators such as industry or reputation from peers, or input indicators, for example, availability of resources, both financial and human, the standards that are applied, or outputs such as publication of the scientific basis of approval.

The availability of technical staff in sufficient numbers, qualifications, and experience could be a measure on how well a regulatory system may perform with respect to quality of the decision making. The MCAZ regulatory work force is about a quarter of the Ghana FDA (474 staff), though it is important to note that Ghana FDA regulates a wide range of products including food, cosmetics, medical devices and household chemicals and has a population of 26 million people compared to Zimbabwe’s 15 million people. In addition, Zimbabwe receives a small number of applications, 252 in 2014 compared to 1,400 applications received by the Ghana FDA in the same period [25]. Standardised technical capacity levels or workload, i.e., # of assessors / dossier received or approved could not be compared as this information was not publicly available for the Ghana FDA or other regulatory authorities in Sub-Saharan Africa.

Regulatory authorities in Sub-Saharan Africa face the challenge of attracting and retaining sufficient number of qualified regulatory scientists / professionals. This is reflected in the relative median years of experience for assessors at MCAZ of 3 years. Most of the technical staff had an undergraduate pharmacy degree and experience in regulatory sciences is primarily obtained on the job. The available expertise may be sufficient to review uncomplicated generic applications, however, expertise in more complex products such as biosimilars or biotechnology products, or full review of API Drug Master File (DMF), clinical review of innovative therapies is lacking. This situation is likely to be consistent across other African regulatory authorities.

Despite the Authority's or continental efforts through the African Medicines Regulatory Harmonization (AMRH) to increase the human capacity in regulatory sciences, attracting and retaining high level expertise in the regulatory agencies is likely to persist due to limited financial resources. Therefore, the most logical approach particularly for complex and innovative therapies, including full reviews of API DMFs or GMP inspections of biotechnology facilities or API manufacturing sites is work-sharing, or potentially centralised reviews leveraging on regional or continental expertise in these areas. For instance, this could be the role of the proposed regional medicines agency under the AMRH or African Medicines Agency. This is important considering the likely increase in the number of NAS seeking first authorisation in African countries for diseases that are endemic in this region [29]. It would make business sense and effectual use of resources to have such regulatory capacity at regional or continental level by pooling resources and expertise.

There is reported correlation between marketing authorisations or WHO prequalification of medicines, and decrease in quality control failure rates in post-marketing activities [30]. Thus, strengthening medicine regulatory systems, including the capacity for granting marketing authorisations, and technical reviews for bioequivalence data and routine post marketing surveillance is one of the key strategies in a multi-faceted approach for combating substandard/spurious/falsely/labelled/falsified/counterfeit (SSFFCs) medical products.

The main limitation of this study is the dearth of information in countries with similar systems for comparison so as to put the results

into context. Further, indicators for regulatory performance focus essentially on the approval metrics and less on the quality of the regulatory performance. Increased transparency by regulatory authorities in settings similar to MCAZ may help the objective assessment of the regulatory performance, i.e., the efficiency and effectiveness of the Authority's marketing authorisation system. More objective and standardized performance metrics, which include both input (e.g., financial, human resources) and output (e.g., number of products approved, approval time) or outcome (e.g., prevalence of SSFFCs products in the market) indicators are required to enable evidence-based decisions to strengthen regulatory systems.

In this study, data were collected by year of registration, in contrast to year of application,[16] which permits the tracking of each application until final regulatory decision, i.e., registration, refusal or withdrawal over time. As such, the data only reflect the products that received a positive opinion (registration) and not all the products for which the Authority issued a final regulatory decision.

In conclusion, although MCAZ has an established and functional marketing authorisation system, the regulatory performance in terms of approval metrics compared to other mostly well-resourced regulatory authorities is low, i.e., the length of the registration process is relatively long and this could be improved by the efficient use of the existing pathways of reliance (verification), abridged reviews and work-sharing to remove duplication of work and maximise the existing resources in a risk-based approach. Lastly, information on key performance metrics such as the actual processing time divided by type of submission, therapeutic field, regulatory route, positive and negative outcomes, time, and resources spent should be routinely published to increase transparency and accountability.

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CHAPTER 3.2

Collaborative Process in Medicines Registration to Improve Access to Medicines in Southern African Countries

submitted

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ABSTRACT

Harmonisation of requirements, collaboration and information sharing between regulatory authorities, particularly in low- and middle-income countries (LMICs) is the most resource–efficient strategy to ensure access to medicines. To this end, this paper presents a collaborative initiative among four countries Zambia, Zimbabwe, Botswana and Namibia (ZAZIBONA) as a case model for collaboration in medicines registration.

The following analytical framework: (1) phase analysis, which reviewed the evolution of the collaborative process, (2) the Bergen model for collaborative functioning, a theoretical framework for collaborative initiatives to analyse the key success factors, and lastly (3) a theoretical framework for sustainability of collaborative initiatives was employed in the analysis. The data for the collaborative model were collected from documents from 2013 to 2015 and analysed using both emergent-inductive and theory-directed approaches.

The ZAZIBONA initiative is in its 3rd year of operation and in the second phase of its implementation since its formation in mid-2013 and has established operational structures and procedures. The identified key success factors include ownership, effective leadership, partner resources, including co-financing, cost efficient model, social capital, clear roles and structure, effective communication, and demonstrable results. Although the model addresses most of the factors that ensures sustainability, some issues such as a monitoring and evaluation framework, committed funding, and institutionalization are required for long term sustainability. Out of the 85 products that were considered in this 2.5-year period, 32 received positive opinion, 15 received a negative opinion, 10 were withdrawn by the applicants, 25 were waiting for responses from the manufacturers and 3 were still under review. The median time for a final recommendation was 10 months (range 5 – 23 months) inclusive of manufacturer time to respond to queries.

Collaboration in assessments and inspections, among LMICs is feasible and a resource-efficient strategy to mitigate against the regulatory capacity limitations in those settings.

INTRODUCTION

The Southern African Development Community (SADC), a regional economic community of 15 countries (Angola, Botswana, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, United Republic of Tanzania, Zambia, and Zimbabwe) has a combined population of 277 million people [1]. On one hand, it is one of the regions with the highest disease burden, e.g., highest average HIV prevalence at 12.6% [1], and 5 of the 22 tuberculosis high-burden countries (Democratic Republic of Congo, Mozambique, South Africa, United Republic of Tanzania, and Zimbabwe) are within the region [2]. On the other hand, the regulatory systems vary from almost non-existing systems that do not ensure that marketed medicines are of acceptable quality, to established systems that may become a barrier due to limited capacity [3].

Harmonisation of regulatory requirements, collaboration and information sharing is one strategy to leverage on the existing resources in the region to improve access to medicines by reducing the registration time, eliminating unnecessary duplication, managing the increasing workload and complexity of scientific issues. To this end, NMRAs in Zambia, Zimbabwe, Botswana, and Namibia (acronym ZAZIBONA) with support from the WHO Prequalification Team-medicines (WHO-PQT-m) decided to cooperate in the assessment of applications for registration of medicines and inspection of product manufacturers for compliance with good manufacturing practice (GMP).

The ZAZIBONA collaborative model is outcome oriented not only in terms of accelerated approvals for applications for registration but also quality of the approved products. The goal of this initiative is (a) availability of quality medicines in the region; (b) reasonable (by industry standards) processing times to grant grant marketing authorisation in the individual countries; and (c) efficient use of resources through work sharing. The specific objectives are to (i) reduce regulatory workload, (ii) accelerate registrations of selected products, (iii) develop mutual confidence in regulatory collaboration, (iv) demonstrate a mechanism of technical cooperation among NMRAs for potential use by others, and (v) provide a platform for capacity building, and collaboration among NMRAs in other regulatory fields.

Eligibility of products for ZAZIBONA process

Generally, essential medicines are accepted under the ZAZIBONA collaborative process. Priority is given to treatments for the 10 priority disease conditions identified by SADC, which are HIV and AIDS, tuberculosis, malaria, acute respiratory infections, diarrhoea, diabetes, cardiovascular, cancer, gastroenteritis and colic, and obstetrics. Products for reproductive health are also included on the priority list as well as those products included in the list of the United Nations (UN) Commission for Live-Saving Commodities for Women and Children [4]. Other medicines that are important from a public health perspective are considered on a case-by-case basis. Products registered by International Council for Harmonisation (ICH) countries are eligible for an abridged review process provided there is access to the assessment reports on which the authorisation was based on and the sameness of product and the dossier can be verified.

This paper presents the framework for collaborative initiatives with special emphasis on the way it is applied in ZAZIBONA, i.e., the components within which collaboration among countries function. First, we review and discuss briefly the theoretical framework for collaborative initiatives, and later describe the ZAZIBONA model of collaboration. Finally, empirical results from the initiative, including achievements, challenges, and potential future directions, are discussed.

METHODS

Data collection

Documents spanning the period from the first assessors' meeting in October 2013 to December 2015 were analysed. The data for the ZAZIBONA collaborative process in medicines registration were analysed using both emergent-inductive and theory-directed approaches. The data were collected from meeting records of the assessors, inspectors and Heads of Agencies (HoA) meetings, excel database of all the applications and their progressive status in the collaborative process and at national level as well as reports on the secured shared network platform.

Processing time was calculated as the period from the date of the initial selection of the product for the collaboration to the date of the assessment meeting at which a final recommendation was made. This

time excludes the elapsed time period from the date of submission to the NMRAs by the applicant to the date of selection for the ZAZIBONA assessment and the post recommendation administrative procedures at national level. The processing time is the total time taken by ZAZIBONA and the applicant to respond to queries.

Analytical framework for a collaborative model for regulatory authorities

There is an increasing need and preference for consortiums, collaborations, partnerships or coalitions among organisations and communities in addressing society's challenges. Various terms have been used in literature to describe this process of coming together such as partnership, alliances, collaboration and teamwork, with inconsistent definitions, sometimes interchangeable [5] or used together, as in the term collaborative partnerships [6]. Multifarious strategies are used to achieve this, which includes networking, coordinating, cooperating and collaborating. Collaboration is viewed as being at the end of the development continuum in this process, as it involves sharing of power, resources and activities for mutual benefit, thus requiring the highest levels of trust, significant investment of time, and ownership [7].

In this paper, collaboration is defined as a process that enables independent individuals and organisations to combine their human and material resources so they can accomplish objectives that are difficult to bring about alone [8]. Collaborative processes are usually built on a voluntary basis and premised on mutual respect, common goals and perceived benefits. In addition, there should be a sense of equality, either in identity, function or in resources contributed to the partnership [6, 9, 10].

Synergy is identified as one of the key benefits of collaborations [11]. It is broadly defined as the extent to which the involvement/contribution of manifold partners improves the ability of the partners to be creative, holistic, realistic, take action, be accountable, respect stakeholders' needs and obtain community support [8, 12]. The other relevant benefit of collaboration is that by combining the individual perspectives, resources, and skills of the partners, the group creates something new and valuable together, 'a whole that is greater than the sum of its individual parts' [8, 11, 13]. Above all these, leadership effectiveness and partnership efficiency are most closely correlated with the achievement of partnership

synergy [11]. These benefits of collaboration, for example synergy, depend on the processes and the way the collaboration functions.

Key success factors have been identified in literature to ensure that the collaboration function effectively. For instance, the impetus for the collaboration should come from within the community to solve a common problem [14, 15]. This will ensure community ownership in terms of determining the vision and mission of the collaboration [10, 14]. Within the collaboration, there should be relations based on mutual trust and respect [16], role clarity and designated responsibilities [10], professional efficacy [12], good communication and formalisation of the status of the relationship [6, 17] and sufficient power distribution [10, 18]. Collaborative capacity is also crucial for the success of any partnership [9]. The individual members within the collaboration should have the capacity to perform the needed tasks and work together within the group.

The analytical framework used for this study includes three parts as follows: (1) phase analysis, which reviewed the evolution of the collaborative process and provides a context, (2) the Bergen model for collaborative functioning, a theoretical framework for collaborative initiatives to analyse the key success factors, and lastly (3) a theoretical framework for sustainability of collaborative initiatives, which was employed to evaluate the sustainability of this initiative.

Phase Analysis

Collaborative initiatives are dynamic, thus evolve with time [13]. Three distinct stages of collaboration can be identified from literature, which are (1) formation, (2) implementation, and (3) maintenance (Figure 1). Taylor-Powell et al 1998 describes these stages as form and focus (getting started), organize and act (enroute) and achieve and transform (arrived) [13]. It is imperative to contextualise collaborative initiatives in light of their stage of development.

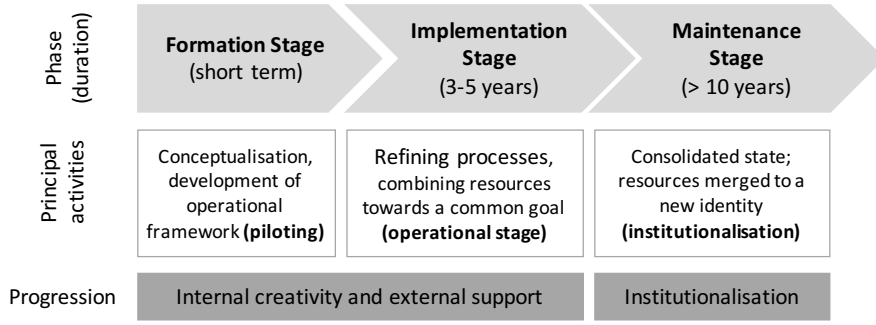

Figure 1: Phases of development of a collaborative model adapted from Taylor-Powell 1998 [13] and de-Graft Aikins et al 2012

The formation stage is generally of short duration e.g., months to less than 2 years, and can be considered the pilot phase when the collaboration is in its formative stage. At the implementation or operational phase, which generally last about 3 to 5 years, processes are refined and resources combined towards a common goal [16]. The last stage may take several years e.g., more than 10 years depending on the nature of the collaboration and the context. At this maintenance stage, the collaborative activities include developing the collective capacity to sustain the efforts, institutionalisation, and integrating functions into the collaborating organisations [13, 16].

From the formation to implementation, the collaboration is mainly driven by internal creativity and external support, but at the maintenance stage the initiative is driven by the institutionalisation. From an evaluation perspective the key focus on each development phase is feasibility at the formation stage, in other words can this actually work? Partner representation and competence as well as structures and processes are the consequential evaluation elements at the implementation stage. Lastly, impact and sustainability is the focus at the maintenance stage [13].

A theoretical framework for collaborative initiatives

The functional processes of the ZAZIBONA initiative were analysed using the Bergen model of collaborative functioning (Figure 2) as described by Corbin and Mittelmark (2008) [12], which focuses on the inputs, throughput and outputs of the collaboration.

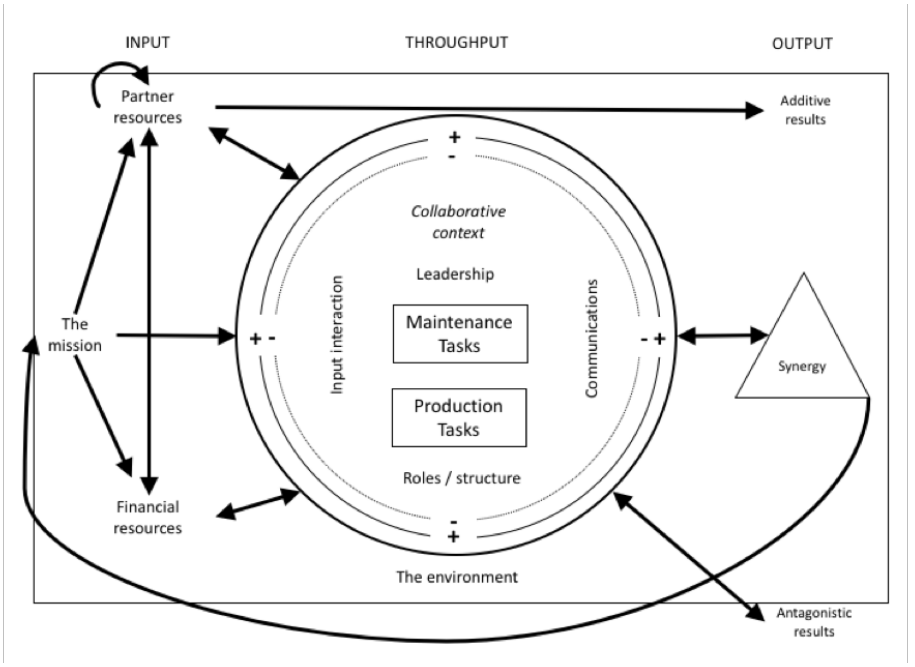

Figure 2: Bergen Model of collaborative functioning adapted from Corbin and Mittelmark 2008

Theoretical framework for sustainability of collaborations

Sustainability is defined as the long term ability to mobilise and allocate sufficient and appropriate resources for activities that meet individual or public health needs [19]. In the development sector sustainability is defined as the ability of a project or programme to continue to deliver after the ceasing of, or with minimal external input (technical, managerial and financial) [19, 20]. Figure 3 shows the conceptual framework for analysing the sustainability of collaborative models, adapted from the open system model for analysing sustainability of health services (Olsen, 1998; Shigayeva and Coker, 2015). In this context resources or inputs refer to human, technology, information and finances.

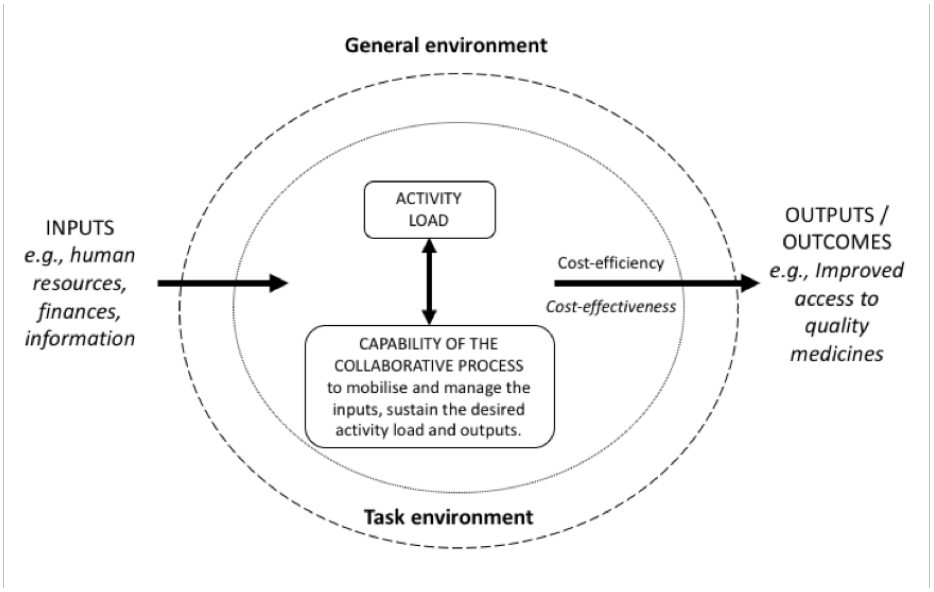

Figure 3: Framework of analysis for sustainability of collaborative models adapted from Olsen 1998 and Shigayeva 2014. NMRA – national medicines regulatory authority. The actors refer to institutional or individual role, interests or influences and aspects of the NMRA system include governance, financing, service delivery and monitoring and evaluation. The capability of collaboration is determined by structure, culture and processes. This is assessed at 5 levels: (a) leadership, (b) capacity, (c) interactions with other regulatory system components, (d) flexibility and adaptability and (e) performance. The activity load is determined by the purpose and technology. Outputs may include; (i) # of products approved, (ii) decrease in the time to approval, (iii) % reduction in duplication, (iv) quality of decision making.

RESULTS

Phase Analysis

The evolution of ZAZIBONA is shown in Table 1. This collaborative medicines registration process was initiated by the WHO PQT-m in consultation with the HoA of the four NMRAs who expressed interest to be involved in the pilot phase. ZAZIBONA's pilot phase was from mid-2013 to end of 2014 (1.5 years). The principal activities in the pilot phase were exploring interests, conceptualisation of the goals and objectives, selection of partners, developing the operational framework of the collaboration, i.e., working procedures, guidelines, building relationships and understanding, and initial structure, similar to what is described elsewhere in this phase [13, 16].

Table 1: Summary of the evolution of the ZAZIBONA collaborative process for medicines registration

Period	2013 – 2014	2015
Phase	Pilot phase (1.5 years)	Implementation phase
Participants	Botswana, Namibia, Zambia & Zimbabwe	Expand to include other interested SADC Member State
Technical Support	WHO PQ	WHO PQ
Expenditure	(USD) 431,940.00	(USD) 357, 540.00
Funding	SARPAM, WHO PQ, UNFPA	WHO PQ, NMRAs
Milestones	First assessors meeting, Oct 2013, Windhoek, Namibia First Heads of Agencies (HoA) meeting, Dec 2013, Johannesburg, South Africa First good manufacturing practice (GMP) joint inspection, Dec 2014, India	Decisions by the SADC Ministers of Health and Ministers Responsible for HIV and AIDS: Official recognition and endorsement, January 2015 Approval of the terms of reference for the collaboration, November 2015
Achievements / results	Five assessment sessions held during the pilot phase 1 inspection planning meeting 2 FPP manufacturers inspected jointly 48 products considered under ZAZIBONA (7 received positive recommendation; 2 received negative recommendation during this period)	Four assessment sessions held in 2015 4 FPP manufacturers inspected jointly 1 good clinical practice (GCP)/ good laboratory practice (GLP) inspection of CRO 54 products considered under ZAZIBONA (25 received positive recommendation; 13 received negative recommendation during this period)

The implementation phase for ZAZIBONA started in January 2015. Principal activities at this `stage are essentially similar to what is described in literature, i.e., creating joint agreements and systems, ensure support of stakeholders, communicating the achievements and progress, expand the interventions and secure resources [13, 16].

The ZAZIBONA Collaborative Process

The external environment

The regional pharmaceutical activities are guided by the Regional Indicative Strategic Development Plan 2005 - 2020, Article 29 of the Protocol on Health (1999) and more specific technical level documents

such as the SADC Pharmaceutical Business Plan 2015 – 2020 and SADC Strategic framework for medicines regulatory affairs 2015 – 2020. Furthermore, the African Medicines Regulatory Harmonization (AMRH) initiative is implementing regional harmonisation activities across the continent [3].

A. INPUT

Based on the Bergen model, the main inputs to the ZAZIBONA process include, financing, human resources, products under assessment as well as the mission of the collaboration, which has already been explained previously.

Partner resources

The participating countries contribute their time, resources and efforts as well as commitment to the collaboration. Technical people (assessors and inspectors) from each country contribute to the work of the collaboration, i.e., generating and reviewing assessment reports or performing GMP inspections of manufacturing facilities. The participating NMRAs not only contribute the personnel, but also their time, effort and commitment required for the partnership. Corbin and Mittelmark (2008) summed it up concisely in that 'a partnership is what is it because of the people involved' [12].

Financial resources

The model is relatively cost effective with an annual budget of USD 360,000 based on the current arrangements and membership of four countries. GMP inspections are performed on a cost recovery basis, i.e., manufacturers pay an inspection fee to cover the cost of the inspection. Funding for the pilot phase was mainly from WHO PQT-m and the Southern African Regional Programme on Access to Medicines and Diagnostics (SARPAM). The United Nations Population Fund (UNFPA) co-sponsored one assessment meeting. The WHO PQT-m and the participating countries are providing the financial resources in the implementation phase.

B. THROUGHPUT

The throughput based on the Bergen model for collaborative functioning includes the collaborative context, leadership, roles and structures, communications, interaction of input factors, maintenance and production tasks. This section will start by describing the collaborative process before analysing its functionality using the Bergen model.

The collaborative process

Figure 4 shows the current process flow for the collaboration in medicine registration. To be eligible for the ZAZIBONA collaborative process the same product application should be lodged with at least half of the participating countries, including a written consent by the manufacturer or applicant for a product to be considered in this process. In addition, the manufacturer / applicant should clearly indicate the other countries to which the same submission was made. In this context the same product is defined as: (a) the same product description, (b) formulation, (c) manufactured at the same manufacturing site(s) (for both the active pharmaceutical ingredient, and finished pharmaceutical product), (d) with the same manufacturing process and equipment, (e) packaging, and (f) shelf life conditions or re-test period whichever is applicable [21].

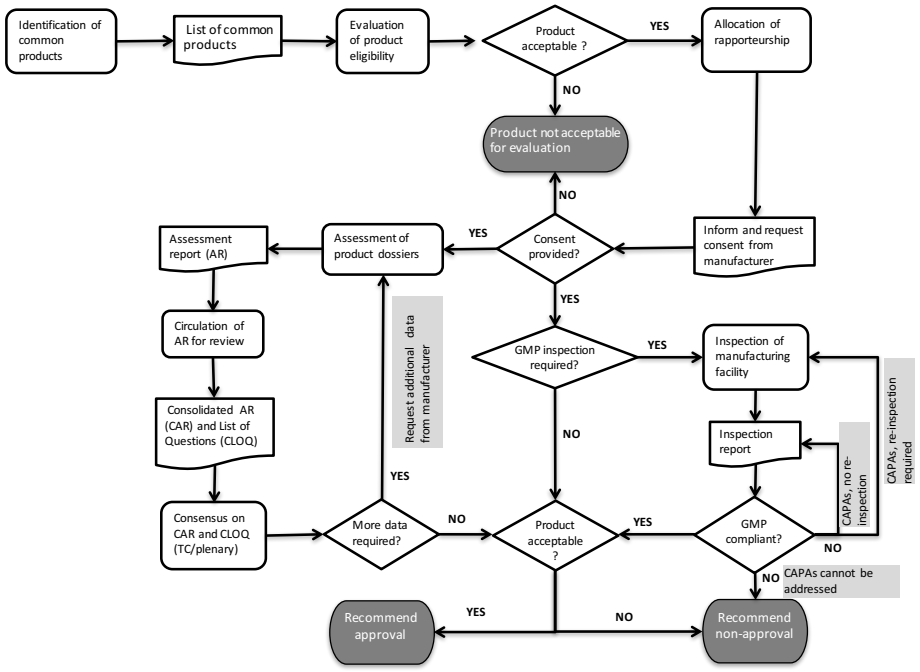

Figure 4: Process flow for the ZAZIBONA collaborative medicines registration process. AR: assessment report; CAR: consolidated assessment report; CLOQ: consolidated list of questions; CAPAs: corrective and preventive action; GMP: good manufacturing practice

There is no central submission process, therefore, all applications must be made to the respective NMRAs following applicable national requirements, e.g., completion of the statutory application forms and

payment of the required application fees. Primary assessments are done in the country within a period of less than 3 months, followed by sharing of the initial reports using a secure electronic interface hosted by WHO, peer review by each participating country and then physical plenary sessions to reach consensus on the assessment reports. The meetings last for 5 days.

Assessment includes chemistry, manufacturing and controls (CMC), safety and efficacy of the product. GMP exemptions are granted to manufacturing facilities that have been confirmed by regulatory authorities from ICH countries or by WHO PQT-m to comply with cGMP or those that are located in ICH regions. For the purposes of collaboration, standardised templates for reports were agreed upon at the start of the collaboration. All the participating countries accept the SADC Common Technical Document (CTD) format, for which Module 2–5 were adopted from ICH. The applicable requirements for ZAZIBONA are described in the SADC registration guidelines that are consistent with WHO guidelines or ICH guidelines where applicable. Bioequivalence is required for all prescription preparations in oral solid dosage forms. Waiver of in-vivo bioequivalence studies are acceptable for BCS class I and III APIs. The reference product should be the innovator product, a WHO recommended comparator or a reference listed drug in an ICH country. The reference product should be procured from an ICH country and documentation to support the country of origin should be provided in the submission.

Collaborative context

The collaborative context describes the circumstances directly related to the collaborative partnership (internal situation within and between or among the partnering organisations). Zambia and Zimbabwe have established autonomous NMRAs, while in Botswana there is a Drugs Regulatory Unit in the Ministry of Health and in Namibia there is a Namibia Medicines Regulatory Council with the Secretariat in the Ministry of Health and Social Services. Botswana is in the process of establishing an autonomous NMRA.

Pre-existing relationship between partners is key to success for partnerships [16]. SADC regulators have a long history of interaction since the 1990s, which created adequate social capital for this partnership and enabled the initiative to overcome the numerous shortcomings at the conceptual stage e.g., differences in technical requirements, assessment practices and formats.

Communications

The communication is based on email, sometimes tele/video conferencing as well as face to face meetings. It is noted that face-to-face meetings offer the best unimpeded exchanges and for building mutual trust and confidence [12]. The assessors have four face-to-face meetings per year, and the HoAs have two face-to-face meetings per year. Furthermore, a secure electronic platform hosted by WHO is used for sharing information, that includes assessment and inspection reports and also acts as a repository for the collaboration. Unlike assessors, inspectors communicate mainly by tele/video conference, and face-to-face meetings occur during the GMP joint inspections. This may partly explain the slow progress with inspections compared to assessments.

Leadership

A sense of ownership is important to the success of partnerships. When leaders share the vision and mission directly with technical people the results are conspicuous. The HoAs are responsible for setting the objectives and agenda for the collaboration. The leadership offers open and direct communication with the assessors through open sessions during the HoA meetings that are held concurrently with the assessors meeting. This offers an opportunity for constant feedback between the technical people and the HoA on successes, challenges and also sharing the expectations.

Roles and structure

The HoA of the participating NMRAs are the decision makers on policy, technical and administrative issues based on recommendations from assessors / inspectors and assure coordination with regional initiatives. NMRAs rotate responsibility for coordinating the specific assessor's meetings, inspection activities and meetings of HoA. The assessors' meetings are held each quarter on a rotational basis in all the four participating countries. The host country act as the coordinating country during that quarter, including chairing the sessions, developing and managing the work plan and programme for that quarter, allocating products to rapporteurs, and follow up, in other words, the host country is responsible and accountable for the work plan and deliverables.

Two coordinators one each for the assessments and inspections were recruited on a part time basis for the general coordination and

maintaining the secure shared electronic database. These were seconded by one of the NMRAs (Zimbabwe), which is also responsible for their remuneration in this role. The WHO PQT-m plays a crucial role not only as a neutral facilitator recognized and accepted by all partners, but also in providing technical support, logistics for the meetings and facilitating capacity building activities. Furthermore, WHO PQT-m performs quality assurance of the assessment outcomes.

All positions are adopted by consensus. Nevertheless, it is important to emphasize that the role of the ZAZIBONA initiative is to make recommendations to NMRAs on the acceptability of an application for registration in terms of quality, safety and efficacy as well as compliance with GMP in the manufacturing process of the product. The final decision on each product remains the responsibility of each NMRA.

OUTPUTS

The outputs or assessment outcomes of this collaborative process are as follows: out of the 85 applications considered for the period 2013 – 2015, 32 (~ 38%) received a positive opinion, 15 (~ 18%) received a negative opinion, 10 (~ 12%) were withdrawn by the applicants after the initial review, and 25 (~ 30%) were waiting for responses from manufacturers and 3 (~4%) were under review. The main reasons for the negative opinion were failure to respond to requests for additional information / incomplete submissions (50%) and bioequivalence related deficiencies (40%). The median time for a positive recommendation was 10.3 months (range 5.1 – 22.9 months) and 12.4 months (range 1.6 – 22.9 months) for a negative opinion. Based on available data from two countries, the median time of the positive recommendation for final approval at the national level was 1.5 months (range 0.2 – 6 months) against a target of 2 months. After considering the country practices with respect to deadlines to respond to questions, i.e., two months in Zimbabwe and Botswana, three months in Namibia and four months in Zambia, it was agreed to use three months for the collaboration. The mean review cycles were 2.5 per product with an estimated average response time of 3 months for manufacturers to respond to queries. This time is included in the total review time for ZAZIBONA.

For the products that received a positive recommendation, 41% were anti-infective, 19% anticonvulsants, 16% cardiovascular, 13%

gastrointestinal, and 6% each for antineoplastic, and immunosuppressive and anti-asthmatic medicine.

According to the Bergen model, the outputs are classified as additive results, synergistic and antagonistic results. Additive results are outcomes that are outside the partnership interaction that have not been affected by the partnership. Antagonistic results are the indirect negative effects of the collaboration and this may have negative feedback to the collaboration. In this context, the number of withdrawals could be antagonistic results that can have a negative perception of the collaboration, e.g., if the applicants withdrew their products because of a potential collective negative opinion perceived to be unlikely if the individual national procedure had been used, this may reduce the number of submissions via this pathway from these applicants. Moreover, in a partnership, the progress is influenced by the weakest link, which can negatively affect the trust and relationships in the collaboration if there are significant disparities between the partners. Lastly, mismatch between the capacity levels and the partnership standards may slow down the overall processing times for some countries. Although the collective targets remain unchanged, work load in the implementation phase is not distributed equally unlike in the pilot phase because of the disparate assessment capacity among the participating NMRAs.

The positive (synergy) outputs from the partnership depends on having measurable goals. To start with, simple goals were agreed upon in the pilot phase, i.e., number of products assessed per year and feasibility of the collaborative registration system. This was set to 32 products by the HoA, which translated to 8 products per quarter or assessment session. The results are presented in Table 1, which shows that in each phase the results surpassed the set targets. The objective in the pilot phase was to strengthen the collaboration and to demonstrate the feasibility of this type of work sharing among regulators notwithstanding the various challenges or differences. Therefore, in this case, the simple goals were sufficient enough for the pilot phase and were easily measurable. Nevertheless, indicators are required for the objectives of the initiative and these should be monitored in the implementation phase. Additional positive outcomes include the complementarity of the individual strengths of the partners and collective resources, e.g., consistent requirements and reviews of bioequivalence data is a monumental achievement considering that not many African countries request bioequivalence

data or have the capacity to assess bioequivalence data, yet most of the applications received in those settings are for generic medicines. The positive outcomes not only motivate the partners, but also generate interest for others to join and for applying a similar model elsewhere.

Perspective on sustainability of ZAZIBONA initiative

Currently, there is loose designations of focal persons and this does not assure accountability for long term sustainability, thus there is a need to formalize the specific roles and responsibilities of focal persons. The initiative is a home grown solution with support from partners to national challenges of ensuring that safe and effective quality medicines are in the market. As an initiative, ZAZIBONA received formal endorsement from SADC Ministers and its terms of reference were officially approved, giving the initiative legitimacy and formalisation to pursue other activities that could not be possible, for instance, having information in the public domain or the publishing of expressions of interests for submission of applications by interested manufacturers.

Human resources are not defined in terms of specific competences and this is something that needs to be specified and ensured, in other words who should participate in the assessments? Can a partner assign a novice for the partnership work or only people meeting a set of competency requirements should be assigned responsibilities for the partnership work? There is risk of fatigue if there is no systematic approach to capacity building with measurable outcomes, i.e., acquired competencies among the participants from the NMRAs. Although the model is relatively cost efficient and NMRAs commit to provide partial funding, external funding is still required to support the partnership. Although at this moment this is not considered a threat, there is no confirmed external funding from 2017 onwards.

From this adapted open system model, collaboration is sustainable if it has the capacity to initiate the desired change (ownership), flexible enough to adapt to the changes in the environment and manage the available resources to produce results in the most-resource-efficient manner while maintaining adequate performance levels (quality). Ownership is therefore present.

At this moment, the model is able to sustain the activity load, however, if the long term intention is to increase, the model has to be

modified to ensure that the capability matches the activity load. Furthermore, as the process is becoming well known and applicants are starting to submit applications through this process, the modus operandi should be flexible to respond to the changing workload. For example, with the present model, reviewing 8 new applications per session appears to be a reasonable workload, extending beyond this number may require re-engineering the collaborative process and in-country processes as well. Presently, the assessment model appears to be heavily reliant on WHO PQT-m for technical support, facilitation and quality assurance of the assessment outcomes; sufficient capacity within the participating NMRAs should be ensured such that progressively this role should be internalized.

Lastly, the sustainability model also considers the ability of the initiative to deliver on the expected output/outcomes. As noted earlier, clear indicators to measure the attainability of the partnership goals is imperative and this is neither clearly defined nor routinely measured due to the absence of a clear monitoring and evaluation framework. The main goal is to improve access to quality medicines in the region. How is this going to be measured? Is it a realistic goal considering that maybe the initiative only covers a portion of the registration work load encountered by the NMRAs? A robust information management system is required to ensure that data are easily collected and reported on the performance of the initiative. Failure to have clear indicators or measures of achievement of the intended results are some of the reasons for failure of partnerships. In the implementation phase going forward, feasibility and practicality are no longer the outcomes, but the demonstration of the achievement of the mission, or vision of the collaboration is important. Nothing has been done to measure the achievement of the overall goal of improving access to quality medicines. However, indications are positive with 32 products having received a positive recommendation in less than 12 months (median total time) and subsequently registered at the national level. Although this shows synergy, it should be considered/measured in the future to ascertain the real value of the collaboration.

DISCUSSION

To our knowledge this is the first publication describing a collaborative model in LMICs to accelerate access to medicines through work

sharing in assessments and inspections of manufacturing facilities for the registration of medicines. Despite the heterogeneity in the regulatory systems, practices and standards, this paper demonstrates that collaboration among regulatory agencies is a resource-efficient approach to address the inadequate regulatory capacity in LMICs. Moreover, not only was the model outcome oriented, i.e., focusing on actual assessment and inspections of submitted product dossiers, but also facilitated the implementation of good regulatory practices e.g., adoption of harmonized guidelines at the national level and good review practices, and capacity building for regulatory agencies in those settings.

There is growing interest on options for approval of new medicines that specifically target endemic diseases in Africa given the shortcomings of the African regulatory systems and the limitations of the current mechanisms such as approvals from ICH countries, WHO prequalification scheme [22], US FDA tentative approval programme, or the EMA Article 58 [23–26]. There is advocacy for more Afrocentric approaches, including proposals for a Pan-African regulatory system. ZAZIBONA could be one such initiative among African regulators in medicine registration. Although the collaborative initiative was established to address the immediate need of reducing backlogs mainly for generic products, this model can be expanded to include reviews of new medicines for diseases that are endemic to Africa as well as recognition of products approved by other authorities applying similar or higher requirements.

Collaborative models have been successfully used elsewhere, mainly the EU model that allows a centralized registration process and immediate access to all the EU countries and the decentralized procedure that facilitates mutual recognition. In contrast to the EU system, the ZAZIBONA collaborative process only makes recommendations, while the final decision on national registration is a national responsibility (countries retain their autonomy to make the final decision in their national best interest). This permits the implementation of such an arrangement without going through the onerous process of updating legislation, which is unpredictable and could take years to be approved. Moreover, binding decisions would require a mechanism of arbitration similar to the EU to resolve divergent views, thus, at this stage, the current framework is preferable as it involves minimal cost/effort and is less disruptive.

ZAZIBONA already assumed a recognized identity and the acronym has been adopted even with the prospect of expansion to include other countries. In the absence of specific funding, it is prudent for the NMRAs to have a budget in two parts, core and strategic budget; the core budget is funding for the key activities, i.e., assessment meetings and HoA meetings and NMRAs could factor this cost in their own budgets; funding from financing partners may be used if available to support those who may not have the ability to self-finance e.g., observers. A strategic budget should address the specific issues for the development of the collaboration, such as an electronic platform for submissions, assessments and information sharing that is interactive to facilitate the assessment process, video conferencing, and online trainings. These are essential elements for efficiency and effectiveness. This two-part budgeting will ensure sustainability of the collaboration beyond the lifespan of the donor or partner funding programmes.

Although the benefits of collaboration are notable, collaboration is not always the appropriate problem solving approach. Measuring the outcomes or results of collaboration as well as efficiency and effectiveness of achieving those and compared with say individual authorisations or those approvals based on other mechanisms is imperative for comparison purposes to objectively evaluate the benefits of collaboration. Although the ZAZIBONA initiative has clear goals, there are no corresponding clear indicators to measure these goals other than the number of products assessed as well as processing times for each step. Some of the key information such as the time from recommendation to final decision in the countries is not available or reported for all the countries. Therefore, there is a need for a comprehensive monitoring and evaluation framework for the collaboration in the implementation phase. Lack of clear indicators is cited in literature as one of the causes of failure of collaborative initiatives as it becomes difficult to measure the intended outcomes or benefits; theoretically achieving synergy in collaborations makes sense, but practically there might not be enough evidence gathered to demonstrate otherwise [8].

Collaboration requires relationship building, developing new procedures and structures, different from the way people are used to operating on their own. This can be a source of frustrations at an operational level. A clear threat for ZAZIBONA collaboration is perceived lack of time to devote to the collaboration work as it

appears in some instances, it is viewed as additional work. The people in the partnership can have competing priorities, which makes it difficult to devote time to the work of the collaboration [11]. Thus, to maintain high functional collaboration is a challenge, at least half of the collaborations do not survive their first year, because of the significant time invested, resources consumed and general complexity of such relationships [8]. However, the approach and system for developing the partnership can offset the resource intensive portion if one considers how much resources would have been used in the long term compared to the group effort. Therefore, the ZAZIBONA HoA envisaged a seamless process for work done for the partnership and nationally reviewed and authorised products. Furthermore, this is seen as an opportunity to facilitate future mutual recognition of products approved by countries outside the collaborative mechanism, as one of those group beneficial effects if implemented.

Pre-existing relationships were not similar for assessors and inspectors, as inspectors by the nature of their work had minimal pre-existing interactions among the countries. Further, unlike assessors that meet face to face, inspectors relied on remote communication which is not ideal in the formative years of a collaborative relationship. As such, attributes like social capital, which are important for success of partnerships, were not evident at a technical level for inspectors compared to assessors, thus differences become pronounced and affect progress. Leadership is a critical success factor, if not handled well it is also one of the major reasons for failure of partnerships. For example, a failure to devolve power to the group can affect the partnership due to lack of trust [10]. Considering the difficulties involved in maintaining collaborations, it is likely that many partnerships do not achieve high levels of synergy [13]. The significant influence of partners or funders or even external organisations or people may result in lack of ownership and hence negatively affect the long term survival of the collaboration [8].

The matter of processing time and collaboration is may be seen as an industry interest, i.e. access to bigger pharmaceutical markets and a reduction in their workload. This may not truly translate into public benefits. Notwithstanding this, it is envisaged that reduced costs on the part of the manufacturers would eventually be passed on to consumers. Effectiveness of the system would benefit patients by keeping potentially harmful medicines and poor quality medicines from the market. Already it was observed that manufacturers may opt

out if the potential opportunity for a wider market may result in loss of the whole market, 10 products have been withdrawn after the initial review due to the high probability of negative opinion based on the shortcomings from the initial assessment.

Conclusion

This paper describes a functioning model for collaboration in medicines registration among four LMICs as a mechanism to overcome some of the prevailing challenges for regulators. It is noted that it is not adequate to have processes only, but also collaboration requires accountability, responsibility and consequences. This can only be achieved through formal roles and possibly some sort of institutionalization.

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CHAPTER 4

REGULATORY PERSPECTIVES ON GLOBAL HARMONIZATION OF BIOEQUIVALENCE STUDIES

CHAPTER 4.1

Global Harmonization of Comparator Products for Bioequivalence Studies

Submitted

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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) recommendations for selecting comparator products and require the comparator product to be obtained from their national markets to ensure switchability between the local comparator and their generics. These recommendations are only feasible in the few countries where the repetition of the bioequivalence study is profitable, but they are impracticable in all other countries. Furthermore, the exclusive use of the local comparator to ensure switchability is ethically and scientifically questionable. The innovator product from well-regulated markets should be the global comparator. This harmonisation is feasible as the concept already applies in the WHO prequalification programme. It is ineffectual to harmonize only the requirements for performing bioequivalence studies, if such a study has to be repeated for every single country simply because of the different comparator product.

INTRODUCTION

An innovator product demonstrates efficacy and safety through the preclinical and clinical development, whereas generic medicines, which are marketed after the expiry of the patent and other market exclusivity rights of the innovator product, only have to show equivalence to the innovator product. Accordingly, the World Health Organization (WHO) recommends the approval of generic medicines by the national medicine regulatory authorities (NMRA) based on demonstration of interchangeability with the innovator product through bioequivalence studies [1], since bioequivalence is accepted as a surrogate for equivalent safety and efficacy.

Interchangeability implies that the generic medicine can be prescribed in place of the innovator product in a new/naïve patient under the same conditions (prescribability) [2, 3], and it can also be substituted in place of the innovator product in patients under chronic treatment (switchability) [4, 5]. Additionally, demonstration of bioequivalence of all generics with the same innovator product is considered to be an indirect demonstration of switchability between the generics [6]. Then, generic medicines become important in public health programmes because they reduce the cost of medicines providing the same level of efficacy and safety as the innovator or comparator product.

Harmonisation of bioequivalence requirements though incomplete, has yielded significant benefits to both industry and regulators. Nonetheless, there is need for complete harmonisation [7] because it is ineffectual to harmonise only the requirements for performing bioequivalence studies if such a study has to be repeated for every single country simply because of the different local comparator product. Presently, each NMRA identifies the comparator product to be used as reference in the bioequivalence studies of the generics for their market, as this is recognised as a national responsibility [8]. Consequently, the choice of the appropriate comparator for a generic manufacturer intending to market in several countries may be confusing, because the selection criteria may be heterogonous between jurisdictions, necessitating multiple studies to demonstrate bioequivalence to the different national comparators. This is further complicated when different innovator products or different dosage forms of the same innovator are available in different markets. Nonetheless, considering the globalisation of the pharmaceutical

industry, it could be considered unreasonable to perform several bioequivalence studies due to differences in the local comparator.

The aims of this paper are to comment on the current recommendations and practices on the selection of an appropriate comparator product, the problems associated with the selection and the possibility of a global or regional harmonisation to use a common comparator product.

WHO recommendations to national medicine regulatory authorities (NMRAs) on selection of a comparator product

The comparator product is defined by the WHO as a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The WHO provides recommendations to national regulatory authorities on how to select an appropriate comparator product [8]. Briefly, in order of priority, the WHO recommended comparator product should be: (i) an innovator product available on the local market, (ii) national market leader product for which a national marketing authorization has been granted, (iii) a WHO comparator product, (iv) an innovator product imported from an ICH country, and lastly, (v) a product that has been granted approval in an ICH country. In some cases, where the innovator has never been available in that market and bioequivalence was never required, the national market leader may not have a direct link to the innovator product in terms of safety and efficacy. The WHO recommends that only when there is no innovator in the local market, should a foreign reference be accepted: first the innovator identified by WHO (iii), and if this selection has not been done by WHO, then, an innovator from a well-regulated market (i.e., ICH countries) (iv) and, finally, if an innovator cannot be identified all over the world because the drug is very old, another product from a well-regulated country (v).

Although it is desirable to select the innovator product available on the local market as a comparator product to ensure switchability between the products on the market, this policy complicates harmonization because the innovator may differ in different countries or may not be marketed in some countries, in which case, the regulator selects the market leader which is different from the innovator product. In any case, the WHO recommends that a generic product should not be used as a comparator as long as an innovator

pharmaceutical product is available [8], because this could lead progressively to less similarity between the systemic exposure that has shown to be safe and efficacious by the innovator (or the systemic exposure of other existing generics) and that of any future generic product that is approved by comparisons to the generic selected as the new comparator. This is called "*biocreep*". If the future generics were not bioequivalent to the systemic exposure that was shown to be safe and efficacious, the prescribability of the new generics would be compromised, and if the future generics were not equivalent to the existing generics that showed to be bioequivalent to the innovator, their switchability would be compromised.

United States requirements for comparator product

The United States Food and Drug Administration (US FDA) publishes in the Orange Book [9,10] the list of products considered to be comparator products for the US market. These comparator products are called Reference Listed Drugs (RLD). Importantly, these reference products have to be obtained from the US market for bioequivalence studies to be considered valid in abbreviated applications for generic products. If the innovator product is withdrawn from the market, one of the existing generics is selected as the new RLD and identified as such in the Orange Book. Further, the generic products that are considered equivalent to the RLD are identified in the US FDA's Orange Book, informing healthcare professionals on products that are switchable in clinical practice.

In order to ensure switchability with the local comparator (RLD) and between the generics of the US market, the use of foreign comparator is not accepted even if the product is marketed by the same company under the same trade name in another ICH country because the US FDA does not know if the foreign comparator complies with the same requirements as its RLD. Despite the existence of confidentiality agreements with other ICH countries to share information, the information required to guarantee that the foreign comparator complies with the same standards and requirements of the RLD (e.g., qualitative and quantitative composition, manufacturing process, manufacturing plant and specifications) is considered a commercial trade secret of the innovator company and this type of information is not shared with other ICH countries. As long as this policy / legislation is maintained, harmonisation with US FDA to accept a common foreign comparator is impossible.

European Union requirements for comparator product

A comparator product (reference medicinal product) in the European Union (EU) is defined as a product for which marketing authorisation is or has been granted based on a submission of complete dossier, i.e., containing pre-clinical and clinical data to demonstrate safety and efficacy of the product [11]. However, the legal basis includes the innovator products as well as mixed-applications where the demonstration of safety and efficacy is proven with that product's own experimental data and literature data. This type of development is particularly useful when demonstration of some level of efficacy and safety is easier than demonstration of equivalence to the innovator product (e.g., when equivalence cannot be shown by means of pharmacokinetic studies and therapeutic equivalence requires the use of clinical endpoints). Furthermore, bibliographical applications that consist only of demonstration of safety and efficacy based on literature data can also be used as reference medicinal products. Finally, some abridged applications called "hybrid" applications can also be considered as reference medicinal products. In conclusion, a large variety of products could be considered as reference medicinal product in the EU. This is further complicated by the use of any of these comparators from any of the Member States of the EU, under the assumption that efficacy and safety (i.e., prescribability) are ensured if the generics are bioequivalent to an already approved product in the EU. This illustrates that the EU legislation does not deal with the switchability of the generic medicines [12], but only with the prescribability of the products. Consequently, the local markets may contain generics of multiple comparators and it is the responsibility of each Member State to inform the healthcare professionals regarding those products that are switchable in clinical practice.

In the case of biosimilars, the EU accepts that some studies (e.g., the phase III therapeutic equivalence trials) can be conducted with a foreign comparator from other ICH countries (e.g., the US), but some studies need to be conducted with the comparator from a EU Member State (e.g., the bioequivalence or comparative bioavailability studies, which are cheaper to duplicate). The same policy could be expanded in the future to complex generics where several studies are necessary (e.g., inhalation products) and, hopefully, to conventional generics since in some cases several bioequivalence studies are required (e.g., modified release products).

Canada requirements for comparator product

Health Canada defines a comparator (reference) product as the innovator product marketed in Canada that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable bioavailability characteristics [13]. In addition, the reference product for the first market entry should be the formulation used in the pivotal clinical trials. For the generic products, considering the increasing globalization of the pharmaceutical industry, Health Canada accepts bioequivalence studies conducted with a foreign reference product under certain conditions defined in a policy entitled Canadian Reference Product [14]. The use of non-Canadian reference products is limited to conventional, immediate-release solid oral dosage forms, i.e., tablets or capsules, of products containing drug substances that exhibit an aqueous solubility of more than 1%, do not possess a narrow therapeutic range, do not display complicated pharmacokinetics, e.g., non-linear pharmacokinetics, and for which there is no documented evidence of bioavailability problems. In order to be acceptable, the foreign reference product must be approved for marketing by a NMRA recognized by Health Canada as having comparable drug assessment criteria to those in Canada. In addition, it should be marketed in that country by the same innovator company, or corporate entity that currently markets the same medicinal ingredient in the same dosage form in Canada, or that it is marketed in the country of origin through a licensing arrangement with the innovator company, or corporate entity which currently markets the product in Canada. Further, in order to be acceptable, the foreign reference product must be a mono-component product, pharmaceutically equivalent to the reference product marketed in Canada, be the same as the Canadian reference product with respect to descriptive characteristics, e.g., colour, shape, and weight, and produce similar dissolution profiles in at least three media within the physiological range.

South Africa requirements for comparator product

According to the Medicines Control Council (MCC) South Africa, the comparator product should be the innovator product registered in South Africa and should be preferably procured in South Africa [15]. Generic products containing active substances for which the innovator product is not registered in South Africa cannot be registered. In those cases, where the innovator is not marketed in South Africa, but other

medicines containing the same drug are marketed in South Africa, which may occur with "old medicines", a generic product in the South African market may be used as a comparator product [16]. If more than one such product is available, the market leader should be used as a reference. In brief, the comparator product, in order of priority, should be: (i) an innovator product registered and procured in South Africa; (ii) a foreign reference product provided the innovator product is registered in South Africa and the reference used in the bioequivalence studies is approved and procured from countries that MCC aligns itself with (ICH countries) [17]; (iii) product from the latest edition of the WHO international comparator products for equivalent assessment of interchangeability maybe acceptable provided the product is purchased from the stated market; or (iv) in any other case (e.g. market leader), the choice of the reference must be made carefully and must be comprehensively justified by the applicant. Where a foreign comparator product is used, demonstration of equivalence through in vitro dissolution studies in the three physiological media, pH 1.2, pH 4.5 and pH 6.8, and the release media if different, between that comparator product and the corresponding innovator product marketed in South Africa is required.

Requirements for comparator products in Zimbabwe

In contrast to the cases discussed previously, Zimbabwe is a low-income country with a population of about 15 million people and with less than 10 generic local pharmaceutical manufacturers, thus largely depended on foreign imported medicines. Zimbabwe applies the requirements for reference products as specified in the Southern African Development Community (SADC) Guidelines on Bioavailability and Bioequivalence [18]. Briefly, in order of preference, the reference product should be: (1) an innovator product, which is imported from a country with stringent regulatory authority such ICH countries where it has been approved on the basis of clinical data demonstrating safety and efficacy, and is currently registered and marketed in that country, (2) the WHO-recommended comparator product, if applicable, (3) nationally authorised innovator, (4) in any other case, a product selected as comparator should be comprehensively justified based on extensive documented use in clinical trials reported in peer-reviewed scientific journals, and long and unproblematic period of post-market surveillance. Foreign comparator products are acceptable and in fact preferred and should be procured from an ICH country.

WHO Prequalification requirements for comparator products

The WHO Prequalification Team-medicines (WHO PQT-m) deals with comparator product issues not faced by NMRA. Prequalified generic products will be employed in many countries and, therefore, comparators selected by WHO PQT-m must be viable choices for the global market. To aid companies seeking to have their generic products prequalified, WHO PQT-m publishes on their website a list of recommended comparator products and the specific markets from which these products should be obtained for bioequivalence studies intended for submission to the Prequalification of Medicines Programme [19]. In some cases, particularly old molecules, more than one comparator product is listed for a given drug product, e.g., first-line anti-tuberculosis medicines [20]. Usually, the recommended comparator product is the innovator product, which was first authorized for marketing, because its quality, safety and efficacy has been fully assessed and documented in pre-marketing studies and post-marketing monitoring schemes. In these cases, the comparator can be obtained from any ICH country. If not available in ICH countries, WHO PQT-m will select acceptable non-ICH country markets from which the comparator may be purchased. In those cases, where the innovator is no longer available, a product, generally a generic, from countries with stringent regulatory authorities is the preferred comparator product for the WHO PQT-m. The rationale for selecting the comparator from these countries is based on familiarity with the pre- and post-market regulatory systems of those countries and, in addition, the availability of extensive documented safety and efficacy data from post-marketing surveillance. In contrast, this documented evidence is largely unavailable in countries with less established and robust post-marketing surveillance and regulatory systems.

A PATH TO HARMONISATION OF REQUIREMENTS FOR COMPARATOR PRODUCT SELECTION

Generic medicines should be manufactured according to current good manufacturing practice (cGMP) requirements, comply with quality standards, and be interchangeable with the innovator product [1].

Notwithstanding this, it has been recognised that different regulatory requirements is a barrier for information exchange between NMRAs, delays access to medicines due to the lead-time to meet different country requirements, and is costly to the industry, which subsequently passes the cost to the patients [21, 22]. Thus, coupled with the globalised nature of the pharmaceutical industry, harmonisation of the requirements for the development of medicines across regions and countries is the most resource-efficient manner to ensure that safe, effective and high quality medicines are developed and registered [22, 23]. Looking specifically at the comparator product harmonisation, the most expedient approach may be to take advantage of the existing harmonisation efforts and include comparators in their scope.

The most notable harmonisation initiative is the ICH established in 1990 [24], driven initially by the EU, Japan and the US with Canada, Switzerland, and the WHO as observers and the associations of the innovative pharmaceutical industry: European Federation of Pharmaceutical Industries and Associations, Pharmaceutical Research and Manufacturers of America and Japan Pharmaceutical Manufacturers Association. ICH has changed recently to expand its membership to other countries beyond the current ICH members with the possibility of including other pharmaceutical sectors like the generic pharmaceutical industry to harmonise also the field of bioequivalence.

In the context of regional harmonisation efforts (e.g., the EU), it may be advantageous to establish a regional comparator product, for which quality, safety and efficacy has been established (i.e., the innovator product from the different countries is considered to be the same because its approval is based on the same documentation proving efficacy and safety and, therefore, acceptable in all countries), in order to facilitate the development of generic medicines and increase access to medicines.

There are already existing regional initiatives such as the Association of Southeast Asian Countries (ASEAN) Pharmaceutical Product Working Group whose goal is to harmonise pharmaceutical regulations in the ASEAN region [25]. Activities of an association such as this could include identification of regional comparator products. Another example can be found in the Americas, where the Pan American Network for Drug Regulatory Harmonisation (PANDRH) was

established in 1999 to promote harmonisation of scientific and regulatory requirements for registration of pharmaceutical products, and to enhance technical cooperation in drug registration within the region [25].

Another regional approach was taken by the Gulf States when they formed the Gulf Central Committee for Drug Registration (GCC-DR) in 2009 with a mission of providing safe and effective medications with reasonable price through group purchasing and harmonisation of the process and requirements for drug and company registration within the region [25].

The African Medicines Regulatory Harmonisation (AMRH) Programme works with African counties through the regional economic communities (RECs) to increase access to essential medicines by building effective medicines regulatory systems through harmonisation and regulatory capacity building [26]. This programme represents another already existing body that could investigate the possibility of adoption regional comparators for demonstration of interchangeability.

The International Generic Drug Regulators Programme (IGDRP) was created as a pilot from 2012 – 2014 and has since evolved into a programme to promote collaboration and convergence in generic drug regulatory programs in order to address the challenges posed by increasing workloads, globalization and complexity of scientific issues [27]. To this end, an Active Substance Master Files/Drug Master File (ASMF/DMF) working group and a Biowaivers working group have been created within this programme to find commonalities in approach among members. In addition, interested IGDRP members (for example, Australia, Canada, and Switzerland) could be observers in the EU Decentralised and Centralised procedures for generic medicines if agreed by the Applicant in order to reach a common assessment. The objective of the information sharing pilot for the evaluation of generic drug applications is to provide a more efficient and consistent review process, while at the same time reducing regulatory burden and facilitating similar timing of market authorisations across jurisdictions. Other members of the IGDRP include Brazil, China, Japan, Korea, Mexico, New Zealand, Russia, Singapore, South Africa, and the US. The WHO and the European Directorate for the Quality of Medicines and Healthcare are observers in this programme.

DISCUSSION

Ideally, globally accepted comparator products would decrease the number of *in vivo* bioequivalence studies, avoid unnecessary drug exposure to humans, and reduce the cost of generic drug development. Therefore, the logical first harmonization step should be the acceptability of foreign or international comparator products. Moreover, there is little knowledge gained by repeating exactly the same design for each individual country where the generic company desires to market its product.

Harmonisation of the comparator would allow for more in-depth studies about a generic-comparator relationship, by asking for additional types of studies if necessary, e.g., fasting and fed studies, with different strengths [28], or in patients under real conditions of use [29] without increases in costs because generic companies have to do many studies as the situation stands now. So, better generics would result from this harmonisation because they could demonstrate bioequivalence to the comparator under more diverse conditions.

Countries with large pharmaceutical market sizes may be able to enforce the requirement for local comparators in bioequivalence studies that have to be submitted for the approval of generic medicines. The US, Europe and Japan account for more than two-thirds of the over US$ 1 trillion global pharmaceutical market [30]. Therefore, from a business point of view, repetition of bioequivalence studies with a local comparator product may be justified in these cases. At most, this will mean a limited number of bioequivalence studies using the US, European and Japanese comparator products. On the contrary, for low-and middle-income countries (LMICs) with relatively small market sizes enforcing procurement of the comparator product from their local markets is impractical because that would reduce the access to medicines by reducing the number of generics and by increasing their cost. For instance, Sub-Saharan Africa has 47 countries and accounts for less than 0.6% of the global pharmaceutical market [31]. Then, each country insisting on bioequivalence studies with the local comparator products from their national markets, or even with a national market leader, is illogical. Furthermore, it is unreasonable to expect a manufacturer to perform these repetitive bioequivalence studies for each country they intend to market their products. The countries that require the exclusive use of the local comparator argue that this is necessary to ensure the

switchability of the generics with the innovator in their market, under the suspicion that the foreign comparator may exhibit a different bioavailability to that of the local comparator. In order to address this problem, we identify some possible scenarios or cases.

Case 1: The easiest case is where a global pharmaceutical company develops an innovator product that is marketed around the world, mainly for the biggest markets of the US and the EU. Ideally, this pharmaceutical company should identify the markets where the product is most similar to the "clinical batches" shown to be safe and efficacious in the pivotal phase III trials (e.g., the same or most similar formula, specifications, manufacturing site and process). Theoretically, this company should identify all markets as similar, because even if the product is manufactured in different sites with minor differences, the product should be similar in order to extrapolate the phase III trial conclusions to all local markets. If not, this implies that in the other markets the product is not as similar as it should be, since in all those markets it has been approved based on the same clinical development.

From the regulatory authority point of view, the NMRA that requires the exclusive use of a local comparator is acknowledging that their local comparator perhaps has a different efficacy or safety profile than the one marketed in the US or the EU. Consequently, the future generics will be switchable with the local comparator that is possibly not prescribable with the same benefit - risk relationship as the comparator in the US or the EU. Moreover, if the rationale for the exclusive use of a local comparator is to ensure switchability, the variations that may exist between the foreign and local comparator product could be of the same magnitude as the post-approval variations made by the innovator on the formulation, specifications, manufacturing site or process of the comparator. However, when the innovator makes such post–approval variations, the approved generics are neither withdrawn from the market nor required to re-demonstrate equivalence with this changed comparator product. Therefore, switchability does not seem to be the real cause of using exclusively a local comparator, but perhaps it is more related to national protectionism.

Case 2: In cases where the local comparator is a national market leader because the innovator product has never been available in that national market and bioequivalence with the innovator was never

demonstrated or required at the time of approval, it is arbitrary to require the other generics to have a bioavailability similar to that of a product approved based on bibliographical references. On the contrary, the local market leader should have been demonstrated to be bioequivalent to the foreign reference product that has shown safety and efficacy. If this was not required at the time of approval, it should be required as soon as possible. Consequently, the local market leader would be approved as a generic of the foreign innovator and this should be the strategy to be followed in those countries where the innovator is not marketed.

Even in those cases where the innovator is only available in a country without a stringent regulatory system, this foreign comparator seems to be the best and only option to link with the efficacy and safety phase III trials.

Case 3: In cases where the local comparator is a national market leader because the innovator product was withdrawn after the approval of the first generics and the regulatory authority selected one of the local generics as the new comparator, we must take into account that the foreign innovator from a well-regulated country is more related to biobatches that demonstrated efficacy and safety, i.e., prescribability, than any local generic. From a switchability point of view, both the local generic and the foreign innovator can be considered as bioequivalent versions of the initial local innovator, under the assumption that the local comparator and the foreign innovator are maintained bioequivalent over the years. This seems more likely in well-regulated markets, therefore, the foreign comparator seems to be the best option in most countries.

Case 4: The last and most difficult case is where the innovator is no longer available at all or it cannot be identified because it is a very old drug. In that case, a product marketed in the country of a stringent regulatory authority should be selected to better ensure the prescribability of future generics. The rationale for selecting the comparator from these countries is based on availability of post-marketing surveillance. Ideally, the same comparator should be selected all over the world.

Designating a global comparator product as the standard to which all generics must be shown to be bioequivalent would avoid variations among generic medicines all over the world and especially for countries with small markets that receive different generic

applications compared with diverse comparator products. Nonetheless, though a global comparator product could be set, it will not be uncommon that more than one comparator product may be accepted; for instance, when two innovator products have been approved based on clinical safety and efficacy data (e.g., transdermal patches of estradiol or nitroglycerine), or the innovator product is no longer marketed and a different comparator product has to be selected. In those cases, where it is possible to have generic products in the market that have been compared with different comparator products, it is important for the regulatory authorities to provide such information to health care professionals to aid in prescribing and dispensing.

Further, with the heightened interest and focus on local pharmaceutical production in Africa, which is also seen in other regional economic blocks, harmonising the regulatory requirements for bioequivalence studies, including the comparator product, becomes imperative not only to facilitate local manufacturers' access to markets outside their countries but also to reduce the unnecessary time and cost of generic product development.

It is acknowledged that differences between the innovator product in one market and the same innovator product in other markets may exist. For example, Tegretol® (carbamazepine) in the US [32] is different than Tegretol® in Europe [33] with respect to the formulation and probably manufactured at different sites. Carbamazepine is an antiepileptic with narrow therapeutic index. This difference in composition and manufacturing may affect the bioavailability and that would mean that the generics made from each of the reference version of Tegretol® are not necessarily interchangeable. These differences may justify the present situation where a European reference product is not acceptable in the US and vice versa. This implies that the product has been changed with respect to the product that was used in clinical trials in any or in both jurisdictions. If it were a recent product, we would consider that the change had no significant impact on its bioavailability because bioequivalence has to be demonstrated for the approval of that variation, but as it is an old product with a narrow therapeutic index that assumption might be questionable. Therefore, we have to assume that in one of these jurisdictions the product differs in bioavailability (in rate and/or extent) compared to the product used in clinical trials. In this specific case the manufacturer has developed

an in vitro-in vivo correlation and a simple dissolution test could provide information about the similarity between these products. If this correlation had not been developed, which is the usual case, the similarity between these two local comparators could be deduced by means of adjusted indirect comparisons [34–37]. Adjusted indirect treatment comparison is only possible if the respective NMRA had assessed a bioequivalence study of the same generic product with the corresponding local comparator. Therefore, if there is interest, it would be possible to share the necessary information to know if a foreign comparator is sufficiently similar as to consider it as a variation (e.g., a previous version or a subsequent version) of the local comparator since the regulatory authorities could share information (e.g., qualitative and quantitative composition, manufacturing site and process and specifications) to confirm that the local comparators are very similar. Nonetheless, this information cannot be shared in some countries for legal reasons.

The EU is the example that demonstrates that the foreign comparator can be accepted if it belongs to the same company as the local comparator, even if it differs in manufacturing site, process, qualitative and quantitative composition or even dissolution profiles. In the EU the generic products of any drug and dosage form can be compared to the reference product from any of the Member States and it has to be accepted in all other member States. Once in the market, these products are switched irrespective of the origin of the comparator that was used as reference in the bioequivalence study.

The WHO PQT-m prequalifies generics in the selected therapeutic areas intended to be supplied to multiple countries, especially in LMICs [38]. Therefore, experiences from WHO PQT-m provide insights in terms of how to identify and obtain an acceptable comparator product in a global context. It is worth mentioning that prequalified products are supplied to many markets and accepted by some national regulatory authorities without requiring further studies, whether dissolution studies or otherwise, with a local comparator product.

Finally, regulatory authorities could compare the respective comparator products to ensure their similarity as if they were a variation of each other or to confirm that they are two different products that deserve to be distinguished and not interchanged. That information should be made publicly available so regulatory

authorities can accept the foreign comparator products from the identified primary markets. The qualitative and quantitative composition, the manufacturing site and process as well as the specifications should be compared to ensure that the comparator products from the different markets are sufficiently similar.

CONCLUSION

The WHO recommendations to national regulatory authorities on the selection of comparator products is only feasible in a few countries or regions in which this makes economic sense, but impracticable in all other countries, particularly in LMICs. It is scientifically questionable to require the exclusive use of the local comparator to ensure switchability and unethical to require multiple repetitions of the same bioequivalence study with similar local comparators. Global harmonization of comparator products for bioequivalence studies is not only feasible, but the concept already applies to some extent, if one considers the EU and the WHO PQT-m approach on selection of comparator products for prequalification of generic products for the target disease areas.

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CHAPTER 5

GENERAL DISCUSSION

DISCUSSION

This concluding chapter of this thesis discusses the relevance of bioequivalence in generic prescribing and substitution policies that are implemented globally and the essential components that can be drawn from the evolution of bioequivalence requirements over the last three decades that impact pharmaceutical regulatory policy. Subsequently, the application as well as methodological issues of the adjusted indirect treatment comparisons in ensuring generic switchability are critiqued. Lastly, the practicality of marketing authorisations in Sub-Saharan Africa that are necessary not only to ensure the generalisability of the results observed with data on adjusted indirect treatment comparison from the World Health Organization Prequalification Team–medicines (WHO PQT-m), but also as a foundation for implementing pro-generic policies in those settings are discussed.

Generic prescribing and substitution policies

Briefly, generic medicines along with the generic prescribing and substitution policies, are essential in public health programs to increase access to medicines regardless of the income level of the country, i.e., low-, middle- or high- income [1]–[4]. With this in mind, national medicines regulatory authorities (NMRAs) have to ensure that generic medicines are therapeutically equivalent to the innovator or reference product. This is done by ensuring that generic medicines demonstrate interchangeability, which includes both prescribability and switchability components, with the innovator product before granting marketing authorisations [5], [6]. This requirement for bioequivalence demonstration between the generics and the corresponding innovator has been adopted by regulators, mostly in high-income countries, over the last three decades [5], [7], [8], however, interchangeability between generics of the same drug is assumed, although it has not been addressed comprehensively by regulators. Consequently, there are divergent views and practices across countries with respect to whether generic medicines, particularly those containing narrow therapeutic index (NTI) drugs, are interchangeable between them since it is easier to detect the failure of bioequivalence for these drugs.

Evolution of bioequivalence requirements

Bioequivalence was first introduced as a regulatory tool in the United States (US) in 1984 as a result of the Hatch-Waxman Act, a federal law officially known as the Drug Price Competition and Patent Term Restoration Act of 1984 [9], [10]. The Act specifically prohibited the US Food and Drug Administration (US-FDA) from requesting for any additional data other than bioequivalence for approval of generic medicines. In other words, generics were exempted from the requirement to submit clinical safety and efficacy data. The assumption is that the generic medicine would be similar to the innovator product, and this is interpreted nowadays as meeting the 80 - 125% bioequivalence criterion [5], [7], [8]. In addition, if a generic product is shown to be bioequivalent to the innovator product, it is expected that it would exhibit the similar efficacy and safety profile in patients.

Bioequivalence facilitated the development of generic medicines in lieu of repeating the expensive and time consuming clinical trials to demonstrate safety and efficacy of the same drug. For instance, after 1962 but before the Hatch-Waxman Act, only 15 generic medicines of the 150 off-patent medicines during this period were approved by the US-FDA because generic companies were not willing to invest resources in repeating the clinical safety and efficacy studies [10]. The regulatory burden for the generic drug development was further reduced in 2000, when the US-FDA introduced the waiver of *in vivo* bioequivalence studies by using *in vitro* comparative dissolution studies based on the Biopharmaceutical Classification System (BCS) [11]. The BCS concept was introduced by Gordon Amidon et al. in 1995 [12]. This concept classifies drug products into four classes based on their aqueous solubility and intestinal permeability/absorption. Globally, the concept of BCS-based waivers of *in vivo* bioequivalence studies is now widely accepted and there is convergence in its application among the US-FDA in its 2015 draft guidance [13], the European Medicines Agency (EMA)[8] and WHO [5]. In these guidelines, biowaivers for drug products that have a BCS class I drug are accepted if; (a) there are no differences between the generic product and the innovator product in excipients that are known to affect the rate or extent of absorption, (b) both the generic and the innovator product releases more than 85% within 30 minutes (*rapidly dissolving*) in three buffered media at 0.1 N HCl, pH 4.5 and pH 6.8, and (c) the dissolution profiles for the two products in these

conditions are similar. Biowaivers are also acceptable for BCS class III drugs provided both the generic drug product and the innovator release more than 85% of the drug within 15 minutes (*very rapidly dissolving)* in the three media and the generic formulation is qualitatively the same and quantitatively very similar to the innovator, e.g., any differences are within scale-up and post-approval changes (SUPAC) IR level 1 and 2 changes [14].

The current regulatory requirement for the demonstration of bioequivalence based on average bioequivalence has been criticised as inappropriate for NTI drugs or highly variable drugs, with individual and population bioequivalence proposed to ensure switchability and prescribability, respectively [15]–[18]. The authors taking this position argue that average bioequivalence does not address the within-subject variability or the subject-by-formulation interaction, thus may not be sufficient in some cases to ensure switchability. Moreover, average bioequivalence does not account for the total variability to ensure prescribability in new patients. Nevertheless, these approaches have not been accepted by regulatory authorities for the following reasons: the proposed aggregate method [19], [20], which compares the means between the generic and the reference, differences between the intra-subject variability and the subject-by-formulation interaction, may lead to approval of generic products that fail bioequivalence using the average bioequivalence because one factor may compensate for the others, i.e., a generic product with large difference in the means but with no differences in intra-subject variability or subject-by-formulation interaction [20]–[22]. Further, individual bioequivalence would require a four- or three-period replicate design to estimate the intra-subject variability of the generic and the reference. Disaggregate approaches have also been described, however, these would require a large sample size because the estimation of the distribution of the variability is imprecise [23]. Subject-by-formulation interaction may be considered a scientific artefact that is not relevant except in rare cases [23], e.g., use of sorbitol in one formulation, but not in the other because some subjects are sensitive to sorbitol and sorbitol may decrease absorption in sensitive subjects [24]. In practice, average bioequivalence has been used and is sufficient to evaluate interchangeability for most drugs that have a wide therapeutic window and low to moderate intra-subject variability, without any unnecessary complications [21], [23], [25].

Additionally, to ensure interchangeability between the generic and the reference for NTI drugs, some regulators, for example EMA and Health Canada, apply narrowed acceptance limits of 90.00 – 111.11% for the area under the plasma concentration time curve (AUC) [8], [26]. Narrowed acceptance limits are applied to the peak plasma concentration (C_{max}) only in those cases when C_{max} is considered important for efficacy and safety monitoring, otherwise the conventional limits of 80 –125% applies for C_{max} for the 90% confidence interval in Europe [8], [26] or for the point estimate in Canada [26]. The US-FDA applies scaled average bioequivalence not only for highly variable drugs as described in the bioequivalence recommendations for progesterone oral capsules [27], but also for NTI drugs as described in the product specific bioequivalence requirements for warfarin [28], which is also applied for tacrolimus [29]. This approach scales the average bioequivalence acceptance limits based on the variance component of the reference (within-subject variability). In these cases, replicate designs are necessary to estimate the intra-subject variability of the reference. For these NTI drugs, the US-FDA recommends a fully replicate design to ensure that the pharmaceutical quality of the generic product is similar to that of the innovator based on F-test of the within-subject variability of the test and of the reference.

Although, there is convergence of regulatory requirements for the approval of generic medicines to ensure prescribability, there are still gaps in addressing the practical situation that occurs in clinical practice with respect to generic substitution, i.e., switchability. For example, both the European Union (EU) and WHO PQT-m only assures prescribability of generic medicine and refer the issue of generic substitution as a national responsibility [8], [30]. The US-FDA publishes a list of approved products that are proven to be interchangeable [31]. Likewise, Health Canada includes a declaration of equivalence in the summary basis of approvals for generic medicines. This enables clinical decision-making by healthcare professionals regarding prescribability and also substitution. Some regulators only indicate products that are not permitted to be switched in practice such as NTI drugs (e.g., *Spain and Denmark*), while it is assumed that unless advised otherwise, the approved generic medicines may be interchanged (prescribed and switched) in practice not only with the reference, but also between them.

Adjusted Indirect treatment comparisons of bioequivalence studies

There are three important points that are evident from the evolution of the bioequivalence concept and regulatory requirements. One, there is a commitment to progressively reduce the regulatory burden for generic drug development without compromising patient safety or health [32], [33]. Two, three decades after the concept of bioequivalence was introduced as a regulatory requirement, the issue of generic interchangeability continues to receive significant attention from a scientific and public health perspective based on the number of publications on this subject. Three, any proposed approaches to ensure generic interchangeability over the current requirements should be scientifically rigorous and practicable without adding an unwarranted burden on industry or the regulator [25], [34]. With this in mind, using available data from the WHO prequalification, we have shown that the current regulatory requirements are generally sufficient to ensure prescribability and switchability not only of generic products with the reference, but also between generics that have been compared with the same reference [35], [36], *See Section 2.4*. The next subsections discusses the methodology and results of the adjusted indirect treatment comparison in more detail.

Methodological issues in adjusted indirect comparison

We explored the different approaches for calculating adjusted indirect comparisons [35]. In this thesis, we compared six methods that can be used to calculate the width of the confidence intervals based on *z* distribution ($z_{0.9}$) or Student's *t-test* distribution ($t_{0.9,\ d.f.}$). Four methods that assumed small sample sizes with Student's *t-test* distribution are (a) Chow and Liu meta-analysis method [37], which assume all studies had 2 x 2 cross-over design and homogeneity of variances in all studies, (b) homoscedastic method which assumes homogenous variances, (c) heteroscedastic method which assumes heterogeneous variances, and (d) a pragmatic approach which does not require the assumption of homogeneity of variances between studies with small sample sizes. The two methods which assume large sample sizes with a standardised normal distribution ($z_{0.9}$) are (a) Chow and Shao meta-analysis method [38], and (b) the *z*-distribution method with no assumption of homogeneity of variances [39]. We concluded that although the differences were minor, the homoscedastic method that uses the Student's *t*-test distribution to

calculate the width of the confidence interval is recommended, unless there are clear differences in variances, because it is the most conservative approach for estimating the confidence intervals for adjusted indirect comparisons.

Application of adjusted indirect treatment comparison of generics

Using the homoscedastic method, the most conservative approach, we investigated the differences in bioavailability between generics prequalified by the WHO using adjusted indirect comparisons [35], [36], *see Section 2.4*. These studies investigated a diverse group of products from the antimalarial artemether/lumefantrine [35], first-line antituberculosis drugs [36], and first-line antiretroviral drugs with a total of 394 indirect comparisons. In contrast to the ± 20% acceptance range used for direct comparisons, a ± 30% acceptance range is proposed for adjusted indirect comparisons [35], [36],s*ee Section 2.4*, due to the limited precision of indirect comparisons [40], [41], and because this difference does not seem to have clinical relevance.

First, these studies on WHO prequalified generics demonstrate the utility of adjusted indirect treatment comparison to compare the bioavailabilities between generic products that had been compared with the same reference product in direct comparisons. Second, the outcome of these comparisons indicates that the antimalarial artemether/lumefantrine, first-line antituberculosis, and first-line antiretroviral generics prequalified by WHO can be interchanged without any safety and efficacy concerns in the clinical settings. Although some comparisons were outside the conventional acceptance limits of ± 20% for direct comparisons, there were no generic-generic comparisons outside the ± 30% for indirect comparisons, except one comparison for efavirenz C_{max}. Failure to show equivalence within a ± 30% acceptance range in one out of 394 adjusted indirect comparisons should be interpreted as an insignificant number since it is less than 0.3% of the comparisons. Furthermore, in clinical practice the difference in C_{max} at steady state between test and reference product is known to be much lower than the difference observed in the single dose bioequivalence study [42].

Nevertheless, failure to show equivalence in indirect comparisons may be of concern for drugs such as efavirenz that is not an NTI but for which changes in C_{max} may result in increased incidence of adverse

events when patients are switched between generics. The results for efavirenz highlight two important aspects: one, regulatory authorities should not indiscriminately widen the limits, unless when C_{max} is considered clinically irrelevant, otherwise the reference scaling approach for average bioequivalence should be applied to highly variable drugs. Two, the limitation of the current limits of 80 –125% for average bioequivalence is that a drug with low intra-subject variability such as efavirenz, in generic products that are poorly formulated with respect to the reference, i.e., exhibit statistically significant differences between the formulations and a large point estimate difference (e.g., a 90% CI from 81 to 85% in one generic and a 90% CI from 120 to 124% in another generic), would be approved as the 90% CI would be within the 80–125% acceptance limits. However, such generics would not be interchangeable between them, as illustrated in the case with one formulation for efavirenz.

We observed that assurance regarding interchangeability of two generic products is reduced when either the point estimate ratios in the original studies are shifted from unity by more than 5% or when the width of the 90% confidence interval is large in the direct comparisons [43]. Therefore, we investigated using computations the influence of point estimates, variability of the pharmacokinetic parameters (C_{max} and AUC), and the sample size in the original studies on the ability to demonstrate bioequivalence between generics in the adjusted indirect comparisons [44]. Sample size and variability are not independent since the sample size is calculated based on the expected variability and the desired statistical power. Thus, statistical power is the most relevant parameter for consideration in the computations.

In these computations, we calculated the outcome of adjusted indirect comparisons for 14,592 scenarios using 57 possible differences between point estimates from 0 to 14% and 16 possible study powers from 50 to 99.99%. The study results illustrate that demonstrating bioequivalence within the conventional acceptance limit of 80 – 125% by means of adjusted indirect comparisons is only possible if the difference between the point estimate is small (< 5%) for any sufficiently powered study (> 80%). Furthermore, even when both studies are overpowered, the difference cannot be larger than 14%. This study showed clearly that in cases where generic-generic switching may be of concern, regulators might consider a point estimate constraint in the original studies.

To ensure switchability between the generic and reference and between generics, the generic and the reference should not differ significantly. For NTI drugs, it is assumed a difference of up to 10% in the pharmacokinetics is not clinically relevant [25], [45], [46]. In this thesis, we have also demonstrated that in such cases, particularly where the regulators do not provide guidance to health professionals on the switchability of approved products or when generic substitution is recommended by national governments or the third party reimbursement agencies, an additional point estimate constraint of ± 10% may be employed as a general requirement for bioequivalence [36], [47] to assure switchability between generics. A lower constraint for the point estimate, e.g., ±5%, could be applied to NTI drugs, especially where neither generic switching of these drugs is restricted nor narrowed bioequivalence acceptance limits applied. In the US-FDA new guidance on NTI drugs, there is an additional restriction on the potency of the drug product to be within 95 – 105% of the labelled amount throughout the shelf life [28], [48]. In the EU, this assay limit already applies for all products at release to ensure pharmaceutical quality and consistency in the manufacturing process to minimise large differences between batches [49]. The intention of using the adjusted indirect treatment comparison and the point estimate constraint is to ensure that the fluctuations in plasma levels that are experienced when patients are switched between generics are similar to those experienced within the reference (batch-to-batch variation) and between the reference product and the generic.

The results obtained with the prequalified generics are consistent with the outcomes reported elsewhere using data from other regulatory authorities [12–14]. Herranz et al. showed that exposures obtained with generic tacrolimus formulations in the Spanish/European market were within the ± 20% acceptance range based on adjusted indirect treatment comparisons [50]. In addition, results from adjusted indirect comparisons were consistent with those from direct comparisons for multiple generic formulations of gabapentin products marketed in the Netherlands [51]. Using data from bioequivalence studies submitted to the Dutch Medicines Evaluation Board for atorvastatin, bicalutamide, naratriptan, olanzapine, perindopril, venlafaxine, cyclosporine, tacrolimus, and mycophenolate mofetil, Yu and colleagues showed that in 80% of the cases the indirect comparisons between generics fulfilled the

conventional acceptance limit of ± 20%, while the remainder were within ± 30% [52].

Limitations of adjusted indirect treatment comparisons

The variance for the adjusted indirect comparison is additive, $SE_{AC}^2 = SE_{AB}^2 + SE_{BC}^2$. For this reason, the major limitation of adjusted indirect comparisons of bioequivalence studies is the reduced precision. On the one hand, the inability to show bioequivalence by means of indirect comparisons is not proof of inequivalence, but it may be simply that there is not enough statistical power to make this conclusion. On the other hand, when bioequivalence is shown within the conventional acceptance limit for indirect comparisons despite the reduced statistical power, we can consider not only that the generic products are bioequivalent but also very similar.

The validity of indirect comparisons is dependent on the methodological quality and assumptions. Similarity of trials involved in adjusted indirect comparisons should be carefully assessed to ensure that there are no important differences between the trials under comparison in aspects that could bias the estimated formulation effect. Although standard requirements are applied to the design, conduct and analysis of the results of the bioequivalence studies submitted for the prequalification of generics [5], in some cases different study designs might be employed. For example, metabolite *vs.* parent as the analyte, or plasma *vs.* urine as the biological fluid collected for analysis, or multiple *vs.* single dose studies. Studies with these different study designs cannot be compared because the formulation effect cannot be expected to be the same between them, because they have different sensitivity to detect the differences that may exist. However, we consider the results from conventional 2 x 2 crossover designs and replicate designs as combinable. There is no consensus on whether parallel and crossover trials should be combined in indirect comparisons [53], however, this may be possible if the participants and interventions are comparable. In all the analyses performed, all the studies were crossover trials.

In contrast to adjusted indirect comparisons of efficacy trials, confidence in the methodological quality and similarity of adjusted indirect comparisons of bioequivalence studies is assured because of the general consistency in the basic design of these studies. For instance, the characteristics of participants in bioequivalence studies are commonly defined, i.e., usually healthy adult male and/or female

volunteers within 18 - 55 years of age, which controls for the differences in baseline characteristics between treatment groups, whereas differences in disease state in efficacy trials is of concern. The objective of bioequivalence studies is to evaluate formulation differences and external validity of the results is based on the assumption that the effect of the drug in the target populations, i.e., patients would be the same for the test and reference. Nevertheless, in some cases, subject – by – formulation interaction could occur, e.g., when one formulation has excipients that are not tolerated by specific sub-groups of patients that are not present in the other formulation. This is often mitigated by the regulatory requirement to declare such excipients on the product label.

Despite the utility of the indirect comparisons, the evidence from such analyses should be interpreted with caution. The internal validity of direct comparisons should be carefully evaluated to reduce bias. In the analysis of the prequalified generics, methodological quality of the studies was not assessed as part of the adjusted indirect comparisons since only the generics that were prequalified were included in the analysis. The prequalification process entails stringent assessment, including inspection of the contract research organizations at which the studies were performed, thus providing assurance of the quality of the prequalified product. Therapeutic doses are usually standardised as highest available strength, although in some cases the studies used lower doses. Nonetheless, the results are reported as mean ratios, thus the effect of dose on the outcomes is negligible. The studies were all single dose studies with the same outcome measure of pharmacokinetic parameters C_{max} and AUC in all the studies, estimated using validated software. The parent compound in plasma was analysed using validated bioanalytical methods. Despite the general consistency with the bioequivalence studies used in the adjusted indirect comparisons, changes in the requirements over time encompassing several revisions of the guidelines could potentially impact on the methodological quality between studies conducted at different time points; this may be corrected by the use of the same reference product in the different bioequivalence studies. Only the studies using a common reference product as listed by the WHO PQT-m were compared in the adjusted indirect comparisons. Though US and European reference products are both accepted in the WHO PQT-m, and no distinction was made in the analysis, because they are assumed to be the same product, but this may not always be the case.

In summary, adjusted indirect comparison is a useful tool to compare relative bioavailabilities between generics that have been compared with a common reference in direct comparison to ensure interchangeability between the generics. The investigated antimalarial – artemether/lumefantrine, first-line antituberculosis and antiretroviral generic products prequalified by WHO were considered interchangeable without safety and efficacy concerns. We have also demonstrated that the ability to show bioequivalence between generic products by means of indirect comparisons depends on the difference between the point estimates of the bioequivalence studies, which is the point estimate of the indirect comparison, and the power of the bioequivalence studies that are combined. In this respect, concluding equivalence in the indirect comparison within the conventional acceptance limits of 80 – 125% is only possible when (a) point estimate difference between generics are low (< 5%) for any sufficiently powered study (> 80%), or (b) the differences do not exceed 14% when both studies are overpowered. Therefore, in cases where it is important to ensure generic interchangeability, the regulatory authorities may consider a point estimate constraint in the original bioequivalence studies. In the general case, due to the reduced precision of indirect comparison, a slightly wider acceptance limits (± 30%) is proposed for indirect comparisons.

Marketing authorisations mechanisms in sub-Saharan Africa

The work described in Chapter 2 in this thesis on adjusted indirect treatment comparison highlights some important aspects: (1) the WHO prequalification ensures interchangeability of generics with the reference, and (2) prequalified generics may be interchanged between them without any safety and efficacy concerns. This is pivotal in supporting generic prescribing and substitution policies, which are important in increasing access to medicines for the world's poorest. WHO PQT-m is a mechanism that is specifically designed to address the quality assurance shortcomings in the low- and middle-income countries (LMICs), particularly Sub-Saharan Africa that has a high infectious disease burden due to HIV and AIDS, tuberculosis and malaria. To what extent can these results observed with prequalified products be extrapolated to nationally approved products in those settings? This section discusses the results described in Chapter 3 within the context of the findings obtained in Chapter 2.

The WHO recommends that medicines should be registered in the country before marketing and national medicines regulatory authorities (NMRAs) should ensure that generic products are interchangeable with the reference among other requirements before granting approval [5]. On the one hand, despite this recommendation, this is not widely practiced, particularly in LMICs, due to regulatory capacity limitations. On the other hand, many countries, both LMICs and high-income countries apply the WHO recommended generic prescribing and substitution policies. Significant cost savings could be realised in LMICs if generic substitution is fully implemented [2]. Notwithstanding these benefits, pro-generic policies require assurance that the NMRAs have approved generic products based on sufficient demonstration of interchangeability with the reference product. This is important considering that the generic market share in LMICs is larger compared to high-income countries [54], and that in the LMIC settings branded generic medicines dominate compared to unbranded generic medicines. Healthcare professionals and consumer perceptions suggest this is due to the association of brand with quality as well as the high cost with quality in those settings [54]–[56], potentially indicating the inadequacy of the regulatory systems. This leaves the healthcare professionals and the consumers to ascertain the quality of the medicines in the market on their own.

In this thesis, data from WHO PQT-m shows that prequalified generic products for antimalarial artemether / lumefantrine, first-line antituberculosis and first-line antiretroviral medicines were interchangeable with the reference product as well as demonstrating them to be interchangeable between them using adjusted indirect treatment comparisons [35], [36], *See section 2.4*. The WHO PQT-m addresses a gap in the regulatory systems in LMICs, however, the WHO PQT-m standards may not be similar to the standards in the intended markets, lowering the external validity of the observed results in those settings that may employ different requirements and review practises. Therefore, to address this issue, we analysed the performance of the marketing authorisation system in Zimbabwe, a low-income country (See Section 3.1). In this study, we noted that it is possible to have the necessary arrangements for product registration for generic medicines that will ensure that both WHO PQT-m and nationally approved products are of sufficient quality and interchangeable and to adopt resource-efficient approaches without duplications. Further, this case study demonstrated the applicability

of WHO PQT-m requirements with respect to bioequivalence, including the WHO PQT-m approach to comparator products for bioequivalence studies.

Although the case study showed the practicality of applying a marketing authorisation system for generic products as recommended by WHO, the approval time was noted to be longer when compared to well-resourced regulatory authorities. This could be counterproductive if patients have delayed access to needed medicines simply due to capacity limitations. One strategy to enhance the capacity of regulatory authorities in those settings is through harmonisation and work-sharing through regional economic groups [57]. This approach has been applied in the EU system since the 90s and is now extending beyond the EU system with the International Generic Drug Regulators Programme (IGDRP) pilot for generic medicines [58]. The IGDRP pilot involves countries outside the EU system participating as observers in the centralised and decentralised system for approving generic medicines in the EU. Could similar arrangements work in the Sub-Saharan setting? Theoretically, this could also work in those settings, however, this has neither been tested nor reported in literature, though there are known similar initiatives that are ongoing in other regional economic communities. While this thesis looked at the use of adjusted indirect comparisons for demonstration of interchangeability, we emphasise that this approach works only when a country applies similar and consistent standards like WHO PQT-m. This may not be valid in most Sub-Saharan African countries because of the lack of robust marketing authorisation systems.

To address these two issues; one, ensuring interchangeability of generic medicines by regulators as the foundation for applying generic prescribing and substitution policies, and two, limited capacity and performance of African regulators, we looked at the use of a collaborative model in medicine assessment and registration among four LMIC countries, Zambia, Zimbabwe, Botswana and Namibia (ZAZIBONA initiative) in Sub-Saharan Africa. The initiative started in mid -013. Specifically, the study analysed the collaboration process, identified the key success factors using a theoretical framework for collaborative models described in literature [59], and evaluated its potential long-term sustainability. This initiative shows potential to overcome the capacity limitations for African regulators through work-sharing; however, its medium- to long-term sustainability depends on

the success in institutionalising or formalising this initiative and integrating the collaborative process internally within the participating regulatory authorities. Further, the ZAZIBONA model in the context of global harmonisation efforts, not only in LMICs, but also in high-income countries demonstrates that collaboration in assessments is feasible and probably the most pragmatic approach that countries in LMIC should use to build capacity and to ensure quality and interchangeable medicines in the market. This model also provides a platform to apply standards similar to WHO PQT-m including requirements and assessment of bioequivalence data for generic applications. In fact, applying these standards showed that apart from incomplete applications, failure to demonstrate bioequivalence was one of the major causes of negative opinions in this collaboration. Notwithstanding this, most African countries and those in South America do not require bioequivalence studies for all prescription products, or lack the capability to conduct such assessments. As such, generic substitution policies are used in those settings without evidence, exposing the public to potentially unsafe and ineffective medicines.

Global harmonisation of comparator products for bioequivalence studies

An important aspect in collaboration mechanisms described in the previous section is the requirement for harmonised requirements. Therefore, following the WHO recommended approach to selecting a reference product for bioequivalence studies [60] in the ZAZIBONA case would require four individual bioequivalence studies, each with the innovator product obtained from the national market of the participating countries, or if this is no longer available, a market leader in each national market that is likely to be different between the countries. Notwithstanding the small pharmaceutical market sizes of African countries or the continent as a whole relative to high-income countries, this situation is complicated further by the fact that the innovator products of some drugs may never be marketed in those settings and a generic product may be the first to be marketed. Additionally, this first market-entry generic could be approved based on bibliographic application, although, the most appropriate choice would be to require demonstration of bioequivalence between this generic and the innovator product obtained in an International Council of Harmonisation (ICH) country. Moreover, most of these countries have limited to no local pharmaceutical production with dependence

on imports mainly from India [61]. This is consistent with data from Zimbabwe that shows Indian generics constituting more than 70% of all approved generic products (*See section 3.1*). In most cases, the generic product development is made with the intention of supplying several markets, thus the requirement of using a national reference product purchased from the local market is impractical. This may be feasible for larger emerging markets. For example, Brazil enforces this requirement and the innovator should be manufactured in Brazil.

Notwithstanding this, we propose a global approach to the selection of reference products for bioequivalence studies so as to minimise the costs in product development for generics as well as an unnecessary regulatory burden. We propose that WHO PQT-m approach for selecting reference products in the prequalification programme is one approach that could be followed. At this present moment, 27 countries (www.who.int/prequal), mainly African countries officially participate in the WHO PQT-m collaborative medicines registration procedure [62]. This entails facilitated national marketing authorisations based on WHO prequalification status. Thus, bioequivalence data submitted to prequalification to demonstrate interchangeability is acceptable in these countries without any further requirements with respect to interchangeability, i.e., no requirement to demonstrate pharmaceutical equivalence or dissolution testing between the national reference product and the reference product used in the bioequivalence submission to WHO PQT-m as it is practised by other countries, South Africa for example.

Furthermore, in the case studies presented in this thesis for Zimbabwe and the ZAZIBONA collaborative initiative, the WHO PQT-m approach for selecting comparator products is applied successfully and facilitates harmonisation among these four countries, i.e., one bioequivalence study is sufficient for all the four countries. In these cases of regional harmonisation, the EU model could also be applied, assuming market control in each of the countries is essentially similar. This is an approach that should be considered at the regional and continental level to lower and facilitate generic product development, particularly in the context of promoting local pharmaceutical production. In any case, manufacturers are on the safe side to apply the WHO PQT-m approach in the absence of national or regional guidance with respect to comparator products, as this is likely to reduce the chances of repeating the studies if marketing is extending to other countries in the region or continent. Furthermore, a global

reference product will ensure that irrespective of the origin of the manufacturer, the reference product used in bioequivalence studies is likely to be the same, hence ensure that all products of the same drug in the market will be interchangeable regardless of the country of origin. This will lower the regulatory burden for LMICs in terms of determining suitable reference products in their own markets.

General limitations

The utility of adjusted indirect treatment comparison was demonstrated using generic products that were prequalified by the WHO PQT-m. Therefore, the results may not be extrapolated to other settings or to products approved by other regulatory authorities, unless similar standards and levels of assessment are applied. Nevertheless, the results are consistent with what has been reported in similar studies in Europe. Therefore, despite this limitation in the focus of the analyses, the methodology is applicable in all settings and the conclusions should be valid in other settings, provided similar standards are applied. Further studies should be done using data from other regulatory authorities, particularly African countries using the same methodology that we described [35]. The challenge that we anticipate, particularly in the African setting, is lack of availability of these data in the public domain. To our knowledge, none of the African regulators publish the summary basis of approvals, including the type of information that was accessed from WHO PQT-m and used in performing the adjusted indirect treatment comparisons. None of this information is considered confidential, therefore, it should be possible to obtain it by request to the regulatory authorities.

The case studies looked at a specific country situation and a specific collaborative initiative and this may not be representative of the situation in other countries or regional economic groups. In Sub-Saharan Africa regulatory authorities are often classified based on the existence of a functional regulatory system that performs all the regulatory functions as recommended by the WHO. The collaborative model includes countries that had varying institutional frameworks, i.e., independently and semi-autonomous statutory entities such as in Zambia and Zimbabwe and those that are within the Ministry of Health structures, such as the case in Botswana and Namibia. Thus, as long as the country has mechanism for medicines assessment, inspections and registration, collaborative frameworks should be feasible as well as applying the requirements for demonstration of interchangeability.

Nonetheless, further studies of specific country situations to assess the regulatory performance for the registration of medicines as well as analyses of other on-going regional initiatives such as the East African Community, Association of South East Asian Nations, Gulf Cooperation Council or Pan American Network on Drug Regulatory Harmonisation is necessary to understand fully the situation with respect to product registration and feasibility of collaborative initiatives in those settings.

Regulatory Policy Implications

The current regulatory requirements, as applied in the WHO PQT-m, on average bioequivalence are sufficient for most drugs to ensure interchangeability between generic medicines that have been demonstrated to be bioequivalent to the same reference product. To assure generic interchangeability, adjusted indirect treatment comparison approach could be used. Therefore, the regulators should consider making the information on approved bioequivalence studies publicly available to facilitate evidence based clinical decisions by healthcare professionals. Moreover, for some drugs where switchability is of concern, the regulators may wish to add a point estimate constraint of ± 10%, or tighter, for example ± 5% for NTI drugs, as a bioequivalence acceptance requirement.

Generic prescribing and substitution policies are only meaningful if the respective country has mechanisms to ensure that products in the market are only approved after demonstration of interchangeability as recommended by the WHO. The requirement for the demonstration of interchangeability with the reference product should be part of the approval process for prescription preparations, where applicable. Further, the regulatory authorities should have sufficient capability to assess the bioequivalence data as per the recommended WHO norms and standards or equivalent. This could be done through regional collaborative arrangements.

Global harmonisation of the reference products for bioequivalence studies is essential to facilitate generic drug development, reduce duplication of unnecessary studies, and facilitate information sharing and collaboration between regulatory authorities. The ICH focuses on harmonising requirements for innovative therapies and clinical studies performed following the recommended guidelines are acceptable across regions with minimal additional country specific requirements. In general, harmonisation on the conduct of bioequivalence studies is

largely complete, except for the requirements for reference products. Despite differences across some countries, experiences from WHO PQT-m showed that it is feasible to apply a global reference product for bioequivalence studies that could be acceptable across countries.

Conclusion

First, this thesis demonstrated using the WHO prequalified products that in general generic medicines that are bioequivalent with the same reference product are also interchangeable between them without any changes in the quality of therapy. Second, this thesis demonstrates the utility of adjusted indirect treatment comparison in assessing switchability between generics. Furthermore, the ability to show equivalence through adjusted indirect treatment comparison is reduced if the point estimate ratios in the bioequivalence studies are shifted from unity (1.0) by more than 5% for sufficiently powered studies. Therefore, in those specific cases where switching is of concern, e.g., NTI drugs regulatory authorities may employ an additional requirement of a point estimate constraint in the original bioequivalence studies, e.g., ± 10% or tighter limit of ± 5 % for NTI drugs to ensure interchangeability between generics.

Third, the practicality of ensuring switching of generics using adjusted indirect treatment comparison requires regulatory authorities in all settings, particularly LMICs to apply similar standards as recommended by the WHO in demonstrating interchangeability and as practised in the WHO PQT-m. Along the same lines, this thesis demonstrates using data from Zimbabwe a low-income country as a case model, the feasibility of regulatory authorities in those settings to apply sufficient mechanisms of granting marketing authorisations for generic medicines, including bioequivalence demonstration. Nevertheless, the performance data on approval metrics in Zimbabwe suggests that there is limited capacity that may act as a barrier to access of medicines. Therefore, collaborative mechanisms in medicines registration such as the ZAZIBONA initiative of four sub-Saharan countries could be an alternative approach to overcome the regulatory capacity limitations in LMICs, remove duplication and ensure interchangeability of generic medicines before granting marketing authorisations.

Lastly, such collaborative mechanisms require not only the harmonisation of requirements for the conduct of bioequivalence studies, but also the acceptability of a common reference product for

bioequivalence studies among countries. This requires harmonisation of the selection and procurement of the reference products for bioequivalence studies beyond the current recommendations of using reference products obtained in the national market or the market leader as the preferred options, but to consider the global approach practised by the WHO PQT-m as a practical solution. Moreover, use of a common reference product is imperative for ensuring interchangeability between generics using adjusted indirect treatment comparisons.

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CHAPTER 6

SUMMARY AND SAMENVATTING

CHAPTER 6.1

Summary

SUMMARY

This thesis addresses three main interlinked issues with respect to interchangeability of generic medicines, particularly in low- and middle-income countries (LMICs) in a global context. **Chapter 1** provides a general introduction to these issues that are addressed in this thesis.

First, the importance of generic medicines as a cost containment measure in public health programs is evident regardless of the country income levels. Generics are generally cheaper compared to innovator products partly due to reduced development costs as they are approved by regulatory authorities based on bioequivalence studies with the innovator or comparator product. Bioequivalent products are considered interchangeable, i.e. prescribable and switchable, which is the basis for generic prescribing and substitution policies. Prescribability means the generic medicine can be prescribed in place of the innovator product in a new/naïve patient under the same conditions, while switchability means the generic can be substituted in place of the innovator product in patients under chronic treatment. Interchangeability between generics of the same drug is assumed, although it has not been addressed comprehensively by regulators. Consequently, there are divergent views and practices across countries with respect to whether generic medicines, particularly those containing narrow therapeutic index (NTI) drugs, are interchangeable between them since it is easier to detect the failure of bioequivalence for these drugs. Therefore, using empirical evidence, this thesis investigates the interchangeability between generics using adjusted indirect comparisons.

Second, while regulatory systems and policies in high-income countries exist to govern the approval and use of generic medicines to ensure both prescribability and switchability, there is a dearth of information on the systems and policies in LMIC to support pro-generic policies. Further, while mechanisms such as the prequalification of medicines by the World Health Organization (WHO) may ensure prescribability through bioequivalence demonstration of products supplied in LMIC settings, generic substitution is considered a national responsibility that should be addressed at country level. Thus, this thesis also analyses the approval of generic medicines in Sub-Saharan Africa by reviewing the registration data from Zimbabwe and a collaborative medicine registration process involving four

Southern African Development Community (SADC) countries as case models.

Third, harmonization of bioequivalence requirements, though incomplete, has yielded significant benefits to both industry and regulators. Nonetheless, it is ineffectual to harmonize only the requirements, if such a study has to be repeated for each country because of the different comparator products selected at the national level for the same drug. Hence, the last main objective of this thesis reflects on the use of a common comparator product globally for bioequivalence studies.

Chapter 1 also introduces the concept of indirect comparisons that are employed in instances where multiple interventions exists and there is insufficient evidence to evaluate their relative effectiveness from direct comparisons. A bioequivalence study comparing a generic and an innovator is a form of direct comparison. Performing direct comparisons between all available generics of the same drug is not only impracticable, but also not a regulatory requirement for approval of generic medicines. Therefore, indirect treatment comparison is a useful approach to identify those generic products whose interchangeability can be guaranteed to support or ensure switchability in clinical practice without concerns for efficacy or safety due to the switching.

Several methods are available for performing indirect comparisons: (1) naïve or unadjusted indirect comparisons, (2) modelling approaches based on the individual patient data (meta-regression), (3) mixed treatment comparisons based on Bayesian statistics (logistic regression), and (4) statistical methods using aggregate data, such as a simple weighted combination of separate estimates (adjusted indirect comparison). In this thesis, the adjusted indirect comparison approach is employed as it is the simplest and most suitable method for bioequivalence studies, because it uses publicly available data, and partly preserves the power of randomized controlled trials.

Chapter 2, ***Adjusted indirect treatment comparison of generic products prequalified by the World Health Organization,*** investigates the interchangeability between generics using adjusted indirect comparisons using data from the WHO prequalification of medicines as case studies. This chapter explored the methodological issues and the applicability of adjusted indirect

treatment comparisons in bioequivalence studies using the generic products prequalified by WHO for antimalarial, first-line antituberculosis, and first-line antiretroviral medicines. These three classes of medicines target the three main infectious diseases that affect LMICs, particularly Sub-Saharan Africa.

Chapter 2.1, investigates the different methods for performing adjusted indirect treatment comparisons for bioequivalence studies using artemether / lumefantrine generics prequalified by WHO as a case model. In this study, we compared six methods that can be used to calculate the width of the confidence intervals for the comparison based on *z* distribution ($z_{0.9}$) with no assumption of homogeneity of variances or Student's *t* distribution ($t_{0.9,\ d.f.}$) with or without assumptions of homogeneity or heterogeneity of variances. Data from three bioequivalence studies conducted independently that compared three generics with the same reference product were used to indirectly determine the relative bioavailability between the generics themselves. Although, the different methods of indirect comparison examined in this study provide consistent results, the homoscedastic method that uses the Student's *t*-test distribution to calculate the width of the confidence interval is recommended, unless there are clear differences in variances, because it is the most conservative approach for estimating the confidence intervals for adjusted indirect comparisons.

Given the precision of the area under the time-concentration curve (AUC) data, it is possible to conclude that the extent of exposure of artemether and lumefantrine is bioequivalent between the generics studied. However, given the precision of the drug peak concentration (C_{max}) data, it is not possible to demonstrate equivalence within the conventional acceptance range for all comparisons; though it is possible to conclude bioequivalence within the widened acceptance range 75-133%. The lack of the necessary precision to demonstrate bioequivalence between generics with respect to C_{max} within the conventional acceptance range does not preclude considering them as interchangeable, if necessary, since C_{max} is considered of less clinical relevance for the relevant therapy.

We noted that although indirect comparisons are an effective approach for confirming the interchangeability of generics, the approach is subject to less precision than direct comparisons. Therefore, **chapter 2.2** investigated the influence of the point

estimates and the study power on the ability to show bioequivalence between generics using adjusted indirect treatment comparisons. Power was considered as a determining factor instead of variability and sample size, because the sample size is calculated based on variability and desired power. Scenarios were computed combining a range of point estimate differences (0–14 %) and statistical power of the studies (50–99.99 %). This study showed that the indirect comparisons could conclude equivalence between generics only when (a) point estimate differences between generics were low (<5 %) for any sufficiently powered study (>80 %), or (b) the differences were large (but less than 14 %) and both bioequivalence studies were overpowered (e.g., 10 % difference and power ≥95 %). We concluded that the ability to demonstrate the interchangeability between generics is dependent not only on the real differences between the products, but also on the design of the original generic *vs*. comparator bioequivalence studies being combined, as earmarked by their respective power.

Chapter 2.3 and **2.4** applied the adjusted indirect treatment comparisons to the diverse first-line anti-tuberculosis medicines and first-line antiretroviral medicines prequalified by the WHO respectively. These two studies explored the utility of the recommended approaches from the previous two studies in investigating the bioequivalence between generics, as well as the value of additional constraints on bioequivalence requirements with respect to the point estimates in the original studies. The majority of adjusted indirect comparisons of the generic first-line antituberculosis, and the first-line antiretroviral medicines prequalified by WHO, were within the typical acceptance limits of ±20%, and there were no generic-generic comparisons outside the ± 30% for indirect comparisons, except one comparison for efavirenz C_{max}. Failure to show equivalence within a ± 30% acceptance range in one out of 394 adjusted indirect comparisons should be interpreted as an insignificant number since it is less than 0.3% of the comparisons and clinically irrelevant for the difference in C_{max} at steady state between test and reference product is known to be much lower than the difference observed in the single dose bioequivalence study. In these studies, we concluded that to ensure interchangeability between generics, the original studies should be sufficiently powered, i.e. >80%, and the point estimate ratios should not exceed the 10% difference. Thus, a point estimate constraint in

the original studies is recommended where it is important to ensure generic interchangeability, e.g. narrow therapeutic index drugs.

In summary **chapter 2;** *firstly,* shows that adjusted indirect comparison is a useful tool to compare relative bioavailabilities between generics that have been compared with a common reference in direct comparison to ensure interchangeability between the generics. Further, in contrast to the ± 20% acceptance range used for direct comparisons, a ± 30% acceptance range is proposed for adjusted indirect comparisons, due to the limited precision of indirect comparisons and because this difference does not seem to have clinical relevance.

Secondly, the outcome of these comparisons indicates that the antimalarial artemether/lumefantrine, first-line antituberculosis, and first-line antiretroviral generics prequalified by WHO can be interchanged without any safety and efficacy concerns in the clinical settings.

Thirdly, to ensure switchability between the generic and comparator and between generics, the generic and the comparator should not differ significantly. In this respect we propose an additional point estimate constraint of ± 10% as a general requirement for bioequivalence, particularly for LMICs where the regulators may not provide guidance to healthcare professionals on the switchability of approved products or when generic substitution is recommended by national governments or the third party reimbursement agencies. A lower constrain for the point estimate of ±5%, is proposed for NTI drugs, especially where neither generic switching of these drugs is restricted nor narrowed bioequivalence acceptance limits applied.

Chapter 3, *Marketing authorisations in Sub-Saharan Africa*, describes two studies that put the results obtained in **Chapter 2** into context i.e., the WHO prequalified products are mainly in Sub-Saharan African countries with the highest disease burden of HIV and AIDS, tuberculosis (TB) and malaria. In addition, this chapter attempts to provide answers on whether the adjusted indirect treatment comparison results for WHO prequalified generics could be extrapolated in those settings.

Chapter 3.1 describes the performance of the medicines registration system in Zimbabwe, a low-income country in Southern Africa with a functional medicines regulatory system as a case model.

In this study, we noted that Zimbabwe has four regulatory routes, which include (1) full review, (2) abridged review, (3) verification, and (4) regional work-sharing through the ZAZIBONA '*meaning looking into the future*' collaborative registration process. A total of 2,083 applications were received, and 1,002 products were approved between 2003 – 2015. It takes almost 24 months (without start/stop clock system) to have a product approved in Zimbabwe (overall median time for all products was 710 days (IQR 422; 1065)). This study showed that it is possible to have the necessary arrangements for product registration for generic medicines that will ensure that nationally approved products are of sufficient quality and interchangeable, and to adopt resource-efficient approaches without duplications. Further, this case study demonstrated the applicability of WHO PQT-m requirements with respect to bioequivalence, including the WHO PQT-m approach to selection of comparator products of bioequivalence studies.

Although the case study of Zimbabwe in **chapter 3.1** showed the practicality of applying a marketing authorisation system for generic products as recommended by WHO, the approval time was longer when compared to well-resourced regulatory authorities. This could be counterproductive if patients have delayed access to needed medicines simply due to capacity limitations. One strategy to enhance the capacity of regulatory authorities in those settings is through information and work-sharing through regional economic groups. **Chapter 3.2** looks at a collaborative medicines registration process among four Southern African countries as a model to ensure not only the quality but also interchangeability of generic medicines in those countries. The analysis focused on the evolution of the collaborative process, the key success factors and explored the sustainability of this initiative.

The ZAZIBONA initiative started in mid 2013 and is in its 3rd year of operation. The identified key success factors include ownership, effective leadership, partner resources, including co-financing, cost efficient model, social capital, clear roles and structure, effective communication, and demonstrable results. Although the model addresses most of the factors that ensures sustainability, some issues such as a monitoring and evaluation framework, committed funding, and institutionalisation is required for long term sustainability. Out of the 85 products that were considered in this 2.5-year period, 32 received positive opinion, 15 received a negative opinion, 10 were

withdrawn by the applicants, 25 were waiting for responses from the manufacturers and 3 were still under review at the end of 2015. The median time for a final recommendation was 10 months (range 5 – 23 months) inclusive of manufacturer time to respond to queries. The ZAZIBONA model in the context of global harmonisation efforts, demonstrates that collaboration in assessments is feasible and probably the most pragmatic approach that countries in LMIC should use to build capacity and to ensure quality and interchangeable medicines in the market.

Chapter 4, *Regulatory perspectives on global harmonization of bioequivalence studies*, presents a commentary on the selection of the comparator products in bioequivalence studies in the context of global harmonisation. Performing an adjusted indirect treatment comparison requires the use of a common comparator for the results to be valid. There is considerable progress with respect to harmonisation of the conduct of bioequivalence studies, however, there are still disparities with respect to requirements for comparator products for bioequivalence studies that affect not only the harmonisation but also interchangeability between generics. This commentary reviewed and discussed the current requirements in specific jurisdictions, including the WHO guidelines for comparator products with the focus on the requirements for the comparator products and proposed options for a harmonised global comparator product. A comparator product should have a direct link with the innovative product that was shown to be safe and efficacious in pivotal clinical trials to ensure prescribability and switchability. Most countries follow the WHO recommendations for selecting comparator products and require the comparator product to be obtained from their national markets to ensure switchability of their generics. These recommendations are only feasible in the few countries where the repetition of the bioequivalence study is profitable, but they are impracticable in all other countries. Furthermore, the exclusive use of the local comparator to ensure switchability is ethically and scientifically questionable because information could be shared to know if the foreign comparator is sufficiently similar as to be considered a "variation" of the local comparator. An acceptable global comparator product would be the innovator product or a reference listed drug from well-regulated markets. This global harmonisation is feasible as the concept already applies in the WHO prequalification programme and will ensure real harmonisation because it is

ineffectual to harmonise only the requirements for performing bioequivalence studies, if such a study has to be repeated for every single country simply because of the different comparator products selected at the national level.

Chapter 5 is a general discussion of the papers presented in this thesis. This concluding chapter discusses the relevance of bioequivalence in generic prescribing and substitution policies that are implemented globally. This chapter also addresses benefits and limitations, including methodological issues of the adjusted indirect treatment comparisons. The discussion concludes with specific regulatory policy recommendations for assuring generic prescribability and switchability.

The current regulatory requirements, as applied in the WHO PQT-m, on average bioequivalence are sufficient for most drugs to ensure interchangeability between generic medicines that have been demonstrated to be bioequivalent to the same reference product. To assure generic interchangeability, adjusted indirect treatment comparison approach could be used. Moreover, for some drugs where switchability is of concern, we propose a point estimate constraint of ± 10%, or tighter, for example ± 5% for NTI drugs, as a bioequivalence acceptance requirement.

Generic prescribing and substitution policies are only meaningful if the respective country has mechanisms to ensure that products in the market are only approved after demonstration of the interchangeability as recommended by the WHO. The requirement for the demonstration of interchangeability with the comparator product should be part of the approval process for prescription preparations, where applicable. Further, the regulatory authorities should have sufficient capability to assess the bioequivalence data as per the recommended WHO norms and standards or equivalent. This thesis demonstrates using data from Zimbabwe a low-income country as a case model, the feasibility of regulatory authorities in those settings to apply sufficient mechanisms of granting marketing authorisations for generic medicines, including bioequivalence demonstration. Nevertheless, the performance data on approval metrics in Zimbabwe suggests that there is limited capacity that may act as a barrier to access of medicines. Therefore, collaborative mechanisms in medicines registration such as the ZAZIBONA initiative of four sub-Saharan countries could be an alternative approach to overcome the

regulatory capacity limitations in LMICs, remove duplication and ensure interchangeability of generic medicines before granting marketing authorisations. The ability to have the marketing authorisation systems that are necessary not only to ensure the generalisability of the results observed with the data on adjusted indirect comparison from the WHO PQT-m but also as a foundation for implementing pro-generic policies especially in LMICs are emphasised in **chapter 5**.

An important aspect in collaboration mechanisms described in the **chapter 3.2** is the requirement for harmonised requirements, thus the requirement of using a national comparator product purchased from the local market is impractical in this regard as it would require several bioequivalence studies with a national comparator product for each country. We propose a global approach to the selection of comparator products for bioequivalence studies so as to minimise the costs in product development for generics as well as an unnecessary regulatory burden. In this regard, we propose that WHO PQT-m approach to selecting comparator products in the prequalification programme is one approach that should be followed.

CHAPTER 6.2

Samenvatting

SAMENVATTING

Dit proefschrift behandelt voornamelijk drie onderling samenhangende aspecten met betrekking tot de uitwisselbaarheid van generieke geneesmiddelen, met name in laag en middelhoge - inkomen landen (LMIL) in een mondiale context. **Hoofdstuk 1** geeft een algemene inleiding op deze kwesties die worden behandeld in dit proefschrift.

Ten eerste, het belang van generieke geneesmiddelen als kostenbeheersingsmaatregeling in volksgezondheidprogramma's is evident ongeacht het inkomenspeil van een land. Generieke geneesmiddelen zijn over het algemeen goedkoper in vergelijking met innovator geneesmiddelen, wat deels te wijten is aan de verminderde ontwikkelingskosten, omdat ze zijn goedgekeurd door de regelgevende instanties op basis van bioequivalentiestudies met de innovator of een comparatorproduct. Bioequivalente geneesmiddelen worden beschouwd als onderling uitwisselbaar, dat wil zeggen voorschrijfbaar en verwisselbaar, hetgeen de basis is voor het beleid van het voorschrijven van en substitutie door generieken. Voorschrijvenbaarheid betekent dat het generieke geneesmiddel kan worden voorgeschreven in plaats van het innovator product in een nieuwe/naïeve patiënt onder dezelfde voorwaarden, terwijl uitwisselbaarheid betekent dat de innovator kan worden gesubstitueerd door het generiek in patiënten onder chronische behandeling. Er wordt vanuit gegaan dat generieke geneesmiddelen met hetzelfde geneesmiddel uitwisselbaar zijn, hoewel dit niet uitgebreid door de regelgevende instanties is onderbouwd. Als consequentie hiervan zijn er verschillende opvattingen en toepassingen in landen met betrekking tot de vraag of generieke geneesmiddelen onderling uitwisselbaar zijn, met name geneesmiddelen met een smalle therapeutische index (NTI), aangezien het falen van bioequivalentie voor deze geneesmiddelen makkelijker aan te tonen is. Derhalve beschrijft dit proefschrift het onderzoek van de uitwisselbaarheid tussen generieke geneesmiddelen, met behulp van empirisch bewijs, door middel van gecorrigeerde indirecte vergelijkingen.

Ten tweede, terwijl regulatoire systemen en beleid in landen met hoge inkomens bestaan om de goedkeuring en het gebruik van generieke geneesmiddelen van zowel voorschrijven en uitwisselbaarheid te regelen, is er een gebrek aan informatie over

deze systemen en beleid in LMIL om pro-generisch beleid te ondersteunen. Verder, terwijl werkwijzen zoals de prekwalificatie van geneesmiddelen door de Wereldgezondheidsorganisatie (WHO) zorg kan dragen van de voorschrijfbaarheid door middel van het aantonen van bioequivalentie van producten geleverd in LMIL situaties, wordt generieke substitutie beschouwd als een nationale verantwoordelijkheid die op nationaal niveau moet worden aangestuurd. Derhalve analyseert dit proefschrift als casus modellen ook de goedkeuring van generieke geneesmiddelen in Afrika bezuiden de Sahara door het analyseren van de registratiegegevens uit Zimbabwe en van een gezamenlijk geneesmiddelen registratieproces, waarbij vier landen van de "Southern African Development Community" (SADC) betrokken zijn.

Ten derde, harmonisatie van de vereisten voor bioequivalentie, hoewel niet volledig, heeft belangrijke voordelen voor zowel de industrie en de regelgevers opgeleverd. Echter is het ineffectief om alleen de eisen te harmoniseren, als een bioequivalentie studie moet worden herhaald voor elk land vanwege de verschillende comparatorproducten die op nationaal niveau voor hetzelfde geneesmiddel moet worden geselecteerd. Derhalve reflecteert de laatste doelstelling van dit proefschrift over het gebruik van een algemeen wereldwijd comparatorproduct voor bioequivalentiestudies.

Hoofdstuk 1 introduceert ook het concept van indirecte vergelijkingen die zijn toegepast in gevallen waar meerdere interventies bestaan en waar onvoldoende bewijs is voor evaluatie van hun relatieve effect van directe vergelijkingen. Een bioequivalentiestudie tussen een generiek en een innovator is een vorm van directe vergelijking. Het uitvoeren van directe vergelijkingen tussen alle beschikbare generieke geneesmiddelen van hetzelfde geneesmiddel is niet alleen onpraktisch, maar het is ook geen regulatoire vereiste voor goedkeuring van generieke geneesmiddelen. Derhalve, een indirecte vergelijking van een behandeling is een praktische benadering om generieke geneesmiddelen te identificeren waarvan uitwisselbaarheid kan worden gegarandeerd, om zodoende uitwisselbaarheid in de klinische praktijk te ondersteunen zonder zorgen ten aanzien van de werkzaamheid of veiligheid als gevolg van uitwisseling.

Verschillende methoden zijn beschikbaar voor het uitvoeren van indirecte vergelijking: (1) naïef of niet-gecorrigeerde indirecte

vergelijkingen, (2) modellering gebaseerd op individuele patiëntgegevens (meta-regressie), (3) gemengde vergelijkingen van behandelingen op basis van Bayesiaanse statistiek (logistische regressie), en (4) statistische methoden met behulp van geaggregeerde gegevens, zoals een eenvoudige gewogen combinatie van aparte schattingen (gecorrigeerde indirecte vergelijking). In dit proefschrift is de gecorrigeerde indirecte vergelijking toegepast, daar het de eenvoudigste en meest geschikte methode voor bioequivalentiestudies is, omdat het gebruik maakt van publiek beschikbare gegevens en deels de kracht van gerandomiseerde gecontroleerde studies behoudt.

Hoofdstuk 2, Gecorrigeerde indirecte vergelijking van behandelingen van generieke geneesmiddelen pre-gekwalificeerd door de Wereldgezondheidsorganisatie, onderzoekt de uitwisselbaarheid tussen generieke geneesmiddelen met behulp van gecorrigeerde indirecte vergelijkingen gebruikmakend van gegevens van de prekwalificatie van geneesmiddelen door de WHO als case studies. Dit hoofdstuk gaat in op de methodologische kwesties en de toepasbaarheid van gecorrigeerde indirecte vergelijkingen van behandelingen in bioequivalentiestudies met WHO pre-gekwalificeerde generieke geneesmiddelen voor antimalaria, eerstelijns antituberculose en eerstelijns antiretrovirale geneesmiddelen. Deze drie klassen van geneesmiddelen omvatten de drie belangrijkste infectieziekten die invloed hebben op LMIL, met name in Afrika bezuiden de Sahara.

Hoofdstuk 2.1 bestudeerde de verschillende methoden voor het uitvoeren van gecorrigeerde indirecte vergelijkingen van behandelingen voor bioequivalentiestudies met artemether/lumefantrine generieke geneesmiddelen pre-gekwalificeerd door de WHO als een case model. In deze studie vergeleken we zes methoden die kunnen worden gebruikt voor het berekenen van de breedte van de betrouwbaarheidsintervallen voor de vergelijking op basis van *z* distributie (*z*0.9) zonder aanname van homogeniteit van varianties of van Student *t*-verdeling (*t*0.9, d.f.), met of zonder aannames van homogeniteit of heterogeniteit van varianties. Gegevens uit drie onafhankelijk uitgevoerde bioequivalentiestudies waarin drie generieke geneesmiddelen werden vergeleken met hetzelfde referentieproduct, werden gebruikt om indirect de relatieve biobeschikbaarheid tussen de generieke geneesmiddelen zelf te bepalen. Hoewel de verschillende onderzochte

methoden van indirecte vergelijking in deze studie consistente resultaten lieten zien, wordt de homoscedastische methode die gebruikmaakt van de Student *t*-test verdeling voor het berekenen van de breedte van het betrouwbaarheidsinterval aanbevolen, tenzij er duidelijke verschillen in varianties zijn, omdat het de meest conservatieve benadering is voor het bepalen van de betrouwbaarheidsintervallen voor gecorrigeerde indirecte vergelijkingen.

Gezien de precisie van de oppervlakte onder de concentratie-tijd curve (AUC) data kan men concluderen dat de mate van blootstelling van artemether en lumefantrine bioequivalent is tussen de bestudeerde generieke geneesmiddelen. Echter, gezien de precisie van de piek concentratie (C_{max}) van het geneesmiddel, is het niet mogelijk om equivalentie aan te tonen binnen de conventionele acceptatiegrenzen voor alle vergelijkingen, hoewel het wel mogelijk is om bioequivalentie te concluderen binnen de verwijde acceptatiegrenzen van 75-133%. Het ontbreken van de nodige precisie om bioequivalentie tussen generieke geneesmiddelen aan te tonen met betrekking tot de Cmax binnen de conventionele acceptatiegrenzen, indien nodig, hoeft onderlinge uitwisselbaar niet te beletten, aangezien C_{max} minder klinische relevant wordt beschouwd voor de relevante therapie.

Waargenomen werd dat hoewel indirecte vergelijkingen een effectieve benadering is voor het bevestigen van de uitwisselbaarheid van generieke geneesmiddelen, deze benadering onderhevig is aan minder precisie dan directe vergelijkingen. Daarom werd in **hoofdstuk 2.2** de invloed van de puntschatting en de power van de studie om bioequivalentie aan te tonen tussen generieke geneesmiddelen met behulp van gecorrigeerde indirecte vergelijkingen van behandelingen onderzocht. De power werd beschouwd als een bepalende factor in plaats van variabiliteit en de grootte van de steekproef, omdat de grootte van de steekproef wordt berekend op basis van variabiliteit en de gewenst power. Scenario's werden berekend waarbij een reeks van verschillende puntschattingen (0 – 14%) en statistisch power van de studies (50-99,99%) werden gecombineerd. Deze studie toonde aan dat de indirecte vergelijkingen equivalentie tussen generieke geneesmiddelen aantoonde alleen wanneer (a) de puntschatting verschillen tussen generieke geneesmiddelen klein waren (<5 %) voor elke voldoende gepowerde studie (=>80%), of (b) de verschillen

waren groot (maar minder dan 14%) en beide bioequivalentie studies waren 'overpowered' (bijvoorbeeld 10% verschil en power ≥95%). Wij concludeerden dat de mogelijkheid om uitwisselbaarheid tussen generieke geneesmiddelen aan te tonen niet alleen afhankelijk is van de echte verschillen tussen de producten, maar ook van de opzet van de gecombineerde oorspronkelijke generiek vs. referentie bioequivalentie studies, in combinatie met de power.

Hoofdstuk 2.3 en 2.4 past de gecorrigeerde indirecte vergelijkingen van behandelingen op respectievelijk diverse eerstelijns anti-tuberculose medicijnen en eerstelijns antiretrovirale geneesmiddelen pre-gekwalificeerd door de WHO toe. In deze twee studies werd de bruikbaarheid van de aanbevolen benaderingen van de vorige twee studies in het onderzoek naar de bioequivalentie tussen generieke geneesmiddelen onderzocht, alsmede de waarde van extra beperkingen in bio-equivalentie eisen met betrekking tot de puntschattingen in de oorspronkelijke studies. De meerderheid van de gecorrigeerde indirecte vergelijkingen van de generieke eerstelijns antituberculose middelen en de eerstelijns antiretrovirale geneesmiddelen pre-gekwalificeerd door de WHO, waren binnen de normale acceptatie grenzen van ±20%, en er waren geen generiek-generiek vergelijkingen buiten de ±30% voor de indirecte vergelijkingen, behalve één vergelijking voor efavirenz C_{max}. Het niet aantonen van equivalentie binnen de ±30% acceptatiegrenzen in 1 op 394 gecorrigeerde indirecte vergelijkingen moet worden geïnterpreteerd als een insignificant aantal, aangezien het minder dan 0,3% is van het aantal vergelijkingen en het verschil in C_{max} klinisch niet relevant is, ook omdat het waargenomen verschil tussen het test en het referentieproduct in een bio-equivalentiestudie na enkelvoudige dosis, in 'steady state' normaal gesproken kleiner is. Uit deze studies kan worden geconcludeerd dat, om uitwisselbaarheid tussen generieke geneesmiddelen te garanderen, de oorspronkelijke studies voldoende power moeten hebben, dat wil zeggen > 80%, en het verschil in de puntschatting ratio's niet groter dan 10% moet zijn. Dus, een beperking van de puntschatting in de oorspronkelijke studies is aan te bevelen indien generieke uitwisselbaarheid van belang is, bijvoorbeeld in geval van geneesmiddelen met een smalle therapeutische index.

Ten eerste, **hoofdstuk 2** toont aan dat gecorrigeerde indirecte vergelijkingen een bruikbaar instrument is om de relatieve biobeschikbaarheid te vergelijken tussen generieke geneesmiddelen

die zijn vergeleken met een gemeenschappelijk referentie product in directe vergelijkingen, om uitwisselbaarheid tussen generieke geneesmiddelen te garanderen. Verder, in tegenstelling tot de ±20% acceptatie grens gebruikt voor directe vergelijkingen, wordt een ±30% acceptatiegrens voorgesteld voor de gecorrigeerde indirecte vergelijkingen, vanwege de lagere precisie van indirecte vergelijkingen en omdat dit verschil niet klinische relevant lijkt te zijn.

Ten tweede, de uitkomst van deze vergelijkingen geeft aan dat de antimalaria artemether/lumefantrine, eerstelijns antituberculose en eerstelijns antiretrovirale generieken pre-gekwalificeerd door de WHO kunnen worden uitgewisseld in de klinische praktijk zonder enige zorgen ten aanzien van de veiligheid en werkzaamheid.

Ten derde, teneinde uitwisselbaarheid tussen het generiek en comparator en tussen generieke geneesmiddelen te garanderen, moeten het generiek en de comparator niet significant verschillen. In dit verband stellen wij een extra beperking van de puntschatting voor van ±10% als een algemene voorwaarde voor bioequivalentie, met name voor LMIL waar de regelgevers mogelijk geen richtlijnen kunnen geven aan gezondheidswerkers ten aanzien van uitwisselbaarheid van goedgekeurde producten, of in geval van generieke substitutie aanbevolen door de nationale regeringen of vergoedingsagentschappen. Een grotere beperking voor de puntschatting van ±5% wordt voorgesteld voor NTI geneesmiddelen, met name waar generieke uitwisselbaarheid van deze middelen niet beperkt is, noch vernauwde bioequivalentie acceptatie grenzen worden toegepast.

Hoofdstuk 3, Handelsvergunningen in Afrika bezuiden de Sahara, beschrijft twee studies die de resultaten verkregen in **Hoofdstuk 2** in de juiste context zet, dat wil zeggen, de WHO pre-gekwalificeerde producten zijn voornamelijk in sub-Saharisch Afrikaanse landen met de hoogste incidentie van HIV en AIDS, tuberculose (TBC) en malaria op de makt. Bovendien probeert dit hoofdstuk antwoord te geven of de resultaten van de gecorrigeerde indirecte vergelijkingen van behandelingen voor de pre-gekwalificeerde generieke geneesmiddelen naar deze setting kunnen worden geëxtrapoleerd.

Hoofdstuk 3.1 beschrijft de uitvoering van het registratiesysteem van geneesmiddelen in Zimbabwe, een laag-inkomen land in zuidelijk Afrika met een functioneel medicijnen regelgevend systeem, als een

casemodel. In deze studie stelden we vast dat Zimbabwe vier regelgevende routes heeft, waaronder (1) een volledige review, (2) een 'abridged' review (3) verificatie, en (4) regionale werkverdeling door het ZAZIBONA 'meaning looking into the future' gezamenlijke registratieproces. Een totaal van 2083 aanvragen werden ontvangen en 1002 producten zijn goedgekeurd tussen 2003 – 2015. Het duurt bijna 24 maanden (zonder start/stop klok systeem) om een product in Zimbabwe goed te keuren (totale mediane tijd voor alle producten was 710 dagen (IQR 422; 1065)). Deze studie toonde aan dat het mogelijk is om de nodige regelingen voor productregistratie van generieke geneesmiddelen te hebben die ervoor zorgen dat producten toegelaten op nationaal niveau van voldoende kwaliteit zijn en uitwisselbaar, en om resource-efficiënte benadering zonder doublures toe te passen. Verder, deze casestudie toont de toepasbaarheid van WHO PQT-m eisen aan met betrekking tot bioequivalentie, met inbegrip van de WHO PQT-m benadering van selectie van comparator producten van bioequivalentie studies.

Alhoewel de case study van Zimbabwe in **Hoofdstuk 3.1** de uitvoerbaarheid aantoonde van de toepassing van een marketing vergunningensysteem voor generieke geneesmiddelen zoals aanbevolen door de WHO, was de goedkeuringstijd langer in vergelijking met goed toegeruste regelgevende instanties. Dit kan contraproductief werken als patiënten vertraagde toegang hebben tot de benodigde geneesmiddelen alleen vanwege beperkingen in de capaciteit. Een strategie ter verbetering van de capaciteit van regelgevende instanties in deze omstandigheden is via informatie en gezamenlijke werkverdeling door middel van regionale economische groepen. **Hoofdstuk 3.2** kijkt naar een collaboratieve geneesmiddelen registratieproces tussen vier landen in zuidelijk Afrika als een voorbeeldfunctie om niet alleen de kwaliteit maar ook uitwisselbaarheid van generieke geneesmiddelen in die landen te garanderen. De analyse richt zich op de ontwikkeling van het gezamenlijke proces, de belangrijkste succesfactoren en onderzocht de duurzaamheid van dit initiatief.

Het ZAZIBONA initiatief begon in medio 2013 en is bijna 3 jaar operatief. De geïdentificeerde belangrijke succesfactoren zijn eigendom, effectief leiderschap, middelen van partners, waaronder cofinanciering, efficiënte kostenmodel, sociaal kapitaal, duidelijke rolverdeling en structuur, effectieve communicatie en aantoonbare resultaten. Hoewel het model de meeste factoren aan de orde stelt

die zorgen voor duurzaamheid, sommige kwesties zoals een monitoring en evaluatiekader, toegezegde financiering, en institutionalisering zijn vereist voor duurzaamheid op lange termijn. Van de 85 producten die werden beschouwd in deze periode van 2,5 jaar, ontvingen 32 een positief advies, 15 ontvingen een negatief advies, 10 werden ingetrokken door de aanvragers, van 25 werd nog een reactie van de fabrikanten verwacht en 3 waren nog onder review aan het einde van 2015. De mediane tijd voor een uiteindelijke laatste aanbeveling was 10 maanden (variërend van 5 - 23 maanden) inclusief de tijd van de fabrikant om te reageren op vragen. Het ZAZIBONA-model in het kader van globale harmonisatie-inspanningen toont aan dat samenwerking in beoordelingen haalbaar is en waarschijnlijk de meest pragmatische aanpak die landen in LMIL moeten gebruiken om capaciteit op te bouwen en om de kwaliteit en uitwisselbaarheid van geneesmiddelen op de markt te garanderen.

Hoofdstuk 4, Regelgevende perspectieven op globale harmonisatie van bioequivalence studies, becommentarieerd de selectie van comparatorproducten in bioequivalentiestudies in het kader van globale harmonisatie. Het toepassen van gecorrigeerde indirecte vergelijkingen van behandelingen vereist het gebruik van een gemeenschappelijk comparator om geldige resultaten te verkrijgen. Er is een aanzienlijke vooruitgang geboekt met betrekking tot de harmonisatie van de uitvoering van bioequivalentiestudies, echter, er zijn nog steeds verschillen met betrekking tot eisen voor comparator producten voor bioequivalentiestudies, die niet alleen de harmonisatie, maar ook de uitwisselbaarheid tussen generieke geneesmiddelen beïnvloeden. Dit commentaar beoordeeld en bediscussieerd de huidige voorschriften in specifieke jurisdicties, met inbegrip van de richtlijnen van de WHO voor comparator producten met de nadruk op de vereisten voor de comparatorproducten en voorgestelde opties voor een geharmoniseerde globaal comparatorproduct. Een comparatorproduct moet een directe link hebben met het innovatieve product waarvoor veiligheid en effectiviteit is aangetoond in 'pivotal' klinische studies om voorschrijfbaarheid en uitwisselbaarheid te garanderen. De meeste landen volgen de aanbevelingen van de WHO voor het selecteren van comparatorproducten en eisen dat het comparatorproduct wordt verkregen van hun nationale markt om uitwisselbaarheid van hun generieke geneesmiddelen te garanderen.

Deze aanbevelingen zijn alleen haalbaar in die weinige landen waar de herhaling van de bioequivalentiestudie winstgevend is, maar het is niet praktisch in alle andere landen. Bovendien roept het exclusieve gebruik van de lokale comparator om uitwisselbaarheid te garanderen ethisch en wetenschappelijk vragen op, omdat informatie kon worden gedeeld om te achterhalen of de buitenlandse comparator voldoende vergelijkbaar is en als een "variatie" van de lokale comparator kan worden gezien. Een aanvaardbaar globaal comparatorproduct zou het innovatorproduct of een aangewezen referentie product van goed gereglementeerde markten kunnen zijn. Deze globale harmonisatie is haalbaar, omdat het concept reeds wordt toegepast in het WHO prekwalificatie programma en echte harmonisatie garandeert, aangezien het zinloos is om alleen de eisen voor het uitvoeren van bioequivalentiestudies te harmoniseren, indien zo'n studie moet worden herhaald voor elk land vanwege de verschillende geselecteerde comparatorproducten op nationaal niveau.

Hoofdstuk 5 is een algemene discussie over de artikelen die in dit proefschrift zijn voorgelegd. Dit afsluitende hoofdstuk behandelt de relevantie van bio-equivalentie in generiek voorschrijvings- en substitutiebeleid die wereldwijd worden geïmplementeerd. Dit hoofdstuk behandelt ook voordelen en beperkingen, met inbegrip van methodologische kwesties van de gecorrigeerde indirecte vergelijkingen van behandelingen. De discussie eindigt met specifieke regelgevende beleidsaanbevelingen om generieke voorschrijfbaarheid en uitwisselbaarheid te garanderen.

De huidige regelgeving, zoals toegepast in de WHO PQT-m, ten aanzien van gemiddelde bioequivalentie zijn voldoende voor de meeste geneesmiddelen om uitwisselbaarheid tussen generieke geneesmiddelen waarvoor bioequivalentie is aangetoond met hetzelfde referentieproduct te garanderen. Om generieke uitwisselbaarheid te waarborgen, kan de benadering van de gecorrigeerde indirecte vergelijkingen van behandelingen worden toegepast. Tevens, voor sommige geneesmiddelen waarbij uitwisselbaarheid kritisch is, wordt een beperking van de puntschatting van ± 10%, of strenger, bijvoorbeeld ± 5% voor NTI geneesmiddelen, als een bioequivalentie acceptatie eis voorgesteld.

Een generiek voorschrijvings- en substitutiebeleid is alleen zinvol als het desbetreffende land beschikt over werkwijzen die garanderen dat producten op de markt alleen zijn goedgekeurd na demonstratie

van uitwisselbaarheid zoals aanbevolen door de WHO. De eis voor het aantonen van uitwisselbaarheid met het comparator product moet deel uitmaken van het goedkeuringsproces voor middelen op voorschrift, indien van toepassing. Verder, de regelgevende instanties moeten voldoende capaciteit hebben om bioequivalentie gegevens te beoordelen volgens de aanbevolen WHO normen en standaarden of gelijkwaardig daaraan.

Dit proefschrift toont, door gebruikmaken te maken van gegevens uit Zimbabwe, een land met lage inkomens als een case model, de haalbaarheid aan van de regelgevende instanties in deze situaties om voldoende werkwijzen toe te passen voor de toekenning van vergunningen voor generieke geneesmiddelen, met inbegrip van demonstratie van bioequivalentie. Niettemin, de uitvoeringsgegevens op goedkeuring statistieken in Zimbabwe suggereert dat er beperkte capaciteit is die als een belemmering fungeren kan voor toegang tot geneesmiddelen. Daarom, collaboratieve werkwijzen in geneesmiddelen registratie zoals het initiatief van de ZAZIBONA van vier sub-Saharisch landen kan een alternatieve benadering zijn om de beperkingen van de regelgevingscapaciteit in LMIL te omzeilen, om duplicatie te voorkomen en uitwisselbaarheid van generieke geneesmiddelen te garanderen, voordat handelsvergunningen worden verleent.

De mogelijkheid om een systeem van handelsvergunningverlening te hebben die nodig is, niet alleen om de resultaten waargenomen met de gegevens van gecorrigeerde indirecte vergelijking van de WHO PQT-m, maar ook als basis voor de implementatie van pro-generisch beleid vooral in LMIL, worden benadrukt in **Hoofdstuk 5**.

Een belangrijk aspect in samenwerkingsverbanden zoals beschreven in **hoofdstuk 3.2** is de behoefte aan geharmoniseerde regelgeving; dus de vereiste van het gebruik van een nationale comparatorproduct verkregen van de plaatselijke markt is onpraktisch in dit opzicht omdat het meerdere bioequivalentie studies vereist met een nationale comparatorproduct voor elk land. Wij stellen een globale benadering voor van de selectie van comparatorproducten voor bio-equivalentie studies om de kosten van productontwikkeling voor generieke geneesmiddelen, alsmede onnodige administratieve lasten te minimaliseren. In dit verband stellen wij voor dat de WHO PQT-m benadering voor de selectie van comparatorproducten te volgen.

CHAPTER 7

ADDENDUM

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