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Promoting access to biosimilars: a public–private partnership model for biosimilar development in underserved populations

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Biologicals represent the future of pharmaceutical treatments and innovation. Yet, emerging and developing markets lack access to these often essential medicines. Biosimilar development represents a potential solution to this problem, by offering lower cost and improved access, but is also associated with patient safety issues. In order to synergize these divergent challenges, targeted public–private partnerships that bring together shared goals and resources of the public sector, global firms, and local manufacturers need to be explored. Crucial to their success will be equitable intellectual property rights management and coordination and collaboration with effective governance and incentives.

Keywords: Biosimilars, emerging markets, follow-on biologics, global health, immunogenicity, patient safety, public–private partnerships

Background

The 'business of global health' has become a driving force in economic development worldwide, with a variety of government, industry, philanthropic, and non-governmental organization participation in this multilateral, multi-billion dollar effort. A critical aspect of these efforts is promotion of pharmaceutical development and treatments to address key, but underserved, global health needs. These needs include improving access to biologicals (large, complex biotechnology molecules generally made from living organisms) in emerging and developing markets now experiencing an epidemiological shift to non-communicable diseases. With the global biologicals market predicted to be valued at some US$200 billion by 2015 and estimates that global spending will increase up to 800%, it will be crucial to tap into this growth potential to improve access to biological products for underserved populations [1].

Though biologicals represent the future of pharmaceutical treatments and innovations, they are exceedingly expensive due to complexity in manufacturing processes, longer development times, logistical challenges and limited coverage [2-4]. To address these access challenges, follow-on biologics or biosimilars–similar but not identical versions of innovator biopharmaceutical products–have emerged as a strategy in drug development. These 'generic' biologicals have the potential to improve access through abbreviated regulatory approval. For example, WHO has developed biosimilar regulatory guidelines and in some high-income markets biosimilar regulatory regimes are currently in development. For instance, some 14 biosimilars have been approved in the EU yet only a handful of biosimilars have entered investigational new drug application status in the US [4-6]. Entry of these products has the potential to increase patient access, offer lower pricing, and save billions in national healthcare expenditures, similar to entry of generic small molecule chemical entities [6, 7].

However, due to their size and complexity, biologicals as well as their biosimilar counterparts have safety challenges, including immunogenicity [8]. Immunogenicity occurs when a drug induces an unwanted immune reaction that may render therapy ineffective due to development of anti-drug antibodies in patients [8, 9]. Yet, it is extremely difficult to predict, investigate, and conduct surveillance for these patient safety events [7, 8, 10].

The risk of immunogenicity-related adverse events are further magnified with biosimilars, given that manufacturers often do not have access to drug development and manufacturing data from the originator. Indeed, even when multinational firms jointly cooperate and share/license information to produce a biosimilar product, immunogenicity can occur, with fatal consequences for patients, e.g. the case of Eprex in the EU [7, 11, 12]. In addition, depending on the market, drug regulatory regimes may require confidential protection of biological clinical test data due to local laws and obligations of free trade agreements [13]. These factors create significant barriers for both ensuring patient safety and incentivizing production in underserved markets.

Despite these challenges, there is potential for shared opportunity and benefit among various global health stakeholders in promoting access to biosimilars. This can be accomplished through sound global health governance, engaging a multitude of public and private sector actors through the development of targeted public–private partnerships (PPPs). PPPs are a well established concept in global health, and lessons can be learned from other global health initiatives that have attempted to leverage these partnerships as a forum for mobilization and sharing of resources/funding towards common public health goals [14-16]. Recent developments in neglected tropical disease (NTD) drug development serve

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as important examples of cooperation by industry, the public sector and philanthropies towards combating NTDs and can be applied for biosimilars.

However, equally crucial in developing effective PPPs is to understand the need to synergize diverse and often conflicting interests of intellectual property rights (IPR) and public health priorities of providing access to medicines. In this paper we will critically examine these challenges, and propose an innovative PPP model targeted for biosimilar development in emerging and underserved markets.

NTD PPP experience

Neglected tropical diseases have traditionally been overlooked in commercial drug research and development. Yet these diseases affect ~1 billion people globally in over 149 countries and have a profound impact on both the health and social and economic status of mostly impoverished patient populations [17, 18]. They also represent significant development barriers to public health progress and economic prosperity, limiting these countries' potential as present and future markets. Lack of investment and innovation in these markets are also severe impediments to the health-related United Nations Millennium Development Goals [18]. In addition, existing NTD treatments are often antiquated, high-cost, have low efficacy and safety profiles, and are difficult to administer [19-23]. The private sector has largely ignored this need due to lack of incentives and pathways for development, leaving drug pipelines conspicuously absent of NTD medicines [21, 24].

In response, PPPs have been explored as a possible solution to encouraging NTD innovation. This includes partnerships between Merck, Pfizer, GlaxoSmithKline (GSK), and the leadership of the WHO's Special Programme for Research and Training in Tropical Diseases [19, 20]. GSK stands out as focusing on innovative approaches to meet the diverse needs of global markets across multiple global health issues. They have initiated a number of projects, including open access to their proprietary databases at their *Tres Cantos* research facility, partnering with Pfizer to provide HIV/AIDS drugs to least developed countries through their joint enterprise ViiV Healthcare, and working with the GAVI Alliance to develop a pneumococcal vaccine utilizing an advanced market commitment followed by a technology transfer agreement to the Brazilian research organisation, FIOCRUZ.

Recently, some of the world's leading public health actors also announced a new collaboration focused on NTDs. This includes 13 pharmaceutical companies, three governments, the Bill & Melinda Gates Foundation, and the World Bank [25]. It also includes the non-profit, product development partnership, Drugs for Neglected Disease initiative (DND*i*). DND*i* focuses on drug development for six specific neglected diseases. The management of IPR by this ground-breaking initiative will undoubtedly set the precedent for future partnerships but its overall impact remains unknown as it is still in its infancy.

Although these PPPs represent progress and raise important public attention to the global health burden of NTD, they have not yet met the vast needs of patients who still lack access to fully developed and available life-saving treatments. This situation leaves patients untreated and markets underserved. Learning from these lessons, forms of IPR management in concert with targeted PPP development should be critically examined for future application in promoting biosimilar innovation and production.

Importance of intellectual property rights management

With blockbuster pharmaceuticals falling off the 'patent cliff' and losing IPR protections in the context of limited new drug targets in pipelines, the pharmaceutical industry faces unique business challenges and the need for a paradigm shift when considering innovation and drug commercialization beyond use of traditional IPRs [26]. In addition, with the World Trade Organization's Trade Related Aspects of Intellectual Property Rights Agreement (TRIPS), which establishes minimum global IPR protections, transitioning developing countries to more robust IPR regimes in the near future, pressure will grow on the multinational pharmaceutical industry to meet the needs of resource-poor populations [27]. If industry fails to meet these challenges, developing countries may exercise compulsory licensing, e.g. allowing a non-patent holder to produce a patented product without consent; available under existing TRIPS flexibilities that allow for public health concerns to override IPR considerations, that may result in less than favourable outcomes for global innovator firms [28].

In response to these pressures, innovator manufacturers may employ forms of IPR management in order to better manage IPRs that both meet commercial needs and provide needed access to underserved and emerging population groups. This includes critically aligning divergent interests of manufacturers, the public sector, and patients into flexible licensing, pricing and technology transfer schemes for different markets. Existing IPR management tools such as differential/tiered pricing (offering different pricing for the same product based on socio-economic status), voluntary licensing (licensing of patented product by innovator to third party for manufacture, market or distribution), patent pools (creating pool of patents often to produce combination treatments), and promotion of local manufacturing have been explored in the public health context but are fragmented and not well coordinated [29-31].

In addition, novel forms of IPR management are emerging, including open source drug discovery/lead generation and computational bioinformatics (using computer models and lab experiments to identify existing drugs that have potential to treat other diseases) for repositioning existing drugs for neglected diseases, all aim at providing open development and access to new disease treatment options [32, 33]. Manufacturers can potentially integrate these IPR management solutions into drug portfolio management strategies sensitive to global health populations and commercial needs while also utilizing high-volume/low-margin business strategies for segmented developing markets.

Although companies such as ViiV Healthcare and Roche have entered into voluntary licensing programmes to meet some of these needs, these initiatives are still few and far between. GSK is also implementing differential/tiered pricing for their Rotarix vaccine for diarrheal disease, but expanded use of IPR management strategies for use in underserved populations who lack access to biological drugs remains largely unaddressed.

Targeted biosimilar PPPs: promoting quality and access to essential biologicals

Given increased global investment, unmet needs of emerging and developing markets,

and extant public health and patient safety considerations of biosimilar development, targeted PPPs may represent the optimal strategy to improve access to biosimilars if properly structured. Through appropriately governed PPPs, alignment of effective IPR management, local manufacturing capacity building, development of patient safety systems, and location sensitive marketing and delivery of biosimilars, can all occur in an efficient and coordinated ecosystem.

Importantly, by focusing on patient safety and access to essential biologicals, PPPs can synergize partnerships between global firms, local manufacturers, civil society, and provider and patient needs for high quality and safe biosimilar development that meets local needs. This can be accomplished through a combination of global firm technology transfer and technical assistance, local manufacturer infrastructure and human capital, and public health sector leadership and coordination within the appropriate regulatory and product marketing environments. Success will require joint development of patient safety and pharmacovigilance systems addressing the risks of biosimilars, while also providing the appropriate incentives further outlined below for drug development and manufacture.

To meet these shared goals, public health agencies/ministries could begin with identifying essential biological products that meet their own crucial local health needs in consultation with providers and civil society, and prioritize the development of these biosimilars through request for proposals (RFPs) for targeted biosimilar PPPs. In order to qualify for RFP submission, proposals should require a model partnership structure between an innovator firm, local manufacturer, and the public sector based on minimum terms including:

- Manufacture per current good manufacturing practices (cGMP) standards as set by innovator company's jurisdiction/ drug regulatory agency
- Agree to engage in equitable technology transfer and data sharing to ensure relative bioequivalence to innovator product
- Agree to domestically specified and regulated differential pricing based on ability of segmented market to pay (with appropriate countermeasures for inequitable parallel trade, such as use of resale restrictions and enhanced labelling)
- Agree to allocate greater than a majority of local manufacturing capacity to local/ underserved needs, i.e. not substantially for export market
- Joint commitment to implement, finance and maintain immunogenicity patient safety and pharmacovigilance systems

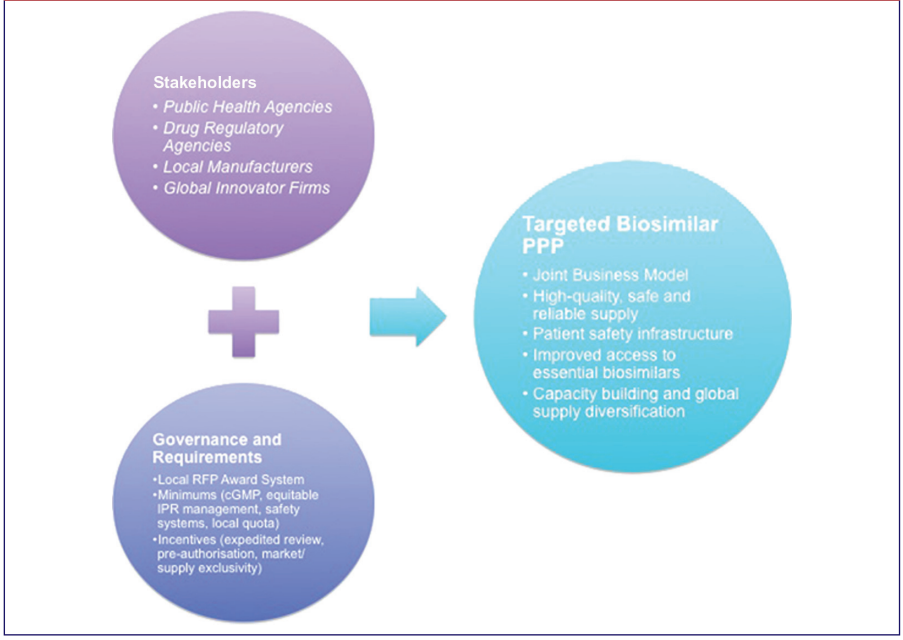
Those proposals offering the most favourable terms of access, safety and manufacturing capacity would be awarded proposed RFPs and operationalised through partnership with local public health and drug regulatory agencies who would participate in implementation.

In consideration of RFP-based commitments and partnership to invest in technology transfer, safety systems, local manufacturing capacity, and joint development of life saving essential biologicals, drug regulatory agencies could commit to providing favourable regulatory terms, including: (i) expedited regulatory review of essential biosimilar product; (ii) pre-authorisation for government formularies/procurement agencies and possible expedited designation of interchangeability; and (iii) extending a period of market exclusivity for PPP-developed biosimilar products on the basis of safety and relative bioequivalence to innovator product to reduce initiation barriers of expensive development and regulatory approval costs. Public health agencies or national health systems could also reward PPPs for this significant investment and commitment to safety by including in RFP awards guaranteed supply contracts, similar to advanced market commitment incentives already explored [34].

In addition, these shared efforts can be translated to generation of clinical trial data necessary to demonstrate comparable quality, safety, and clinical equivalency to support biosimilar regulatory approval, e.g. comparability data/exercise if required. Specifically, public health agencies could work directly with providers and the community to assist in recruitment, local producers can manufacture candidates at cGMP levels necessary for testing, and global firm partners can provide technical assistance given their extensive experience in clinical trials design and enrolment while also providing necessary capital. Collectively, PPPs can work collaboratively for drug approval and clinical trial engagement, and agree on abbreviated pathways for accelerated approval if necessary conditions, milestones and coordination between partners are met.

Targeted biosimilar PPPs would provide shared benefits for all stakeholders involved through joint collaboration and shared investment, while serving public health needs prioritized by the local community, see Figure 1. Patients and the public health sector benefit from sustainable local

Figure 1: Elements of targeted Public–Private Partnership model for biosimilars



production of essential biologicals, lower and more flexible pricing in exchange for guaranteed commitments, and most importantly, improved access to safe and effective biologicals that are delivered and monitored through a robust patient safety system. Local manufacturers not only gain revenue from product sales, but also benefit from capital investment, technical assistance and technology transfer from innovator firms, lending to capacity strengthening. Global firms equally benefit from accessing important emerging markets that are traditionally difficult to penetrate, but also derive revenue from licensing and favourable treatment through market exclusivity or supply commitment.

As increasing numbers of countries join the 'pharmerging' markets and face similar concerns, this model can be replicated for other global health priorities and targeted development to enhance local access and manufacturing capacity. Further, as these targeted PPPs emerge as centres for local cGMP manufacturing of various biologicals, high-income markets may also benefit from additional sources of high quality and safe medicine production in the event of public health emergencies, disease outbreaks, disasters or drug shortages.

Conclusion

The business of health is increasingly the business of global health. As such, it is one of the most challenging environments because of the need for coordination and cooperation between various stakeholders to meet both local and global needs, especially in relation to access to essential medicines. The need for enhanced biosimilar promotion illustrates these challenges and demands exploration of more efficient strategies to foster these partnerships. Targeted biosimilar PPPs that engage the public health sector, drug regulators, local manufactures, and global innovator firms using effective governance and IPR management strategies may serve as a potential solution. These innovative PPPs can create mutual benefit through shared revenue streams, capacity building, expand existing essential medicine offerings, enhance patient safety and jointly develop underserved markets while meeting global health needs for local and global populations.

For patients

Biological medical innovations are increasingly essential for treating patients globally, but as described in this article, significant economic and patient safety barriers present real challenges. Indeed, many of these complex medicines remain beyond the reach of patients who need them, with developing countries especially lacking access. Biosimilar development and entry can ensure patients get the essential medicines they need, but must be coupled with the correct 'push' and 'pull' incentives such as those mentioned in this article, in order to be effective. Patients and civil society groups advocating on behalf of patients for increased access to medicines should work together with public and private sector actors to ensure that equitable biosimilar availability is a priority in global health outcomes.

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