

**COMMENTARY**

# The controversy around technical standards for similar biotherapeutics: barriers to access and competition?<sup>†</sup>

Claudia Patricia Vaca González  | Carolina Gómez Muñoz**Correspondence**

Claudia Patricia Vaca González. Pharmacist. Pharmacoepidemiologist. Professor at the National University of Colombia. Director of the National University's Think Tank "Medicines, Information and Power". Former Senior Advisor to the Minister of Health of Colombia. Member of WHO Advisory Committee on Safety of Medicinal Products.

Email: cpvacag@unal.edu.co

Carolina Gómez Muñoz. Lawyer. LLM UC Berkeley. Member of National University's Think Tank "Medicines, Information and Power". Former Director of Medicines and Health Technologies, Ministry of Health of Colombia.

Email: cagomezmu@unal.edu.co

**KEYWORDS:** biosimilar pharmaceuticals, developing countries, drug approval, drug substitution, drugs, generic, pharmacoepidemiology, World Health Organization

## 1 | INTRODUCTION

Technical standards for medicines' marketing authorization are technical issues. Nonetheless, policy, political and commercial matters also play a role.

Given that technical standards impact competitor's market entry pace and prices, regulators are compelled to strike a balance between access, safety, and quality,<sup>1</sup> determine which standards are *necessary* to protect human health and tear down *unnecessary* barriers to competition.

There is a consensus that generic medicines can be approved via "abbreviated pathways". However, for biotherapeutics, there is an ongoing global controversy as to whether the abbreviated approach is also applicable. It evolves as emerging evidence about safety and efficacy of biosimilars gets published. We identified three types of regulatory barriers to competition. Here we propose a conceptual approach to analyze them.

The triangle illustrates the rationale behind the debates around the regulatory requirements for biosimilars and the impact of those requirements on access (Figure 1).

## 2 | UNDERLYING IDEA

Biotherapeutics account for a growing proportion of pharmaceutical expenditure. In the Latin American region, payment of biotherapeutics is done mostly with public resources, often through exceptional mechanisms or in compliance with court orders. This results in inequalities, as many biotherapeutics are for rare diseases, autoimmune diseases, and cancer.<sup>2</sup>

Many of the patents for biotherapeutics have begun to expire;<sup>3</sup> therefore, the main obstacle to widen access and lower expenditure are requirements for marketing authorization and usage of competitors.

A rigid regulatory approach for marketing authorization of biotherapeutic competing drugs has been put in place. In the mid-2000s, the main issue around biotherapeutics was quality control, the difficulty to thoroughly characterize complex therapeutic proteins, and to standardize and control a living system.

In absence of sufficient knowledge about their design, evaluation, and usage, a precautionary approach was taken for marketing authorization of generic biotherapeutics. In 2006, EMA issued the first guidelines.<sup>4</sup> WHO Followed suit in 2009.<sup>5</sup>

Both required a comparability exercise between the competitor and the reference biotherapeutic. Bearing in mind the impossibility to prove full identity, the comparability exercise is aimed at showing their *similarity*. The comparability exercise starts with comparative physicochemical and functional characterization and ends with comparative safety and efficacy clinical studies (known as confirmatory clinical studies). These studies may be less extensive, depending on the detected characterization differences, but they are nonetheless always required.

**Abbreviations:** EMA, European Medicines Agency; INN, International Nonproprietary Name; INNBNQ, International Nonproprietary Name Biological Qualifier; PD, Pharmacodynamics; PK, Pharmacokinetics; WHO, World Health Organization.

<sup>†</sup>"Acknowledging that national authorities may use different terminologies when referring to similar biotherapeutic products" as established in Resolution WHA67.21. Some other terms will be used in this paper as synonyms of the term "biosimilar": biogenerics or bio-competitors, used in economics papers to refer to off-patent drugs.

Several analytical techniques are now available to characterize the structure and biological activities of biotherapeutics; evidence has shown that detected physicochemical differences are not clinically relevant.<sup>6</sup> Hence, it is possible now to consider waivers of confirmatory trials, without compromising the safety of the population.<sup>7,8,9</sup>

In 2014, EMA updated its guidelines to allow waivers of confirmatory trials:<sup>7</sup> *"In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product..."*

The World Health Assembly, in 2014, gave WHO the mandate *"to update the 2009 guidelines, taking into account the technological advances for the characterization of biotherapeutic products"*.<sup>1</sup> Since then, WHO has issued guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products which allow, on a case by case basis, and in exceptional circumstances, to waive confirmatory trials: *"...The clinical comparability exercise is a stepwise procedure that should begin with PK/PD studies and usually continues with one controlled clinical trial addressing comparative safety and efficacy. In exceptional circumstances, data obtained in clinical PK/PD studies may suffice to confirm biosimilarity established in preceding steps (see 6.2.1)..."* It also published, in October 2018, the *"WHO Questions and Answers: similar biotherapeutic products"* document where it implies, in Question V-6, that it is possible to waive the comparability efficacy study. Both WHO documents reflect a less rigid approach.<sup>8,9</sup>

### 3 | THE TRIANGLE OF TECHNICAL BARRIERS EXPLAINED

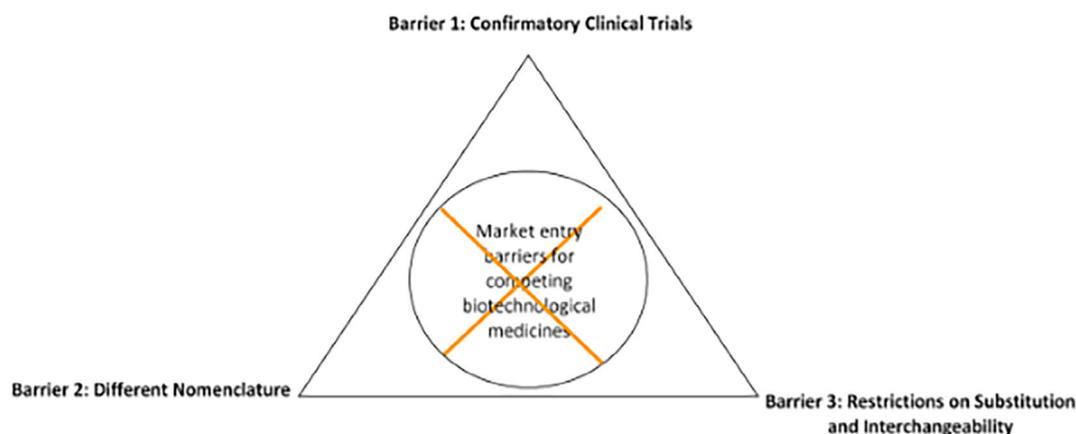
The Triangle of Technical Barriers is a useful tool to analyze the arguments expressed by different stakeholders in public policy debates around regulation of biosimilars. We will briefly comment on each angle (Figure 2).

#### KEY POINTS

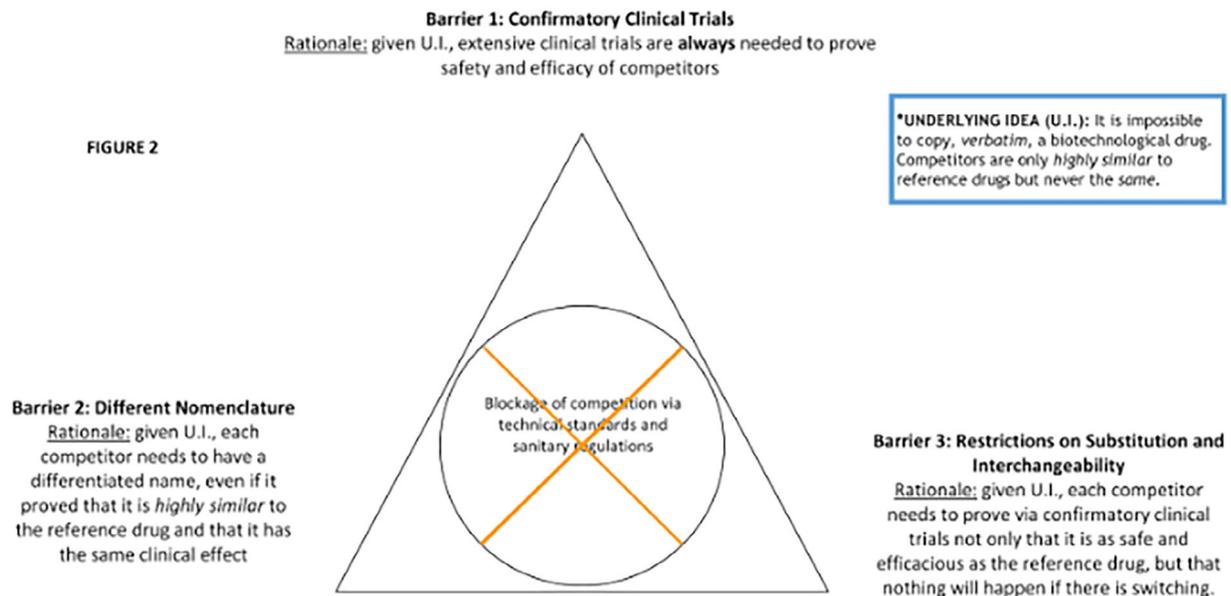
- Some technical standards for market authorization of biosimilars could constitute unnecessary barriers to competition and, therefore, access to such medicines.
- There are at least three types of regulatory requirements for biosimilars that have created controversy: (i) requiring extended confirmatory clinical trials for all biosimilars seeking marketing approval; (ii) naming each biosimilar differently, by using suffix that "qualifies" the International Nonproprietary Name (INN) in order to distinguish each producer; and (iii) restricting biosimilar substitution/interchangeability/switching.
- The stand taken by local regulators in such controversy, will determine whether such requirements constitute a barrier to biosimilar competition and access.
- The stand taken by each local regulator in such controversy is not only a technical or scientific matter but it is also a matter of political economy and commercial interests.
- The triangle of Technical Barriers proposed in this commentary constitutes a useful tool for analyzing the controversy.

#### 3.1 | Barrier 1: Confirmatory clinical trials

The comparability paradigm, introduced by EMA and WHO guidelines, entails performing a complete comparability exercise including always confirmatory clinical trials, as a requirement for marketing authorization of all generic biotherapeutics.



**FIGURE 1** Potential technical obstacles to competition. Source: self-drafted



**FIGURE 2** Rationale behind technical barriers to competition and access

It has been shown that such confirmatory trials entail considerable efforts that are unnecessary, time-consuming, and costly. Development costs of a biosimilar vary between 100 and 200 million dollars and can take more than 5 years.<sup>10</sup> In the case of rare disease, for statistical or clinical reasons, it might be difficult to comply with the requirement of comparative non inferiority clinical trials.

McCamish et al. 2013 and Frapaise 2018 show that phase III trials are not fit to detect clinical differences between biosimilars and originators and that analytics provide more sensitive information than clinical studies. Scientific advances and increased knowledge about proteins justify a flexibilization of the current paradigm that requires, in all cases, a confirmatory clinical trial for biosimilar approval. We propose, therefore, that confirmatory trials should be made the exception instead of the general rule. This revision of the comparability exercise constitutes a good incentive for market competition without raising any concerns regarding safety. Exceptions would be applied to more complex proteins, as Frapaise and other authors suggest.<sup>11-14</sup>

The EMA is moving slowly to revise the comparability paradigm, as commented before,<sup>7</sup> and some middle-income countries, like Colombia and Brazil, have allowed simplification or even waivers of confirmatory trials in specific circumstances, too.<sup>15</sup> It has also been documented that both the FDA and the EMA have approved less complex therapeutic proteins via abbreviated pathways.<sup>3,16</sup>

The adoption of this simplified and pro-competitive approach in the global south would be facilitated if WHO amended its guidelines, so that they expressly include language about waivers of confirmatory efficacy and safety trials, encourage PK/PD studies as a minimal requirement instead, and clarify that this should be the general principle that should guide the writing of regulations. The amendment should be complemented by the recommendation to strengthen pharmacovigilance systems by including regulations that require

sponsors to present risk management plans as a requisite for marketing approval obtaining a certification on Good Pharmacovigilance Practices.

### 3.2 | Barrier 2: Different nomenclature for bio-competitors

Usage of generic names (International Nonproprietary Names -INN-) instead of brand names reduces information asymmetry.<sup>17</sup> The use of INN on prescription, dispensation, labels, and pharmaceutical advertising is part of WHO's ethical criteria for medicinal drug promotion.<sup>18</sup>

However, there have been voices asking to instate a different mechanism for naming biotherapeutics. It is called the INN Biological-Qualifier (BQ), aimed at differentiating biotherapeutics according to their producers. Adding a BQ for the INN would send a wrong signal regarding trust on biosimilars.

The INN BQ<sup>19</sup> has been embraced by some countries (US, Japan, and Australia).<sup>20</sup> The Federal Trade Commission of the USA drew attention on the negative effects it could have on substitution and the confusion it could create on prescription and dispensation of biosimilars.<sup>21</sup> The INN BQ was initially endorsed by WHO,<sup>22</sup> but several countries, predominantly from the global south, opposed it.<sup>23</sup> The EMA also rejected it.

### 3.3 | Barrier 3: Restrictions on substitution/interchangeability

The presence of various competitors in any given pharmaceutical market does not ensure perfect competition. Many restrictions have been introduced to the possibility of simply choosing the cheapest available

medicine. In the case of synthetic generics, those restrictions comprise an explicit list of generics allowed for switching.<sup>24</sup>

In the case of biotherapeutics, there is debate as to whether a competitor can automatically be used to replace the reference product, which is usually more expensive.

The EMA gave freedom to countries to decide on interchangeability for biosimilars. While Spain introduced strong restrictions,<sup>25</sup> Norway has encouraged switching by the government, based on monitoring and clinical studies.<sup>26</sup> Recently, European experts stated that it is unlikely that two products, comparable in terms of the population exposed, would show any differences in safety or efficacy in individual patients after a switching; therefore, it should be concluded that biosimilars authorized by the EMA are interchangeable.<sup>27</sup> The FDA took the opposite approach at recently published guidelines for interchangeability.<sup>28</sup>

WHO guidelines do not address the issue, but any recommendation should bear in mind that biased information and marketing strategies also end up having a placebo effect on patients, when they are aware of substitution from the branded biotherapeutic to the cheaper generic.<sup>14</sup>

In this context, probably no guideline on interchangeability or substitution needs to be issued at an international harmonization setting. What countries need, especially developing ones, is just a simple signal that the marketing authorization issued to a competitor means that it has sufficiently proved its clinical equivalence with the reference product.

We think that public policies, rather than clinical trials, that spread unbiased information and counterbalance marketing strategies are the best way to address the lack of confidence in generics. WHO could advocate for this alternative, instead of promoting redundant trials to address fears by physicians and patients. As for the demand by physicians to have clinical data, in order to reduce their mistrust in biosimilars, PK/PD studies provide sufficient and relevant clinical information.

## 4 | CONCLUSION

Technical standards for approval of medicines impact competition, access, and the right to health. The adoption process of such standards takes place in contexts where there are political and commercial interests by politicians, industry, and other stakeholders. It is desirable that regulations be widely, publicly, and transparently discussed before they are formally adopted. The Triangle of Technical Barriers is a useful tool of analysis for those discussions.

### CONFLICT OF INTERESTS

The authors declare no conflict of interests.

### ACKNOWLEDGEMENTS

The authors did not receive any funding for this research.

The authors wish to thank the contributions and support by Mrs. Luisa María Gómez, pharmacist, who has conducted research on the

placebo effect caused by misinformation regarding generic substitution and helped review the paper, in particular, the section "Barrier 3: Restrictions on Substitution".

### ORCID

Claudia Patricia Vaca González  <https://orcid.org/0000-0001-5489-2671>

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**How to cite this article:** González CPV, Muñoz CG. The controversy around technical standards for similar biotherapeutics: barriers to access and competition? *Pharmacoepidemiol Drug Saf*. 2020;1-5. <https://doi.org/10.1002/pds.5100>