Accessibility of life saving biotherapeutics is still a dream for citizens in low- and middle-income countries (LMIC).

Kaveesha J. Wijesinghe, Faculty of Science, University of Colombo, Sri Lanka (kwijesin@chem.cmb.ac.lk)

Abstract

Due to high costs associated with their production, biotherapeutics remain largely inaccessible to citizens of LMICs even though many are included in the WHO model list of essential medicine. If essential biotherapeutics can be produced within LMICs, it will increase their affordability and accessibility to a wider population and improve treatments options available for the patients. Cost of production for essential biotherapeutics can be reduced if the technology and approved cell lines required for their production is made available for LMICs. This initiative could drastically improve the capabilities of LMICs to invest in biotherapeutics production. In parallel, LMICs must adapt national biotechnology policies that will promote biosimilar production within the country.

Introduction

Biotherapeutics are drug therapies containing active ingredient/s derived from a biological source (Johnson, 2018). The advent of recombinant DNA (rDNA) technology made mass production of therapeutic proteins in bacterial and cultured eukaryotic cells a possibility, cutting down massive costs associated with traditional modes of extraction, such as the use of animal sources and paving way for novel, innovative fully humanized therapies (Ghaderi et al., 2012; Yehuda and Padler-Karavani, 2020). While therapeutic proteins (hormones, growth factors, cytokines etc.) produced from rDNA technology and monoclonal antibodies (mAbs) still remain the most commonly prescribed biotherapeutics in market, many other therapies of biological origin are available, including gene therapy products, vaccines, cell based products, genome editing therapies, tissue-engineered products, and stem cell therapies (Ghaderi et al., 2012; Cheraghali, 2014; Johnson, 2018; Yehuda and Padler-Karavani, 2020). The portion of biotherapeutics entering the global market has significantly risen each year, and in 2022, the number of biologics approved by the Food and Drug Administration (FDA) of USA equalled the number of small molecule drugs or the new molecular entities (NMEs) approved (Senior, 2023). Biotherapeutics provide cures, or assist in managing a plethora of life-threatening diseases, including cancer, immunological disorders, infectious diseases, genetic disorders, and non-communicable disease like diabetes, cardiovascular disease etc. As a result, a number of biotherapeutics are now included in the WHO model list of essential medicine (WHO World Health Organization Model List of Essential Medicines, 2021; Morin et al., 2023). Despite the success of biotherapeutics in curing and managing diseases, due to the costs associated with research and development, production costs, and patent protection regulations, new biotherapeutics are often unaffordable even to citizens in developed countries.

Economic implications of biotherapeutics to the global north vs global south

Biosimilars are biological molecules that have the same action and efficacy to an original reference molecule but is produced by a different manufacturer. With many patents expiring for reference biological molecules, biosimilar production has successfully taken off. Europe is notably leading the way with 70 biosimilars entering the European market in 2022. In USA, 19 biosimilars were approved by FDA, and have entered the market (Niazi, 2022). The competition due to multiple biosimilars in the market has reduced their list prices. It is estimated that biosimilars resulted in list price savings amounting to EUR 5.7 billion compared to the reference biologics and captured 10-40% of the total biologic sales in the market (Niazi, 2022). It is estimated that the price of insulin, which is considered as an essential medicine, could cost USD 72-133 per year or less, if there are multiple competitive biosimilars in the market (Expanding access to monoclonal antibody-based products: a global call to action, 2020). Even though biosimilars have brought down the prices, biotherapeutics remains unaffordable to citizens of low- and middle-income countries (LMICs). For example, according to a report published in 2020 (Gotham, Barber and Hill, 2018), 80% of the global sales of monoclonal antibodies occurred in the territories of USA, Europe and Canada, while the rest of the world shared the remaining 20%. More than 80% of the world's population live in low- and middle-income countries (LMICs), and middle-income countries are the home for 62% of the world's poor (World bank in middle income countries, 2022). Yet, these countries carry the highest burden of both communicable and non-communicable diseases (Stevens and Huys, 2017). Despite the burden of

diseases, access to lifesaving biotherapeutics remain poor for many in these countries due to the high costs associated with their production, import and distribution. This inequality in the accessibility to biotherapeutics has prevented patients from receiving the treatment/s that could have markedly improved their survival rates for some diseases or improved the quality of their life (Gotham, Barber and Hill, 2018). It has been suggested that mortality rates associated with certain forms of cancer are not reducing at the same pace between high income countries (20% reduction in mortality rates between 1995-2005) and low-income countries (5% reduction in mortality rates between 1995-2005), owing to the unavailability of biotherapeutics as a treatment option to patients in low-income countries (Morin et al., 2023).

Challenges to make biotherapeutics accessible to all

While pursuing a shared prosperity for the world, healthcare should be considered a universal right. Inequal accessibility of essential biotherapeutics must be addressed to ensure patients are offered with the best treatment option currently available, to cure or manage the disease/s regardless of their financial ability, where they are geographically residing and to ensure that the health indicators of LMICs are improving at a similar pace to the high-income countries. Reduction of costs associated with essential biotherapeutics will allow LMICs to save on healthcare funding and reallocate them to further improve other health indicators. Competing biosimilars that are produced in Europe, USA, and in other high-income countries have brought down the prices of biologics significantly within these markets. However, the effects of the cost reduction associated with competing biosimilars have not trickled down to LMICs sufficiently to broaden their patient accessibility. Biosimilar development does involve significant capital costs and time, which are estimated to be around 100-250 million USD and may take upto 7-8 years (Kvien, Patel and Strand, 2022). EMA and WHO guidelines published for the regulation of biosimilars require strict comparison between the reference and the biosimilar, for non-clinical and clinical aspects of the product (Cheraghali, 2014). This is another contributing factor for high costs associated with biosimilar production, which makes them less accessible to LMICs. Despite multiple biotherapeutics with expired patents being in the market for several decades, many LMICs have not acquired the ability to produce biosimilars that are considered as essential. If biosimilars for biotherapeutics that are deemed essential could be produced within many LMICs, this would improve the affordability of them, broadening their accessibility to a wider population. And improved accessibility of biotherapeutics will lead to improved health indicators for the country.

Policy recommendations to broaden biotherapeutics accessibility to LMICs

Many LMICs will not be able to afford the capital costs for the development of biosimilars, which includes gathering of the expensive non-clinical and clinical data, along with costs for setting up of the production facility based on EMA or WHO guidelines. If a mechanism is set up to develop essential biosimilars with the purpose of transferring technology developed to LMICs at affordable/concessionary rates after obtaining approval from regulatory authorities such as WHO and EMA, the LMICs will only need to invest into setting up of production facilities. In the technology know-how transfer process, the recipient LMICs will receive protocols that are developed on the production, purification, and quality control of the specific biosimilar they are interested in producing, along with cell banks and other key ingredients necessary to initiate the production. When LMICs gain capacity to produce essential biologics within the country itself, a significant price drop for these biologics can be expected, which would broaden the affordability and accessibility to a wider population. Such mechanisms are in place even today. Biotechnology development unit of international center for genetic engineering and biotechnology (ICGEB) develops biosimilars and makes the technology and developed protocols available for its member states at affordable prices. If such initiatives can be expanded to ensure their availability to all LMICs, this type of model could not only be mutually beneficial, but sustainable as well. Also, it is necessary for LMICs to formulate and adapt national biotechnology policies that promote biosimilar production within the country. Public-private partnerships for setting up of production facilities for biotherapeutics could be mutually beneficial to the government and the industry, and ultimately it will benefit patients by expanding their treatment options. Another consideration is that not all LMICs will be able to produce all essential biotherapeutics that the country requires. This is because multiple manufacturing facilities, even if they are small scale,

sufficient only to meet the country's demand, is not feasible. In such cases, regional co-operation would be necessary, with different countries in the region prioritizing a specific biosimilar. Countries within the region should enter into agreements to cooperate and share within the region. This would ensure goals of shared prosperity and universal access to biosimilars a reality.

Conclusions

With the economic downturn observed globally following the COVID-19 epidemic, many LMICs were left struggling to import lifesaving medicine for their citizens. Along with the medicine scarcity, medicines that were available became too costly and beyond reach for a large fraction of the population in these countries. Averting such humanitarian crisis long term requires building resilience in the healthcare systems, which can be partially achieved through instilling capabilities in LMICs to produce essential medicines, especially biotherapeutics. This will contribute to ensuring that the healthcare system of LMICs will be resilient in the face of another health or economic crisis.

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