Generic medicines

Interchangeability of WHO-prequalified generics

Generic medicines can enable huge cost-savings as they create competition, driving down prices. In medicines regulation and in WHO prequalification, the efficacy of generics is demonstrated by bioequivalence studies.

WHO medicines prequalification has facilitated academic research, and has itself been a subject of academic research. Adjusted indirect comparisons were conducted, using the results of separate bioequivalence studies for WHO-prequalified generics against the same comparator product. The comparisons found that the generics can be considered as clinically equivalent among each other. Recommendations are provided for regulatory assessment of generics in WHO Member States and for possible approaches to harmonization of bioequivalence requirements to facilitate access to needed products.

Impact of generics in public health

Use of generic medicines significantly reduces the cost of medicines to both governments and patients. Generic medicines are those produced without a licence from the innovator company when the patent or other market exclusivity rights on the innovator product has expired.

A striking example of the impact of generics is the evolution of prices on the antiretroviral (ARV) market. The median price per patient per year of first-line ARV therapy dropped from about US$10 000 to less than US$100 with the introduction of generic FDCs, enabling the scaling-up of access to antiretroviral therapy from 0.5 million people on ARVs in 2003 to 15.8 million globally in 2015 *(1)*.

Bioequivalence assessment

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 dose.

The requirement of bioequivalence studies for generics in lieu of clinical efficacy and safety studies was introduced

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The research presented in the PhD thesis was conducted under the umbrella of the Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation (www.pharmaceuticalpolicy.nl), which is based at the Division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University in the Netherlands. The Collaborating Centre aims to develop new methods for independent pharmaceutical policy research, evidence-based policy analysis and conceptual innovation in the areas of policy-making and evaluation in general.

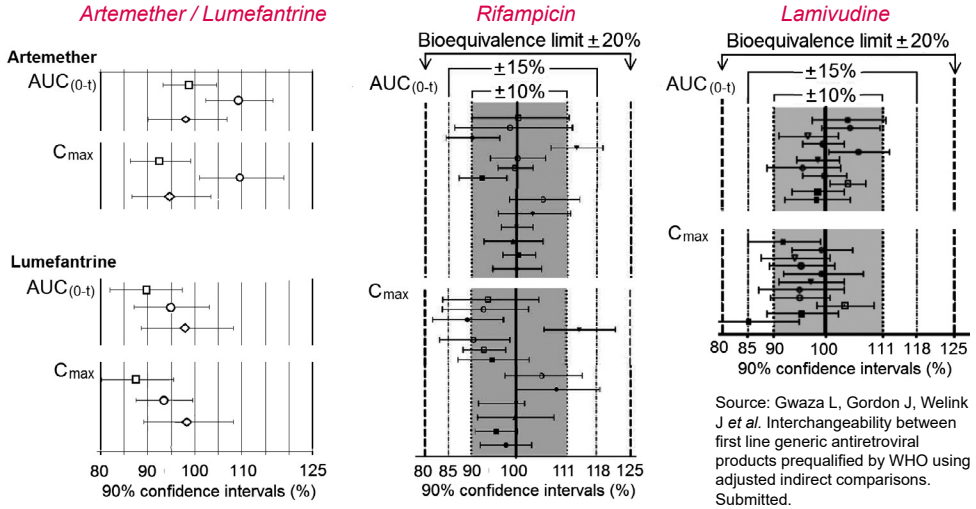
in the United States (U.S.) in 1984 and is now a widely accepted regulatory standard. By applying this approach to ARVs, including fixed-dose combinations, the WHO Prequalification Programme was instrumental in scaling up global access to safe, efficacious, quality ARV treatment at affordable cost in the early 2000s *(2)* .

Adjusted indirect comparisons

Bioequivalence studies compare a generic product with a comparator product, usually the innovator product. However, in practice, it is not unusual for generics of the same drug to be interchanged between each other. Performing direct comparisons between all available generics of the same drug is not feasible. Therefore, adjusted indirect comparisons were performed among WHO-prequalified generics, using data from independent bioequivalence studies conducted against the same comparator product. A total of 59 generic products were compared in two published studies *(3, 4)* and one study submitted for publication *(Figure 1)*.

Figure 1: **Pharmacokinetic parameters for WHO-prequalified generics**

A. Original results (examples)



Source: *(3)*

Source: *(4)*. Also compared, results not shown: Ethambutol, pyrazinamide, isoniazid

Source: Gwaza L, Gordon J, Welink J *et al.* Interchangeability between first line generic antiretroviral products prequalified by WHO using adjusted indirect comparisons. Submitted.
Also compared, results not shown: Efavirenz, tenofovir, emtricitabine.

$AUC_{(0-t)}$ = Area under the time-concentration curve; C_{max} = Peak plasma concentration

□○◊▼■●♦ Different symbols represent different WHO-prequalified generics.

B. Indirect comparisons

- Different computational methods were explored to investigate the ability of indirect comparisons to demonstrate the interchangeability of generics.
- The WHO-prequalified generics were found to be not only bioequivalent with the comparator, but also interchangeable among each other without safety / efficacy concerns.
- The ability of indirect comparisons to demonstrate interchangeability between generics was found to be dependent not only on the real differences between the products, but also on the design of the original bioequivalence (BE) studies being combined. The findings could be used to consider further requirements for BE studies in situations when interchangeability (switchability) of generics is critical *(5)*.

The results show that the different WHO-prequalified generics included in each study can indeed be considered as clinically equivalent.

Regulatory assessment of generics: the example of Zimbabwe

Uptake of generics

The use of generic products is a national responsibility. Registration of generic products and generic substitution policies are well advanced in high-income countries, but are still under development in low- and middle-income countries. WHO is providing norms and standards for medicines quality assurance in Member States, including resource-constrained ones. Nonetheless, in many countries the demonstration of interchangeability remains non-existent or is not fully enforced. Likewise, some pharmaceutical manufacturers in these countries are inexperienced in performing bioequivalence studies to the required regulatory standard.

Even where regulatory review is done according to WHO-recommended standards, including those on of demonstration of interchangeability for generics *(6)*, regulatory resource constraints may hinder the uptake of generic products. An analysis of the regulatory system in Zimbabwe[1] showed that the number of marketing authorization applications received exceeds the available regulatory capacity, resulting in long timelines to approval. In the period from 2003–2015 a total of 2 083 applications were received, and 1 002 products were approved, while the rest were either pending or refused registration. The overall median time from application to registration of a product was 710 days (inclusive of manufacturers' time to respond to queries), with an interquartile range of 422-1065 days.

Collaborative approaches

Collaboration and information-sharing between regulatory authorities are the most resource-efficient strategies to ensure access to medicines, particularly in resource-constrained settings. Harmonization and work-sharing approaches are being implemented in all regions of the world, including the regional economic communities in Africa.

Since 2012, Zimbabwe participates in the WHO collaborative procedure for registration of WHO-prequalified products, which has been taken up by 27 countries including 21 African countries at the time of writing[2]. This procedure entails granting of national marketing authorizations based on a verification that the product is technically the same as prequalified by WHO.

Since 2013, a regional collaborative medicine registration process named Zazibona[3] is practised among Botswana, Namibia, Zambia and Zimbabwe. Applicants submit dossiers to at least two of the four participating authorities. Assessment is done jointly with one authority as rapporteur, leading to simultaneous registration in all relevant countries. WHO provides an electronic platform for information exchange and facilitation support.

Zazibona has enabled product approval with reduced timelines. A review of

[1] Gwaza L, Wekwete W, Dube A, García-Arieta A, Leufkens H. Assessment of the performance of the Medicines Control Authority of Zimbabwe from 2003 to 2005. Draft manuscript.

[2] http://apps.who.int/prequal/info_applicants/collaborative_registration_main.htm

[3] www.mcaz.co.zw/index.php/downloads/category/21-zazibona

documents for 85 applications considered from October 2013 to December 2015[4] showed that 32 had received a positive opinion, 15 had received a negative opinion, 10 were withdrawn by the respective applicant, 25 were awaiting responses from applicants and 3 were under review. The total review time, including the time for applicants to respond to questions, amounted to a median of 10.3 months for a positive recommendation – with an additional 1.5 months until final approval – and 12.4 months for a negative opinion. The main reasons for negative opinions were failure to respond to requests for additional information or incomplete submissions (50%), and bioequivalence-related deficiencies (40%).

Key success factors in the Zazibona initiative have been identified, including ownership, effective leadership, partner resources including co-financing, a cost-efficient model, social capital, clear roles and structure, effective communication and demonstrable results. On the other hand, a monitoring and evaluation framework, committed funding and institutionalization are still required to ensure sustainability. Overall, the Zazibona initiative can be considered as an effective collaborative mechanism to facilitate rapid access to needed medicines, and could serve as a model to be followed by other developing countries.

Selection of comparator product

Collaboration critically depends on harmonized regulatory systems. A major barrier for global harmonization with respect to generic medicines – and for the adjusted indirect comparisons described earlier – is the difficulty to use a common comparator product globally. Despite considerable progress in harmonizing regulatory requirements for bioequivalence studies, disparities remain with respect to the requirements for comparator products.

WHO recommends that the comparator product should be, in order of priority: 1) an innovator product available on the local market, 2) the national market leader, 3) a WHO comparator, 4) an innovator product imported from an ICH country, and 5) a generic product approved in an ICH country *(7)*. WHO recommends against using a generic product as a comparator as long as an innovator pharmaceutical product is available, because this could lead progressively to less similarity between products, a phenomenon called "biocreep".

Most countries follow these general principles and require the comparator product to be obtained from their national markets to ensure that the generics will be interchangeable with the comparator as well as among each other. Some countries accept a comparator from a foreign market, provided there is in vitro demonstration of similarity with the local comparator.

For pharmaceutical companies however, conducting specific bioequivalence studies for each country makes economic sense only if the market size is large. Thus, the recommendation to use a local comparator is impractical in many settings, particularly in LMICs which often have very small market sizes.

In the context of regional harmonization it may be found advantageous to establish a regional comparator product for which quality, safety and efficacy has been established. For example in the European

[4] Gwaza L, Mahlangu GN, Gaeseb J, Selelo S, Mwape E, García- Arieta A et al. Collaborative Process in Medicines Registration to Improve Access to Medicines in Southern African Countries. Draft manuscript.

Union the innovator product as marketed in different EU countries is considered to be the same because its approval is based on the same documentation proving efficacy and safety; it would therefore be acceptable in all countries. In recent years, the cooperation approach has been extending beyond the EU system with the International Generic Drug Regulators Programme (IGDRP) pilot for generic medicines (see also the article on page *361*), with a working group on bioequivalence looking at some of the specific issues mentioned in this paper.

It is acknowledged that differences may exist between the innovator product in one market and the same innovator product in other markets[5]. To ensure the similarity of comparator products, NMRAs could compare their qualitative and quantitative composition, specifications, manufacturing site and process to see whether the products are sufficiently similar, and could make that information public.

Acceptance of foreign or international comparators would reduce the number of in vivo bioequivalence studies needed, saving resources that could be spent on more in-depth studies for example under fasting and fed conditions, on different strengths of a product, or in patients under real conditions of use.

WHO prequalifies generics for supply to multiple countries, especially LMICs, where they are often accepted by NMRAs without requiring any further studies with a local comparator product. Therefore, the experience of WHO PQT provides insights on how to identify and obtain an acceptable comparator product in a global context.

Conclusions and recommendations

The indirect comparisons described earlier in this paper have shown that WHO-prequalified generics may be interchanged among each other without any safety and efficacy concerns. This is pivotal in supporting generic prescribing and substitution policies, which are important to increasing access to medicines.

However, these findings cannot necessarily be extrapolated to other nationally approved products, especially in resource-constrained settings. Although NMRAs should ensure that generic products are interchangeable before granting approval, they may have different requirements and review practices, and many have significant limitations of capacity and resources.

Harmonized requirements for bioequivalence and comparator products are critical for collaboration. It must be noted that this approach works only among countries applying similar and consistent standards in line with WHO guidelines, which may not be the case in most Sub-Saharan African countries.

Nevertheless, the WHO prequalification approach for demonstration of bioequivalence could be followed as a global approach. This is done in the collaborative registration procedure, where

[5] For example, carbamazepine (Tegretol®) in the U.S. is different from carbamazepine (Tegretol®) approved in Europe. This is because the product has evolved separately in the two jurisdictions after the clinical trials, at a time when demonstration of bioequivalence was not yet required for the approval of changes. Carbamazepine is an antiepileptic with narrow therapeutic index, and differences between the reference products could mean that generics approved as bioequivalent to one or the other reference product are not necessarily interchangeable. The European reference product is therefore not acceptable in the U.S. and vice versa. In the specific case of Tegretol® the manufacturer has developed an in vitro-in vivo correlation, so that a simple dissolution test can provide information about the similarity between these products.

the outcomes of bioequivalence studies submitted to WHO are accepted without further comparisons of their comparator product against the national one. Similarly, in the Zazibona collaborative initiative, the WHO prequalification approach for selecting comparator products is applied, and one bioequivalence study is sufficient for all four countries.

To verify generic interchangeability, the adjusted indirect comparison approach described earlier in this paper could be used to support evidence-based clinical decisions by healthcare professionals. To enable such comparisons, the regulators should consider making data from approved bioequivalence studies publicly available. For situations when high assurance of interchangeability among generics is critical, for example for medicines with a narrow therapeutic index, regulators may wish to apply stricter national requirements for bioequivalence.

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