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Research Report

The international debate on generic medicines of biological origin

Research Paper, No. 82

Provided in Cooperation with:

South Centre, Geneva

Suggested Citation: Velásquez, Germán (2017) : The international debate on generic medicines of biological origin, Research Paper, No. 82, South Centre, Geneva

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Research
Paper
November 2017

82

THE INTERNATIONAL DEBATE ON GENERIC MEDICINES OF BIOLOGICAL ORIGIN

Germán Velásquez



RESEARCH PAPERS

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THE INTERNATIONAL DEBATE ON GENERIC MEDICINES OF BIOLOGICAL ORIGIN

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SOUTH CENTRE

NOVEMBER 2017

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EXECUTIVE SUMMARY

The debate on generic medicines is not new. What makes it different today is that attacks levelled against biological products are couched in ever more “technical” and abstruse language that confuses even the World Health Organization (WHO).

Innovative biological drugs, which have been introduced on the market in the past 20 to 30 years,¹ make up, in terms of numbers, no more than 2 per cent² of the WHO Model List of Essential Medicines but, in terms of cost, account for 15 per cent to 20 per cent of national drug expenditure.

The high price of biological drugs stems mainly from two new factors: first, a change in the pharmaceutical industry’s approach to price-setting and, secondly, the introduction of additional barriers to the entry of generics into the market. In any debate on the impossibility of producing “identical” drugs, it should be made clear that what is at stake is not identical products but therapeutic equivalents. What matters to the patient, after all, is whether or not the drug can prevent, cure or mitigate the effects of the illness.

¹ Human insulin was first introduced on the market by Eli Lilly in 1982.

² Eleven products, compared to thousands of chemically synthesized products that flood world markets.

I. INTRODUCTION

Over the past 40 years, transnational pharmaceutical companies have used specious arguments based on quality standards or intellectual property rights to attack and disparage generic drugs in a bid to defend their highly lucrative monopolies. The pharmaceutical industry is currently waging a war against competition from generic biological drugs on the pretext of upholding “technical and scientific standards”.

“Biological medicines are those in which **active protein substances** are extracted from living organisms, and are then purified and modified using advanced biotechnology. Because biological drugs derive from living organisms, they are characterized by more complex structures and functions, and higher molecular weight, than chemically synthesized drugs. There is no consensus on the difference in meaning between “biological” and “biotechnological”, consequently these terms tend to be used interchangeably” [unofficial translation].³

Biological drugs, made from active protein substances that are reproduced through biotechnological methods, are increasingly used worldwide to treat arthritis, diabetes, cancer, haemophilia, multiple sclerosis, hepatitis and a number of rare diseases. By contrast, most drugs in use 20 years ago were either plant-derived or chemically synthesized. According to industry forecasts, pharmaceutical sales are expected to grow annually by 6.3 per cent between 2016 and 2022, when they should total US\$ 1.12 trillion in sales, with biological drugs making up 50 per cent of the market.⁴

Whether or not there is an adequate supply of generic biological drugs available will be crucial to ensuring the economic viability of health systems in both developing and developed countries.

³ V. Vivancos, “¿Qué diferencias hay entre los medicamentos biológicos y los tradicionales?”, INESEM online publication. <https://revistadigital.inesem.es/biosanitario/medicamentos-biologicos-tradicionales/>.

⁴ C. Lindgren, “World preview 2016: Outlook to 2022”, EvaluatePharma. <http://info.evaluategroup.com/rs/607-YGS-364/images/wp16.pdf>.

II. THE PROBLEM OF PATENTS AND DATA EXCLUSIVITY

As we know, the discovery of an innovative product entitles the originator company to take out a patent protecting the product for a minimum of 20 years after its release. At the end of that period, the product falls into the public domain and may be marketed by other companies. When a patent is registered, the data on the product becomes public knowledge but the originator may deny any other company the right to market the product for the duration of the patent in a specified territory.

Once the patent on a medicine expires, other companies are entitled to market products containing the same active principle. These drugs are known as “generics”. Prior to the marketing of a generic, studies must be carried out to demonstrate that it is equivalent to the innovative product.

Since most biological drugs remain under patent protection for at least 20 years, laboratories are able to establish monopolies, frequently setting very high prices, as is the case with many recent cancer drugs.⁵ Previously, when most drugs were chemically synthesized, the pharmaceutical industry set prices based on the estimated cost of research and development (R&D). Today, prices are no longer determined by production costs but by the supposed “value” of the medicine or its effects on or benefits to society. This new price-setting trend threatens the economic viability of our health systems.

Another way to extend monopolies is via “data exclusivity” (or “data protection”), a concept that certain governments, especially those of the United States and the European Union (EU), have included in bilateral trade agreements.

Data exclusivity is a practice whereby national drug regulatory authorities deny access to the registration files of an innovative product to any company seeking to market a therapeutically equivalent generic version, for a fixed period of time (five, eight or more years). Data exclusivity, which is different from a patent, can have a major impact in countries where the product is not protected by a patent, giving rise to the same type of monopolies as patents do.

The type of data covered by exclusivity clauses includes reports on clinical trials and all the other information that pharmaceutical companies must submit to national regulatory authorities in order to register a new medicine that they wish to introduce on the market.⁶

Multinationals have been pushing to obtain exclusive rights over data on their clinical trials in order to delay the entry into the market of competitor generics. In addition to patents and data exclusivity, various legislation exists, for instance in the United States and the EU, granting further market protection in the form of an extra period of time during which authorization to sell a generic is denied.

Chemically synthesized generics have played, and will continue to play, an important role in providing access to medicines in markets dominated by patent-protected drugs that are

⁵ Where treatment can cost over US\$ 100,000.

⁶ MSF Technical Brief: “Data exclusivity in international trade agreements: What consequences for access to medicines?” May 2004.

often priced beyond the means of individuals or health systems. Many countries are striving to ensure broader access to medicines by marketing generics since a sufficient supply of both chemically synthesized and biological products is fundamental to the survival of health systems in both developed and developing countries.

It is estimated that by 2020, half of the biological drugs that currently generate multimillion-dollar profits for transnational corporations will go off patent.⁷ Some patents have already expired, which means that the drugs in question may be reproduced freely unless regulatory barriers are introduced that block or limit their marketing. There is an ongoing debate leading to much confusion over how national regulatory authorities should set standards for the approval of “biosimilars”, “bioequivalents”, “biogenerics” or simply biological generics.

⁷ C. Lindgren, op. cit. <http://info.evaluategroup.com/rs/607-YGS-364/images/wp16.pdf>.

III. WHY ARE GENERIC DRUGS THE “SAME” AND BIOSIMILARS ONLY “SIMILAR” TO THEIR CORRESPONDING REFERENCE PRODUCTS?

The World Health Organization refers to “similar biotherapeutic products”, whereas the EU and the European Medicines Agency (EMA) refer to “biosimilars” or “similar biological medicinal products”. In the United States, the same medicines are known as “follow-on biologics” or “follow-on protein products”.⁸

III.1. Chemically Synthesized versus Biological Medicines

Biological drugs are characterized by a more complex structure and a higher molecular weight than chemically synthesized ones. Thus, their design, characterization, production, storage and conservation can all be more complicated. Most chemically synthesized medicines are administered orally, whereas biological drugs are always administered via injection or infusion in a hospital environment.

The regulations governing biological products also seem more complex than those applicable to smaller molecules of chemical origin. This is in large part because WHO has not set global standards and countries like the United States have adopted their own norms for both types of product.⁹

According to Marie A. Vodicka, biological drugs were not included in the “Hatch-Waxman” (1984) norms applicable to generics simply because, at the time, the science for these products was not sufficiently advanced.¹⁰ In the past 30 years, however, biotechnology has made considerable progress and there is now more evidence supporting the possibility of reproducing biological products.¹¹

Schematic list of the main characteristics differentiating conventional (chemically synthesized) medicines from those of biological origin¹²

Conventional medicines	Biological medicines
Not very complex structure	Very complex structure
Low molecular weight < 1 kD	High molecular weight > 50 kD
Organic synthesis (semi-synthesis)	Synthesis from live cells/organisms
Well characterized structure	Not well characterized
Few critical stages in synthesis	Many critical stages in synthesis
Homogeneous active principles	Complex heterogeneous combinations

⁸ V. Vivancos, op. cit. <https://revistadigital.inesem.es/biosanitario/medicamentos-biologicos-tradicionales/>

⁹ Regulations on biological products: “Public Health Services Act (PHSA) 351”. Regulations on chemically synthesized products: “Food, Drug, and Cosmetic Act (FDCA) 505”.

¹⁰ Marie A. Vodicka, “Why are generic drugs the ‘same’ and biosimilars only ‘similar’ to their corresponding reference products?” <http://www.biosimilarslawblog.com/2012/01/25/why-are-generic-drugs-the-same-and-biosimilars-only-similar-to-their-corresponding-reference-products/>.

¹¹ Ibid.

¹² L. Cuñetti, “Generalidades de los medicamentos biológicos”, *Boletín farmacológico*. http://www.boletinfarmacologia.hc.edu.uy/index.php?option=com_content&task=view&id=104&Itemid=66.

Maximum tolerated dose	Optimal biological dose
Linear dose response curve	Non-linear dose response curve
Known action mechanisms	Unknown action mechanisms
Elimination via metabolism	Elimination via degradation

III.2 Position of the Pharmaceutical Industry

According to the Swiss corporation Hoffmann La Roche:

“The production of monoclonal antibodies involves a highly complex process that relies on an exclusive bank of master cells to which the originator holds the property rights. It also involves procedures that are controlled by the originator. Such antibodies cannot therefore be reproduced by another company (...) It is impossible to create an identical monoclonal antibody since the process uses a different cell line, and the antibody’s final characteristics depends entirely on that process.”

By comparison, products made from small molecules can be reproduced relatively easily by chemical synthesis. These copies are known as generics. A complex biological product such as a monoclonal antibody cannot be copied. Biogenerics do not exist. This term leads to confusion, is scientifically incorrect and should not be used. Copies of monoclonal antibodies are as similar as possible to the originator product and are called biosimilar antibodies” [unofficial translation].¹³

It is on the basis of this position taken by the pharmaceutical industry that WHO justifies the adoption of a biological qualifier scheme, which may well serve as a “technical barrier” to calling these drugs “generic biological medicines”.

III.3. Scientists and Academics hold a Different Opinion

Alexander Caleb of the Bloomberg School of Public Health at Johns Hopkins University (USA) analyzed a broad array of scientific literature comparing the use of biosimilars and reference products in treating rheumatoid arthritis, psoriasis and inflammatory bowel disease, such as Crohn’s disease or ulcerative colitis. This class of drugs suppresses the activity of a key protein in the immune system known as tumour necrosis factor. The literature includes phase 1 clinical trials, to determine safety, and phase 3 trials, carried out prior to marketing. It also includes studies of patients who were first treated with the original medicine and then with the biosimilar.

According to the *Annals of Internal Medicine*, all the clinical trials that were analyzed, whether phase 1 or phase 3, found biosimilars to be within the equivalence margin of 80 per cent to 125 per cent, compared with the reference products. Although these percentages cannot be interpreted as direct evidence that some biosimilars are superior to the originals,

¹³ ROCHE website, “No puede realizarse copias de los anticuerpos monoclonales”. <http://www.roche.com.co/home/investigacion-y-desarrollo/innovacion-y-tecnologia/biotecnologia/productos-biologicos.html>.

Caleb notes that this equivalence margin represents the thresholds of efficacy between products.¹⁴

Caleb concludes that “based on the available evidence, the products we studied appear comparable, and they will definitely be cheaper”.¹⁵

“The biosimilar market is setting the stage for a veritable war”, according to Professor Miguel del Fresno of Spain’s National Distance Education University (UNED), who has spent years studying strategies used to hold up the marketing first of generics and now of biosimilars. And this war will be waged on many fronts, with battles fought over a clear definition of biosimilars, who is authorized to prescribe them, and the choice of name (brand name or name of active principle), as in the case of generics.

Fresno points out that “it will be crucial for public health officials to draw a distinction between public and private interests”, adding that “while patents protect private property, access to reasonably priced medicines protects public welfare” [unofficial translation].¹⁶

III.4. Industry Strategies Aimed at Blocking Access to Generics

Whether the price of drugs, especially cancer drugs, remains high depends largely on the availability or absence of generics. The pharmaceutical industry therefore resorts to various strategies to delay the entry of affordable generic drugs into markets in the United States and worldwide.

Strategies and practices for delaying or blocking the marketing of generics include:¹⁷

- **Reverse payment or pay-for-delay patent settlements**

In “pay-for-delay” settlements, patent holders agree to pay potential generic competitors that challenge the patent of the brand company to delay entry into the market. “Reverse payment” refers to the fact that the patent company pays the generic company, with the payment moving in the opposite direction than what would be ordinarily expected in patent litigation (with a potential infringer typically paying the patent holder to enter the market).

In the past decade, it has become increasingly common for pharmaceutical companies to pay would-be competitors to delay entering the market, thereby securing a longer period of exclusivity. In return for lucrative payments that may even exceed the profits the generic competitor would have earned if it had entered the market, the generic firm

¹⁴ Francine Chinguanco, MHS; Jodi B. Segal, MD, MPH; Seoyoung C. Kim, MD, ScD, MSCE; G. Caleb Alexander, MD, “Bioequivalence of biosimilar tumor necrosis factor- α inhibitors compared with their reference biologics: A systematic review”. <http://annals.org/aim/article/2540851/bioequivalence-biosimilar-tumor-necrosis-factor-inhibitors-compared-reference-biologics-systematic>.

¹⁵ Ibid.

¹⁶ M.A. Criado, “Los fármacos biológicos y sus ‘genéricos’ son igual de buenos”, *El Pais*, Spain, 3 August 2016.

¹⁷ Gregory H. Jones, Michael A. Carrier, Richard T. Silver, Hagop Kantarjian, “Strategies that delay or prevent the timely availability of affordable generic drugs in the United States”, *American Society of Hematology*, 2016.

agrees to delay entry and not contest the patent (...). These settlements have been criticized as anticompetitive and contrary to the public interest.”¹⁸

- **Authorized generics**

“Authorized generic drugs” (AGs) are drugs that are produced by a brand pharmaceutical company or in collaboration with other companies and that are marketed under separate labels at “generic prices”. Patent holders either produce their own AGs or grant their property rights to generic companies under confidential trade agreements that allow them to enter the market before their competitors. This practice is clearly contrary to the principle of free competition that should apply once a patent has expired.¹⁹

- **Measures blocking the importation of medicines**

Several studies²⁰ have shown that the price of same-brand drugs sold outside the United States can be as much as 20 per cent to 50 per cent lower than the price charged inside the country. Moreover, owing to various strategies and lobbying efforts, certain generic drugs are available outside the United States much sooner than inside the country. For instance, in 2014 the brand-name medicine Imatinib cost US\$ 132,000 for a year’s supply in the United States and only US\$ 38,000 in Canada.

In order to obtain drugs at affordable prices, some patients attempt to import them from abroad for their personal use. However, Section 708 of the Food and Drug Administration’s Safety and Innovation Act (FDASIA) permits the destruction of legal drugs imported for personal use and valued at US\$ 2,500 or less “in the interests of public safety”. This discourages patients from seeking to obtain the same drugs in more affordable markets.

Strategies aimed at delaying the availability of affordable generic drugs constitute a worldwide problem. To cite but one example, the European Commission published a study on the pharmaceutical sector in 2009 that focused on practices engaged in by companies to block or delay the development and marketing of competitor generic products. The study found that 22 per cent of the settlements reached between 2000 and 2008 included payments by originator companies to generic manufacturers and restrictions on the marketing of generics.²¹

¹⁸ Swati Shah, Matthew A Silva, & Michael J Malloy, “Are reverse payments and pay-for-delay settlements business as usual or an anticompetitive practice?”, *Nature Biotechnology*, 34, pp. 716–719 (2016), doi:10.1038/nbt.3627. Published online 12 July 2016.

¹⁹ Federal Trade Commission, “Authorized generic drugs: Short-term effects and long-term impact”, 2011, accessed online August 13, 2015. <http://www.ftc.gov/sites/default/files/documents/reports/authorized-generic-drugs-short-term-effects-and-long-term-impact-report-federal-trade-commission/authorized-generic-drugs-short-term-effects-and-long-term-impact-report-federal-trade-commission.pdf>.

²⁰ Gregory H. Jones et al, op. cit.

²¹ European Commission, “Pharmaceutical Sector Inquiry: Final Report 4”, 268-85 (EU, 2009).

IV. CLASSIFICATION OF BIOLOGICAL PRODUCTS BY THERAPEUTIC USE

Biological medicines account for a growing share of national drug expenditure and, as we have seen, are expected to represent 50 per cent of the cost of all drugs sold on world markets by 2022. Nevertheless, they make up a much smaller percentage of markets in terms of the number of products sold. In the most recent WHO List of Essential Medicines, they account for only 2.5 per cent of the total.

The 2017 revised WHO List of Essential Medicines comprises 433 products, 11 of which are biological:²²

- Bevacizumab (eye)
- Erythropoietin(s) [epoetin alfa, beta and theta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, and their respective biosimilars]
- Pegylated interferon alfa (2a [patent expired], or 2b [patent expired])
- Insulins, Insulin(s)
- Filgrastim
- Factor VIII
- Factor IX
- Heparins [enoxaparin, nadroparin, dalteparin]
- Rituximab
- Trastuzumab
- Surfactant

The fact that a relatively small percentage of the drugs needed by a country's population accounts for over 50 per cent of national drug expenditure constitutes a major problem for the viability of our health systems. R&D costs for biological products do not appear to be the source of the problem. The fact is that the pharmaceutical industry has propelled us into a new era in which prices no longer reflect R&D costs plus a reasonable profit margin, but are based instead on a product's supposed "value" in terms of days of life "gained", labour force recovered, or – as argued in the case of Sofosbuvir, a drug used to treat hepatitis C – a liver transplant. To accept this type of logic is tantamount to agreeing that the purpose of the pharmaceutical industry is to speculate on financial markets, not to serve public health interests.

IV.1. Classification of Biological Medicines²³ by Therapeutic Use

1. Products used for active immunization

- Bacterial vaccines
- Vaccines prepared with Rickettsias
- Viral vaccines
- Toxoid vaccines

²² Email from Nicola Magrini and Lorenzo Moja, in charge of WHO List of Essential Medicines, June 2017.

²³ European Commission, "Pharmaceutical Sector Inquiry: Final Report 4", op. cit.

2. **Products used for passive immunization**

- Monoclonal and polyclonal antibodies
- Antivenins / antitoxins
- Immune globulin

3. **Agents used for diagnostic purposes**

- Toxins
- Tuberculin

4. **Human blood and blood derivatives**

5. **Allergens**

V. BASIC PRINCIPLES AND CONCEPTS GOVERNING THE APPROVAL OF GENERIC BIOLOGICAL MEDICINES

As already mentioned, the structure and composition of biological drugs are far more complex than those of conventional, chemically synthesized drugs. Biological drugs are those “in which **active protein substances** are produced from living organisms”.²⁴ It is their biological nature and, consequently, their structural and functional complexity, that distinguishes them from chemically synthesized drugs (or “small molecules”). The relatively recent expiry of patents protecting the first biological medicines to arrive on the market has paved the way for the development and marketing of “biosimilars, generics or bioequivalents”.²⁵

V.1. EU 2006 Guidelines for the Evaluation of Competitor Therapeutic Proteins

The EU has been at forefront of efforts to adopt legislation governing the marketing of biosimilars. In 2006, the EMA adopted Guidelines for the evaluation of competitor therapeutic proteins (biosimilars). According to a recent study, these Guidelines, which establish requirements for biosimilars based on a comparability demonstration, confirm the impossibility of showing that two proteins are identical but acknowledge the possibility of showing their similarity through a stepwise exercise comparing the biosimilar competitor to the reference product, from the characterization stage to the clinical stage (comparative clinical study of equivalence or non-inferiority).

The EMA first approved a biosimilar in 2006 (a recombinant protein) and has to date approved a total of 28 biosimilars (see Annex I).

The concept of a biosimilar was introduced into European legislation through Commission Directives 2003/63/EC and 2004/27/EC, which define biosimilars as biological drugs that are similar in relation to previously approved innovator biological drugs (reference products). A biosimilar (or similar biological medicine) is a biological drug that contains the same active principle as the original reference biological drug.

The ultimate aim of a “biosimilarity” evaluation is to demonstrate that the biosimilar or generic product has a comparable or equivalent therapeutic effect on the patient to that of the reference drug. Countries outside the EU may adopt legislation and standards different from those of the EMA to evaluate biosimilarity or biological generics.

The comparability requirements set out in the EMA Guidelines have been the subject of major criticism.²⁶ Indeed, the debate over whether two chemical substances or two proteins are, or can be identical is of little interest in evaluating their biosimilarity from the perspective of public health since the aim is to establish therapeutic equivalency. The only purpose of insisting on the need to demonstrate that two proteins are identical is to block or delay the

²⁴ V. Vivancos, op. cit. <https://revistadigital.inesem.es/biosanitario/medicamentos-biologicos-tradicionales/>.

²⁵ Fundación Azierta, Science to business, Madrid 2016. <http://azierta.eu/2016/06/02/biologicos-biosimilares-1/>.

²⁶ H. Schellekens, E. Moors, “Clinical comparability and European biosimilar regulations”, available from: <http://www.biosimilars-nederland.nl/wp-content/uploads/2015/09/SchellekensMoorsClinicalcomparabilityandEuropeanbiosimilarregulationsNBT2010.pdf>.

entry of generic products into the market since comparability is not required to demonstrate the therapeutic efficacy and safety of a biosimilar or a generic.

Experience over the past 10 years has highlighted the limitations of clinical comparability exercises as introduced by the EU, which are time-consuming and costly, thereby delaying the entry of biosimilar products into the market.

It is certainly true that developing biosimilars is a process that can take over five years and is more expensive (between 100 and 200 million dollars, depending on the source) than developing generics. This fact is put forward to explain the slow entry into the European market of challengers to drugs no longer under patent and the relatively small savings in cost as compared with chemically synthesized generics.²⁷

In addition, it is difficult to carry out comparative clinical trials requiring large numbers of patients for rare diseases or for cancers with low incidence rates.

According to Gaviria et al., some countries have therefore considered devising pathways to approval other than comparativity exercises. In order to use such a pathway (individuality, simplified or fast-track), a company must first demonstrate a high degree of similarity between the competitor drug and the reference product in terms of quality and it must make sufficient clinical information available to the public.²⁸

V.2. Colombian Decree on Biological Medicines

In 2014, Colombia issued Decree 1782 setting the standards that biological medicines must meet in order to be registered in the country.

The decree, which allowed the entry of new laboratories and products to the closed world of biotechnological drugs, was celebrated as a courageous decision taken in defiance of the pressure exerted by the transnational pharmaceutical industry. The industry is so powerful that it succeeded in convincing the vice-president of the United States, Joe Biden, several United States Senators and the Swiss Government to send letters urging Colombia not to adopt the decree.

Decree 1782 marks an important step forward in defining the conditions governing access to generic biological products. It sets the standards and requirements applicable to new products. Through the decree, the government has opted to prioritize health needs rather than accept the technical barriers that multinationals wanted to impose in a bid to extend their monopolies. The battle is being, and will continue to be waged over whether or not to place public health concerns ahead of profit motives.

A key concept set out in the decree is that of an “abbreviated route”, an unfortunate term that has lent itself to misinterpretation. This route, far from being a shortcut, includes all the requirements, clinical proof or trials involved in obtaining a license for a new drug in most countries. Its purpose is merely to avoid unnecessary delays associated with the repeated technical requirements that multinationals seek to impose.

²⁷ A. Gaviria, C.P. Vaca Gonzalez, C. Gomez Muños, A. A. Morales. “El debate de la regulación de los medicamentos biológicos: Colombia en el contexto internacional”, *Rev Panam Salud Pública* 40(1), 2016.

²⁸ *Ibid.*

As explained under point 5.3. below, WHO has not yet issued any regulations in this field. Resolution 67.21 adopted by the 2014 World Health Assembly simply requested WHO to update its Guidelines on Evaluation of Similar Biotherapeutic Products. We are therefore at the beginning of a complicated process that will take several years.

V.3. WHO 2009 Guidelines

It was in 2009 that the WHO Expert Committee on Biological Standardization published its Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs),²⁹ which promote strict evaluation of the quality, safety and efficacy of biological products along the same lines as the standards set out by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH was created in 1990 on the initiative of the pharmaceutical industries of the United States, Europe and Japan, which promote and fund it, in a bid to influence the standards adopted by national drug regulatory authorities and WHO. During the 2015 World Health Assembly, a number of industrialized countries pushed – albeit unsuccessfully – for the adoption of a resolution approving ICH standards. WHO Guidelines do not, for example, provide for the same exemption from comparative clinical trials for biological drugs as is granted to chemically synthesized generics.

The pharmaceutical industry's main argument, which WHO seems to have accepted, is that it is impossible to make an identical replica of a biological medicine since biological substances, such as proteins, cannot be reproduced exactly. This argument underpins both the 2006 EMA Guidelines and WHO's 2009 Guidelines on Evaluation of Similar Biotherapeutic Products, which require that comparative clinical trials be carried out to demonstrate that a drug is similar but not identical to the reference product. However, as already mentioned, such trials are not always necessary since, from the medical perspective, the aim is not to make an identical product but one that has an equivalent therapeutic effect. If the product has the desired effect, there is no need for it to be identical. The patients who take the medicine are not identical either. The object of the exercise is to obtain equivalent clinical results.

WHO principle of precaution, which requires clinical trials, amounts to an extension of the principle of data exclusivity, and that in turn keeps prices high and ultimately restricts access. It is crucial to draw a clear distinction between measures designed to ensure patient safety and barriers intended to boost monopolies.

It is a well-known fact that many of the standards promoted by ICH are aimed at protecting markets rather than patients: “Under the pretext of harmonizing regulatory requirements for marketing authorization of new drugs, the drug regulatory agencies of the world's wealthiest countries and three pharmaceutical industry trade associations, joined together since 1990 in the ICH, are promoting their own interests by imposing their criteria for evaluating drugs on the whole world. The toxicity standards advocated by ICH sometimes promote faster, cheaper drug development over patient protection. The drug quality standards

²⁹ WHO, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), Expert Committee on Biological Standardization, Geneva, 2009, available from: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.

advocated by ICH sometimes increase manufacturing costs without providing any public health benefit.”³⁰

In the French journal *Prescrire*, ICH is described as “an exclusive club of drug regulatory agencies and drug companies”.³¹

It is against this backdrop that in 2014, a number of South-American countries noted that the WHO 2009 Guidelines had never been submitted for discussion or approval by the organization’s governing bodies. A group of countries, led by Colombia and Argentina, therefore promoted the adoption of Resolution WHA 67.21,³² which urges Member States and WHO “to work to ensure that the introduction of new national regulations, where appropriate, does not constitute a barrier to access to quality, safe, efficacious and affordable biotherapeutic products, including similar biotherapeutic products;”³³ The Resolution also recognizes that “pharmaceutical regulation should contribute to the performance and sustainability of health systems and the general welfare of society.”³⁴ Lastly, the Resolution requests the Director-General to update the 2009 Guidelines on Evaluation of Similar Biotherapeutic Products – which is essentially what the countries that promoted Resolution 67.21 were seeking.

C. Vaca and C. Gómez identified at least three types of technical barrier set out in the WHO 2009 Guidelines: (i) “those associated with the general requirement for sophisticated confirmatory clinical trials prior to registration, (ii) those corresponding to the differentiation and designation of the active principle (differential nomenclature) in relation to prescribing and marketing, and (iii) those tied to restrictions on substitution and interchangeability” [unofficial English translation].³⁵

Let us look at the second type of barrier identified by Vaca and Gómez, namely the differentiation and designation of the active ingredient (differential nomenclature), since WHO is currently trying to impose a scheme³⁶ over which there is no consensus and, as we shall see, may further block access to generic biological drugs.

³⁰ “ICH: An exclusive club of drug regulatory agencies and drug companies imposing its rules on the rest of the world”, *Prescrire International*, August 2010; 19(108):183-6. [Prescrire Int.](#)

³¹ *Ibid.* From its founding, the ICH Management Committee has comprised six members with voting rights, representing Europe, Japan and the United States, respectively: the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA); the Japanese Ministry of Health, Labour and Welfare and the Japan Pharmaceutical Manufacturers Association (JPMA); the US Food and Drug Administration and Pharmaceutical Research and Manufacturers of America, (PhRMA) [1]. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), a group of pharmaceutical corporations with its headquarters in Geneva, Switzerland, serves as the ICH Secretariat.

³² World Health Assembly Resolution WHA67.21: “Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy.” <http://apps.who.int/medicinedocs/documents/s21459en/s21459en.pdf>.

³³ *Ibid.*

³⁴ *Ibid.*

³⁵ C. Vaca and C. Gomez, “Barreras técnicas innecesarias a la competencia y la inequidad en el acceso: El caso de los medicamentos biotecnológicos”, (forthcoming).

³⁶ WHO, Biological Qualifier (BQ): A Global initiative and consequences for not implementing BG, Geneva 1 March. INN Working Doc. 17.411.

VI. INTERNATIONAL NONPROPRIETARY NAMES (INNS) ASSIGNED BY WHO TO BIOLOGICAL MEDICINES

VI.1. International Nonproprietary Names

“Nonproprietary names, also called generic or common names, are intended to be used as public property without restraint, i.e. nobody owns any rights on their usage.”³⁷

Today’s INN system was established in 1950 pursuant to World Health Assembly Resolution WHA3.11 and came into use in 1953, with the publication of the first list of INNs for pharmaceutical substances.³⁸ The current cumulative list includes some 10,000 INNs.³⁹

The purpose of introducing the INN system was to provide health professionals with a unique and universally recognized number to identify each pharmaceutical substance. “The existence of an international nomenclature for pharmaceutical substances, in the form of INNs, is important for the clear and unambiguous identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists, worldwide.”⁴⁰ All generic products reproduced from the first pharmaceutical substance registered and in circulation today have been assigned the same INN.

According to WHO, “INNs are intended to be used globally for the identification of a specific pharmaceutical substance. So as to ensure the universal availability of INNs for their intended purpose, they should be free from any protection by proprietary rights – hence, the designation nonproprietary.”⁴¹

Every INN is a unique name, also known as a generic name that is recognized worldwide and is considered public property.⁴²

VI.2. International Nonproprietary Names “Biological Qualifier” (BQ)

Over the past five years, manufacturers of biological products have pressured WHO to disregard the principle underlying INNs, namely that they “are intended to be used as public property without restraint”. Arguing that it is impossible to produce an “identical copy”, manufacturers have supported the idea of assigning a biological qualifier (BQ) to each product, whether it is biosimilar or bioequivalent or generic.

³⁷ S. Kopp-Kubel, “International Nonproprietary Names (INN) for pharmaceutical substances”, *WHO Bulletin*, Vol. 73, No. 3, 1995, pp. 275-279, 1995.

³⁸ WHO, “Guidance on INN”. <http://www.who.int/medicines/services/inn/innguidance/en/#>.

³⁹ WHO Report. Sixty-ninth World Health Assembly A69/43 (2016). http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_43-en.pdf.

⁴⁰ Ibid.

⁴¹ WHO, “International Nonproprietary Names: Revised procedure”. EB110/3, 2002. http://apps.who.int/gb/archive/pdf_files/EB110/eeb1103.pdf.

⁴² Ibid.

According to certain documents issued by the WHO Secretariat,⁴³ the BQ concept was put forward by the Secretariat itself, in line with the practice followed in Japan, Australia and the United States.⁴⁴ One Secretariat document, however, indicates that the BQ concept was proposed at the request of “several countries” (it does not specify which ones).⁴⁵

In the document “Biological Qualifier: An INN proposal”, the WHO Secretariat states the following: “A scheme is proposed in which a unique identification code named a ‘Biological Qualifier’ (BQ) is assigned to all biological substances having (or eligible to have) INNs. The BQ is an additional and independent element used in conjunction with the INN to uniquely identify a biological substance (...) The BQ is a code formed of four random consonants in two 2-letter blocks separated by a 2-digit checksum.”⁴⁶

The BQ scheme proposed by WHO would only complicate the introduction of generic biological drugs, giving them an individual identity as if each were a distinct product. In addition to restricting the concept of generic biological drugs, the BQ scheme encourages a fragmentation of the market to the detriment of the principle of competition. The scheme may also cause confusion in the dispensing of drugs as it conveys the message that each drug is distinct.

According to a report presented by WHO’s Director-General to the 2016 World Health Assembly:⁴⁷

“66. The International Nonproprietary Names system administered by WHO provides pharmaceutical substances a unique and universally available designated name for the clear identification, safe prescription and dispensing of medicines, and for communication and exchange of information among health professionals and scientists worldwide. The cumulative list contains approximately 10 000 names. (...)”

67. Following requests from some drug regulatory authorities, the International Nonproprietary Names Expert Group considered how WHO might develop a system for assigning biological qualifiers. Following discussions among interested parties, including through a web consultation, the Expert Group at the 61st Consultation on International Nonproprietary Names (Geneva, 13–16 October 2015) recommended a voluntary scheme whereby application for a biological qualifier could be made to the International Nonproprietary Names secretariat. The biological qualifier code would not be a constituent part of the International Nonproprietary Names, but an additional and independent element used in conjunction with it. The Secretariat subsequently initiated an impact assessment study, to report to the International Nonproprietary Names Expert Group in 2016, on whether introducing such biological qualifiers would influence access or affect other aspects of public health.”

⁴³ WHO, “Biological qualifier: An INN Proposal”, INN Working Doc. 14.342, October 2015. http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf.

⁴⁴ Op. cit., p. 2.

⁴⁵ WHO, “Biological qualifier: Frequently Asked Questions”, INN Working Doc. 15.382, October 2015. http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_FAQ_2015.pdf?ua=1.

⁴⁶ WHO, “Biological Qualifier. An INN Proposal”, op. cit. http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf, p. 2.

⁴⁷ See full report in Annex I. WHO, Sixty-ninth World Health Assembly A69/43 (2016), op. cit. http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_43-en.pdf.

In working document 17.411 “Biological Qualifier (BQ): A global initiative and consequences for not implementing BQ” presented in March 2017,⁴⁸ the WHO Secretariat refers to a “global initiative”. An initiative taken where and by whom? The document confines itself to listing the consequences of non-implementation of the BQ scheme without analyzing or even mentioning the consequences of actually implementing the scheme. The title of the document alone suggests that WHO has already decided to introduce the BQ scheme. Yet, to give each biosimilar an individual identity by assigning it a different BQ contradicts the very philosophy and *raison d’être* of the INN system.

In June 2017, the following information appeared on the website of the WHO Department of Essential Medicines:

“Following requests from some drug regulatory authorities, the INN Expert Group recommended that WHO develop a system for assignment of Biological Qualifiers to similar biotherapeutic products (SBPs).

After discussions among interested parties and approval by the INN Expert Group, a voluntary scheme is proposed by which an application can be made to the INN Secretariat for a Biological Qualifier (BQ).”⁴⁹

The proposed BQ scheme, however voluntary it may be, could compromise the entire INN system and further delay the marketing of generic biological drugs. For this reason, it should be rejected by WHO governing bodies.

WHO has delayed issuing clear and universal guidelines while tolerating a situation in which countries may use whatever name they wish,⁵⁰ as some have already started to do. Allowing countries to decide on an individual basis which INN applies to a particular biological product is tantamount to condoning a confusing state of affairs that contradicts the very purpose of the INN system.

⁴⁸ WHO, “Biological Qualifier (BQ): A global initiative and consequences for not implementing BQ”, Geneva, INN Working doc. 17.411, March 2017.

⁴⁹ WHO website, July 2017, http://www.who.int/medicines/services/inn/inn_bio_bq/en/.

⁵⁰ Document A69/43 (2016), cited in footnote 40, states: “Acknowledging that national authorities may use different terminologies when referring to similar biotherapeutic products”.

VII. CONCLUSIONS

The debate on generic medicines is not new. What makes it different today is that attacks levelled against biological products are couched in ever more “technical” and abstruse language that confuses even the World Health Organization.

Innovative biological drugs which have been introduced on the market in the past 20 to 30 years⁵¹ make up, in terms of numbers, no more than 2.5 per cent⁵² of the WHO Model List of Essential Medicines, but in terms of cost, account for 15 per cent to 20 per cent of national drug expenditure.

The high price of biological drugs stems mainly from two new factors: first, a change in the pharmaceutical industry’s approach to price-setting, whereby prices no longer reflect the true costs of research and development plus a reasonable profit margin. They are now based on the product’s supposed “value” to the pharmaceutical industry in terms of financial speculation, not on its role in promoting public health. Secondly, high prices are the result of the unjustified strengthening of intellectual property rights and the introduction of additional barriers to the entry of generic drugs into the market. Instead of clarifying the situation, WHO has created a further obstacle by introducing a biological qualifier (BQ) that unnecessarily assigns a unique code to each generic biological medicine.

It is a source of major concern that WHO has not issued international guidelines based on the principle underlying the INN system, namely that: “International Nonproprietary Names, also known as generic names, are intended to be used as public property without restraint, i.e. nobody owns any rights on their usage”.

In any debate on the impossibility of producing “identical” drugs, it should be made clear that what is at stake is not identical products but therapeutic equivalents. What matters to the patient, as we have said, is whether or not a drug can prevent, cure or mitigate the effects of the illness.

Certain biological drugs have revolutionized the treatment of cancer, arthritis and inflammatory bowel disease. Meanwhile, health-care costs have skyrocketed, with huge profits accruing to pharmaceutical companies.⁵³

There are obviously differences between the reproduction of biological products and that of chemically synthesized ones. However, there is no reason why biological products cannot be reproduced under a clear set of rules that protect patients while ensuring affordable access to all those who need them.

Instead of biosimilars, interchangeable biosimilars or bioequivalents, why not simply opt for biological generics?

⁵¹ Human insulin was introduced on the market by Eli Lilly in 1982.

⁵² Eleven products as compared with thousands of chemically synthesized products that flood world markets.

⁵³ IMS Health, “The global use of medicines: Outlook through 2017”, available from: [http://www.imshealth.com/files/web/IMSH%20Institute/Reports/The Global Use of Medicines 2017/global%20use%20of%20med%202017%20right6%20Biologics Market.pdf](http://www.imshealth.com/files/web/IMSH%20Institute/Reports/The%20Global%20Use%20of%20med%202017%20right6%20Biologics%20Market.pdf).

We hope that WHO will succeed in issuing clear guidelines prioritizing patient protection over the financial interests of pharmaceutical companies.

ANNEX I**Biosimilars Approved by the European Medicines Agency (EMA)**

MEDICINE NAME	ACTIVE SUBSTANCE	COMMON NAME	STATUS	BIOSIMILAR
Abasaglar (previously Abasria)	insulin glargine	insulin glargine	Authorised	Yes
Abseamed	epoetin alfa	epoetin alfa	Authorised	Yes
Accofil	Filgrastim	Filgrastim	Authorised	Yes
Amgevita	Adalimumab	Adalimumab	Authorised	Yes
Bemfola	follitropin alfa	follitropin alfa	Authorised	Yes
Benepali	Etanercept	Etanercept	Authorised	Yes
Binocrit	epoetin alfa	epoetin alfa	Authorised	Yes
Epoetin Alfa Hexal	epoetin alfa	epoetin alfa	Authorised	Yes
Filgrastim Hexal	filgrastim	Filgrastim	Authorised	Yes
Flixabi	infliximab	Infliximab	Authorised	Yes
Grastofil	filgrastim	Filgrastim	Authorised	Yes
Inflectra	infliximab	Infliximab	Authorised	Yes
Inhixa	enoxaparin sodium	enoxaparin sodium	Authorised	Yes
Lusduna	insulin glargine	insulin glargine	Authorised	Yes
Movymia	teriparatide	Teriparatide	Authorised	Yes
Nivestim	filgrastim	Filgrastim	Authorised	Yes
Omnitrope	somatropin	Somatropin	Authorised	Yes
Ovaleap	follitropin alfa	follitropin alfa	Authorised	Yes
Ratiograstim	filgrastim	Filgrastim	Authorised	Yes
Remsima	infliximab	Infliximab	Authorised	Yes
Retacrit	epoetin zeta	epoetin zeta	Authorised	Yes
Silapo	epoetin zeta	epoetin zeta	Authorised	Yes
Solymbic	adalimumab	Adalimumab	Authorised	Yes
Terrosa	teriparatide	Teriparatide	Authorised	Yes
Tevagrastim	filgrastim	Filgrastim	Authorised	Yes
Thorinane	enoxaparin sodium	enoxaparin sodium	Authorised	Yes
Truxima	rituximab	Rituximab	Authorised	Yes
Zarzio	filgrastim	Filgrastim	Authorised	Yes

ANNEX II

World Health Organization, World Health Assembly, Document A69/43, 1 April 2016: “Progress reports”, Report by the Secretariat

H. ACCESS TO BIOTHERAPEUTIC PRODUCTS, INCLUDING SIMILAR BIOTHERAPEUTIC PRODUCTS¹, AND ENSURING THEIR QUALITY, SAFETY AND EFFICACY, (resolution WHA67.21)

60. Pursuant to resolution WHA67.21 (2014), the Secretariat supported Member States in strengthening their capacity in the health regulation of biotherapeutic products, including similar biotherapeutic products. Ever more countries are building the necessary scientific expertise to facilitate the development of solid, science-based regulatory frameworks that promote access to quality, affordable, safe and efficacious biotherapeutic products, taking note of relevant WHO guidelines, which may be adapted to national contexts and capacities.

61. The 16th International Conference of Drug Regulatory Authorities gathered government officials and drug regulatory authorities in Rio de Janeiro in August 2014 to discuss global issues and ways to enhance collaboration among regulatory authorities regarding the quality, safety and efficacy of medicines. Experts from drug regulatory authorities, academia, international and nongovernmental organizations and the pharmaceutical industry participated in a pre-conference meeting on the theme “Ensuring Quality and Safety of Biosimilars for Patients Worldwide”. The meetings encouraged and promoted cooperation and information exchange among Member States in this area and issued recommendations to Member States and WHO on the regulation of biotherapeutics and its impact on access to affordable, safe and efficacious biotherapeutics.²

62. WHO held an informal consultation with regulators, manufacturers and other experts in April 2015 to review draft WHO guidelines on the regulatory assessment of approved biotherapeutics. Following this, the WHO Expert Committee on Biological Standardization was able to finalize and adopt new WHO guidelines on regulatory assessment of approved rDNA-derived biotherapeutics. Addendum to: WHO TRS 987, Annex 4³ in October 2015. Information on this work will be submitted to the Executive Board at its session in January 2017 as part of the reports of advisory bodies.

63. WHO held an informal consultation in April 2015 on the regulatory evaluation of monoclonal antibodies developed as similar biotherapeutic products. It was agreed to develop proposed WHO guidelines on the subject for submission to the 2016 Expert Committee on Biological Standardization. The public consultation phase for the document will begin in early 2016 with its posting to the WHO website⁴ for comments, followed by a technical

¹ Acknowledging that national authorities may use different terminologies when referring to similar biotherapeutic products.

² See

http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/16_ICDRA_Recommendations2014.pdf?ua=1, accessed 25 February 2016.

³ See [http://www.who.int/biologicals/RA_for_BTP_for_WHO_web_editor_2_Nov_2015\(3\).pdf?ua=1](http://www.who.int/biologicals/RA_for_BTP_for_WHO_web_editor_2_Nov_2015(3).pdf?ua=1), accessed 29 February 2016.

⁴ See <http://www.who.int/biologicals>, accessed 29 February 2016.

meeting hosted by the National Institutes for Food and Drug Control of China, a WHO Collaborating Centre, in April 2016.

64. The 2014 International Conference of Drug Regulatory Authorities meeting requested that WHO organize a workshop on implementing the 2009 WHO guidelines on evaluation of similar biotherapeutic products in the African Region, which it did in Accra in collaboration with the Food and Drug Authority of Ghana, in September 2015. The 40 experts participating, including 27 regulators from 16 countries in the African Region, recognized the WHO guidelines as a standard providing science-based principles in establishing national requirements for such products and requested strong, consistent support from WHO for their implementation.

65. WHO, through the Expert Committee on Biological Standardization, establishes international biological reference preparations, and convened an informal consultation in 2015 on reference preparations for biotherapeutic products. WHO reference preparations are used as benchmarks for biological activity, method development and system suitability assessment of biotherapeutic products, and, when linked with a specific and well-validated national, pharmacopoeia or manufacturer's reference standard, facilitate the assessment of the potency of multisource products, support product surveillance, enable product life-cycle management and support the development of novel methods. The Expert Committee recommended that WHO enhance communication on the appropriate use of such standards and advocate for the continued provision by manufacturers of source materials as a public good for the development of WHO standards as public reference materials.

66. The International Nonproprietary Names system administered by WHO provides pharmaceutical substances a unique and universally available designated name for the clear identification, safe prescription and dispensing of medicines, and for communication and exchange of information among health professionals and scientists worldwide. The cumulative list contains approximately 10 000 names. Geneva hosted four consultations on International Nonproprietary Names during 2014 and 2015, where 552 name requests were discussed and 358 new proposed names published, 60% of which were chemicals and 40% biologicals, up from only 5% in 2000. The proportion of International Nonproprietary Names assigned to biologicals has increased from 5% to 40% since 2000.

67. Following requests from some drug regulatory authorities, the International Nonproprietary Names Expert Group considered how WHO might develop a system for assigning biological qualifiers. Following discussions among interested parties, including through a web consultation, the Expert Group at the 61st Consultation on International Nonproprietary Names (Geneva, 13–16 October 2015) recommended a voluntary scheme whereby application for a biological qualifier could be made to the International Nonproprietary Names secretariat. The biological qualifier code would not be a constituent part of the International Nonproprietary Names, but an additional and independent element used in conjunction with it. The Secretariat subsequently initiated an impact assessment study, to report to the International Nonproprietary Names Expert Group in 2016, on whether introducing such biological qualifiers would influence access or affect other aspects of public health.

68. WHO collaborated with the International Pharmaceutical Regulators Forum in 2015 and agreed on three deliverables for joint work in 2016: information regarding the public assessment of biotherapeutics to ensure the consistency and transparency of the review

process; a reflection paper on the extrapolation of biosimilar indications; and a training manual on the analytical comparability of monoclonal antibodies developed as similar biotherapeutic products.

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ISSN 1819-6926