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Access to alternative biopharmaceuticals in low- and middle-income countries

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Alternative biopharmaceuticals could substantially improve affordability of biotherapeutics in developing countries. However, it seems that these countries need a modified regulatory pathway to guarantee timely access to these medicines.

Keywords: Affordability, alternative biopharmaceuticals, regulation

In recent years, biotherapeutics have gained a significant role in the management of life threatening diseases including cancers and diseases of the immune system. Biopharmaceuticals, also known as biologicals, are mostly produced by genetic manipulations of living organisms. Medicines produced through recombinant DNA (rDNA) methods, and monoclonal antibodies, are the most common biopharmaceuticals currently on the market worldwide. Monoclonal antibodies are mostly rDNA-derived proteins or glycoproteins. From a regulatory perspective, their assessment is basically similar to that for rDNA biotherapeutics. Despite their acceptable efficacy in several severe diseases, many patients in low- and middle-income and even developed countries are not able to afford them due to the very high prices.

However, in recent years, substantial numbers of these biopharmaceuticals have come off-patent. Therefore, the production of copies of these medicines, mostly called biosimilars, has received attention from both manufacturers and regulatory agencies worldwide. Pharmaceutical companies in non-World Trade Organization member states have even manufactured copied biopharmaceuticals before their patents have expired and marketed these copied biopharmaceuticals inside the country's boundaries or even exported them to other countries [1].

The manufacturing of biopharmaceuticals is somewhat different to that for small molecule chemical medicines, and the procedure is much more sensitive to change in the production process and even

environmental factors. The possibility of severe immunogenicity reactions is one of the major concerns of the manufacturing procedure of the biopharmaceuticals. Although rDNA-derived biotherapeutics are potentially immunogenic, this differs greatly between molecules.

Constant evolution of manufacturing methods of therapeutic biologicals requires robust quality control methods to assure safety and efficacy of these medicines. Many of these risks could be managed through modern bioprocessing technology, implementing current good manufacturing practice (cGMP) rules and application of validated quality control methods for analysing starting materials as well as intermediate and final product testing. The quality, safety and efficacy of biotherapeutics rely heavily on starting materials and the manufacturing process.

Although biopharmaceuticals are composed of much larger molecules than are conventional chemical medicines, it does not mean that larger molecules are always less safe than small molecule medicines. Toxicity of these compounds is usually related to exaggerated pharmacological effects but not to off-target effects. Therefore, genotoxicity studies routinely conducted for small chemical molecules are not applied to biopharmaceuticals. Standard carcinogenicity bioassays are also generally inappropriate for rDNA-derived biotherapeutics, except for products which may induce proliferation of transformed cells.

Due to the nature, complexity and size of these medicines, it is practically impossible

to manufacture 'identical' copies. But several molecules with similar therapeutic profiles are now marketed worldwide. Different countries name these alternative biopharmaceuticals differently, with names including biosimilars, follow-on biologics, similar biologics, subsequent entry biologics, similar biotherapeutic products, biogenerics, and alternative biopharmaceuticals.

Despite the fact that some international organizations such as the World Health Organization (WHO) and the European Medicines Agency (EMA) have issued guidelines for regulation of these alternative biopharmaceuticals, regulation of these medicines has become a hot and controversial topic.

Sales of biosimilars currently represent a relatively small proportion of the pharmaceutical market in the European Union and the US, but the near future of the biosimilars' market is so lucrative that many companies that produce blockbuster innovator biopharmaceuticals are starting to develop their own biosimilars [2]. The significant price difference between biological originator medicines and their copied versions manufactured in developing countries has created a vital opportunity for patients living in these countries.

Despite the presence of several obstacles, including acceptability among physicians, price and reimbursement policies, and supply and demand trends, regulatory issues are the most important obstacle in the uptake of these medicines in developing

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Submitted: 27 August 2014; Revised: 14 September 2014; Accepted: 15 September 2014; Published online first: 29 September 2014

countries. Most of the guidelines published for regulation of alternative biopharmaceuticals, including WHO guidelines, rely on head-to-head comparative clinical studies for proven similarity between innovator products and alternative biopharmaceuticals. Such comparison involves both quality non-clinical and clinical aspects of the products. However, due to a lack of sufficient resources and expertise, design and implementation of a comparative clinical study, as proposed by WHO or EMA guidelines, in low- or medium-resourced countries is not feasible. It is therefore questioned whether WHO guidelines are in line with the needs, capabilities and interests of national pharmaceutical markets in low- and medium-resourced countries [1, 3].

Currently, many alternative biotherapeutics manufactured in these countries receive their marketing authorization following a loosely designed and practised clinical study. Therefore, some investigators have requested for a more pragmatic guideline for regulating biotherapeutics in low- to middle-income countries [3]. The guideline should be balanced between assured safety and efficacy, and timely availability of these life-saving medicines for these countries. One approach is that alternative biopharmaceuticals could be developed without undergoing lengthy and costly clinical comparative trials and could instead have either a conditional approval based on sufficient efficacy and safety data in real life or undergo a less costly demonstration of efficacy and safety by using historical data from innovator products as a comparison. It should be emphasized

that historical data available based on marketing of the innovator product could shed light on the extent and prevalence of possible adverse reactions, especially immunological reactions following the administration of biotherapeutics.

Although immunological reactions could be considered as a main concern following administration of biotherapeutics, such adverse effects are very rare. Based on the fact that available safety and efficacy data for innovator biopharmaceuticals could be used as a historical record, some experts believe that performing head-to-head preclinical and clinical trials may not be necessary and might deprive patients of cost-effective medicines by delaying market entry of these medicines.

It is a general consensus that price reductions associated with alternative biopharmaceuticals could improve accessibility and affordability of these medicines. Therefore, any unnecessary delay in market entry of these products might compromise appropriate patient treatments. Many regulatory authorities in developing countries are capable of evaluating safety and efficacy parameters of biotherapeutics. Therefore, an alternative approach could be that – following approval of quality control and *in vitro* parameters for alternative biopharmaceuticals according to internationally acceptable standards – instead of requesting a comparative clinical trial, regulatory authorities could issue a time limited, e.g. one year, marketing authorization for the product to be used in few well-established medical centres as a phase IV clinical study. During this period,

the product will be administered under direct surveillance of regulatory authorities and the efficacy data or possible adverse effects, including immunogenicity reactions, will be monitored meticulously by regulatory authorities. If during this period all results were satisfactory, the marketing authorization will be expanded; if not, the product will be removed from the market.

Although such an approach remains a proposal at this stage, I call on readers to keep this field open for further discussion and comments; *GaBi Journal* could play a major role in this forum.

Competing interests: None.

Provenance and peer review: Not commissioned; externally peer reviewed.

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DOI: 10.5639/gabij.2014.0304.038

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