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Do low- to middle-income countries need a biosimilar approval pathway based on a full comparability exercise?

Armando A Genazzani, DPhil, MD; Nicola Magrini, MD

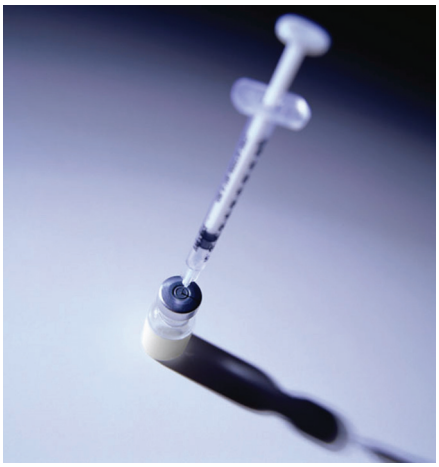
Despite the fact that hepatitis C is a disease of global importance, many countries cannot afford the costly but effective combination treatment of peg-interferon and ribavirin, which was recently included in the World Health Organization Essential Medicines List. Given that peg-interferon is a biotechnological product, should low- to middle-income countries adopt the burdensome biosimilar approval pathway of western countries or should they find a more pragmatic approach, focusing on efficacy and safety to gain access to affordable biotechnological products?

Keywords: Alternative therapeutic products, biosimilar, Essential Medicines List, peg-interferon, regulatory approval pathways, WHO

Hepatitis C is a disease of global importance, and although the global burden of morbidity and mortality is hard to estimate, the approximate prevalence of hepatitis C virus (HCV) infection worldwide is 2.2-3% (about 150 million individuals). There are large variations in prevalence [1]: Southern Mediterranean, Central Africa, South America and South East Asia appear to be among the most affected regions [2]. In recent decades, the HIV/AIDS epidemic (with very effective treatments available) has kept HCV infections out of the spotlight, but we are probably on the eve of a similar growth of interest in HCV management given the presence of more effective treatments for HCV.

In high-income countries, most new HCV infections occur as a result of the use of injectable illicit drugs [3], but in low- to middle-income countries nosocomial transmission due to the reuse of contaminated or inadequately sterilized syringes and needles is still high [4]. HCV infection can lead to acute hepatitis and to chronic hepatitis, the former eventually leading to cirrhosis and, in a proportion of patients, to hepatocarcinoma. Given the natural history of the disease, the treatment of chronic hepatitis is generally considered cost-effective [1], although cost-effectiveness should be tailored to local realities, e.g. cost of medicines, healthcare budget and life expectancy.

The golden standard of therapy was, until recently, the combined administration of peg-interferon and ribavirine, with the goal of producing a sustainable virological response (SVR). Pegylated interferon (PEG-IFN) in combination with ribavirin produces SVR rates around 50% for the genotype 1 subtype of HCV, and up to 80% for the genotype 2 and 3 subtypes [5, 6] when used in western countries and



in low- and middle-income countries [7].

The cost of PEG-IFN and ribavirin in western countries amounts to US$10,000–US$20,000 per treatment [8]. This is obviously unaffordable for most low- to middle-income countries, which have had to use less effective therapies as a result. Highly-regulated markets, e.g. Europe, Japan, USA; have recently approved drugs such as boceprevir and telaprevir that, in combination with PEG-IFN and ribavirin, have increased the effectiveness of treatment (up to 65–70% of SVR in genotype 1). More effective second-generation protease inhibitors, as well as polymerase inhibitors, are also being approved (simeprevir and sofobuvir).

The presence of these new treatments in western countries increases the HCV treatment gap between the west and low-income countries, widening an unacceptable divide between countries in relation to an infectious disease. The problem arising from this divide is that of social inequality, but it also carries unacceptable implications for global health. A global, equitable, sustainable and fairly priced solution, like that achieved for HIV, should be sought to make world class HCV treatments available worldwide. The World Health Organization (WHO) recently approved the inclusion of PEG-IFN in its Essential Medicines List [9], attempting to reduce the gap between countries.

Milani and Gaspani writing in this issue [8] tackle a crucial issue in this field: given that PEG-IFN is a biotechnological drug, and the scientific community accepts

Author for correspondence: Armando A Genazzani, DPhil, MD, Department of Pharmaceutical Sciences, Università del Piemonte Orientale, 6 Via Bovio, IT-28100 Novara, Italy

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that the generic (non-biotechnological) medicine approval pathway is not appropriate for this class of compound, how can affordable PEG-IFN gain access in low- to middle-income countries?

In brief, the structure and physicochemical properties of biotechnological compounds are by definition difficult to fully characterize, and if different producers attempt to generate the same molecule they will come up with distinct molecules. Furthermore, it is accepted that small differences in the structure of biotechnological compounds can lead to large differences in clinical efficacy and safety (it is, however, also accepted that some large differences can lead to no appreciable change in clinical characteristics). To circumvent these issues, the European Medicines Agency (EMA) and other regulatory agencies have decided to approve generic biotech medicinal products (known as biosimilars) based on a comparability exercise aimed at demonstrating superimposable physicochemical, preclinical and clinical characteristics between the originator drug and the biosimilar. It is important to note that the comparability exercise is *per se* expensive and is not designed to demonstrate efficacy and safety. WHO has also issued guidelines that largely overlap with those of the European Union.

While biosimilar production is more expensive than generic drug production, the presence of biosimilars (epoetins, filgrastim) on the European market has allowed for competition and has reduced the cost of treatment considerably.

The big question is: do low- to middle-income countries need biosimilars, as previously defined? Would they be affordable for the interested countries and profitable for the producers? At present, there is no clear answer.

We contend that a biosimilar drug, as defined by both EMA and WHO, might not suit the actual needs of low- to middle-income countries. The main reason is that biosimilars are in part designed to create competition based on sameness/therapeutic equivalence in countries where the innovator product was present. In countries where the products were scarcely available, this model might not be the best way forward. These countries require safe and effective treatments, and trials should be designed to demonstrate just this. A possible solution, highlighted by Milani and Gaspani [8] and by others in different contexts [10], is that alternative therapeutic products could be developed without undergoing a lengthy and costly clinical comparative trial. In brief, the alternative product could either have a conditional approval (gathering sufficient efficacy and safety data in real-life) or undergo a less-costly demonstration of efficacy and safety (without having to use the reference product). Both strategies could use accepted and validated surrogate markers and use historical data on innovators as a comparison. In this respect, it is important to note that therapeutic alternatives to PEG-IFN are already present in developing markets, as highlighted by Milani and Gaspani [8]. Their careful clinical characterization could pave the way to the rapid introduction of affordable, safe and effective PEG-IFN, verifying the overall results on a surrogate measure such as liver function and/or SVR (depending on available data). In brief, this represents a very pragmatic solution to the problem.

WHO issued 'Guidelines on Evaluation of Similar Biotherapeutic Products' in 2009. Although the scientific merit of the guidelines is not in question, we agree with Milani and Gaspani [8] that they should be updated also to include a more pragmatic approach to the problem in countries where the reference product was not widely available due to cost limitations.

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Co-author

Nicola Magrini, MD
Area Valutazione del Farmaco, Agenzia Sanitaria Regionale, 21 Viale Aldo Moro, IT-40126 Bologna, Italy

Drug Evaluation Unit, WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development, Emilia Romagna Health and Social Care Agency

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