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Tipping point: Biosimilars, emerging markets, and public-private engagement to promote global health

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ABSTRACT

Biosimilars, also known as follow on biologics, are complex biotechnology drugs that are similar, but not identical, to original biologic drug forms, and represent potential lower cost versions that may improve access. Yet biologics and their biosimilar forms have a key safety concern: unwanted immunogenicity. Emerging markets have tremendous interest in biosimilars, but are at a tipping point: they are moving from developing country concerns (e.g., communicable disease) to developed country needs (e.g., cancer therapies) that require biologic drugs. Production, however, is at lower than current Good Manufacturing Practice levels standard in highly-regulated markets. Emerging market public-private partnerships between public agencies, local producers, and global pharmaceutical firms, can incentivize biosimilar production at higher quality levels than required for local markets as well as position themselves for entry into developed markets. Public health goals can be reached while increasing economic opportunities in these markets to benefit global health.

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INTRODUCTION

Pharmaceuticals represent some of the most powerful armaments in the medical arsenal. Biologic drugs, also known as biologics, are large, complex, generally injected biotechnology molecules made from living organisms that address disease on fundamental cellular levels. These include hormones, interferons, kinase inhibitors, monoclonal antibodies, vaccines, and other single and multiple chain proteins. These drugs have high potential to improve and increase quality and quantity of life compared with traditional, small molecule, solid pill drugs.

Biologics clearly represent the future in medication treatment. It is estimated they will account for more than half of newly approved drugs worldwide.[1] By 2015, 8 of the 10 top-selling medications are predicted to be biologics,[2] and global spending will reach $200 billion.[3]

However, biologics are expensive, and average costs for innovator biologic treatment can be upwards of $10,000/month.[4] Even in emerging markets, such as Brazil, Russia, India, and China, costs for biologic treatment can be $40,000/year.[5]

The benefits of pharmaceuticals can be accelerated when generic forms are allowed entry into the market through abbreviated approval pathways, which reduce price and increase access. Follow-on biologics, as they are known in the USA, or biosimilars as they are known

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in the EU and elsewhere, represent such a potential for biologics.

However, it is important to note a key safety issue is associated with biologics: immunogenicity, where the drug induces unwanted immune reactions. Reactions can be severe and represent a major medical emergency. Yet specific immunogenicity reactions are notoriously difficult to predict.[6]

Follow-on/biosimilar interest has been driven by increasing costs in developed and emerging markets as well as aging of the global population.[7] However, emerging markets themselves are seen as driving and dominating biosimilar sales due to highly elastic price sensitivity for drugs in these markets, since many of these countries do not cover pharmaceuticals in their insurance systems, and their relatively low development costs.[8]

The EU has relatively recently established procedures for evaluation and marketing approval of biosimilars, and approved a handful since 2006 when the first biosimilar, a version of human growth hormone, was approved.[9-11] The USA has only begun its process of finalizing follow-on biologic abbreviated pathways since passage of healthcare reform.[12,13]

Hence, the follow-on/biosimilars market represents significant untapped potential. Indeed, estimates are that global biosimilars spending will increase 700 to 800% in the 2010 to 2015 time frame,[3] replacing a significant fraction of the approximately $80 billion in global sales of branded biologic drugs coming off patent by 2015.[11]

Emerging markets are consequently at a tipping point. Patients needing less expensive but increasingly complex drugs in these markets can obtain significant public health benefits if delivery systems are able to safely integrate biosimilar production and use. Domestic producers are poised to obtain significant economic benefits from meeting demand for production of biosimilars and follow-on forms. Multinational pharmaceutical firms are also exploring strategies to enter the biosimilars market in rapidly developing emerging markets while also considering these forms for developed countries.

Creating effective public-partnerships between government, local manufacturers, and global pharmaceutical firms has great potential to provide these joint benefits to these stakeholders. Indeed, such public-private partnerships have become important in addressing important global health policy concerns,[14,17] and have been growing as an important source of global health governance as these health issues transcend geopolitical borders.[14-17]

These mutually beneficial relationships for biosimilars, however, must be attentive to safety concerns, local market requirements, and highly-regulated market expertise in order to maximize benefits and minimize risks to patient safety and global health. Only by appropriately focusing on each can the tipping point be pushed forward toward improving global health while positive economic benefits are realized. We address each of these in turn.

PATIENT SAFETY: IMMUNOGENICITY

Original and copied biologic drugs have had safety challenges, primarily immunogenicity.[12] Immunogenicity is a phenomenon in which the drug induces an unwanted immune reaction in the human body. Individuals no longer respond to therapy due to development of anti-drug antibodies.[18] Due to its rarity, immunogenicity is often not acknowledged for the patient safety vulnerability and the life long drain on healthcare resources that it poses.

Immunogenicity is extremely important for biosimilars/follow-on forms. Therapeutic protein biotechnology formulations have immunogenicity potential because of their size, living cell-based manufacture, and protein configuration, compared with small molecule, solid-chemical pills. Yet predicting immunogenicity is exceedingly difficult.[4,19] This clinical phenomenon appears dependent upon a broad array of divergent factors, including molecular structure(s), patient genetics, biologic type, impurities, and other factors including administration route and frequency of use.[1]

Clinically, immunogenicity reactions for innovator biologics can be severe and represent a major medical emergency.[6] Even in developed markets like the USA, approved biotechnology drugs have generated previously unrecognized immunogenicity, and require long-term clinical surveillance to identify.[20] For example, immunogenicity of biologic therapeutics have had negative treatment impacts for inflammatory bowel disease, Crohn's disease, arthritis, as well as multiple sclerosis.[21,22]

Importantly, immunogenicity is a critical patient safety concern even when companies cooperatively license to produce a biosimilar product. The case of erythropoietin licensing from a USA producer to a European Union ("EU") manufacturer is an important example.

Erythropoeitin is a naturally-occurring human protein as well as a biologic drug promoting red blood cell growth. In the late 1990s, Amgen licensed the exclusive rights to produce it in the EU to Johnson & Johnson (as Eprex®), while Amgen retained USA production (as Epogen®). Both purportedly used identical methodology for drug production.[1] Johnson & Johnson made several, what it considered minor, manufacturing changes in Eprex production. After ~2 years, however, multiple patients taking Eprex in the EU developed a rejection reaction resulting in pure red cell aplasia, a severe, life-threatening condition where the bone marrow ceases to

produce red blood cells. No such effect was observed in Epogen patients.

Intense investigation revealed Eprex had a different immunogenicity profile than Epogen, and patients had developed antibodies to Eprex.[23] Beyond creating a rejection reaction to the drug, the new immunogenicity created antibodies against the patients' own, naturally-occurring erythropoietin. This resulted in patients' immune systems attacking their body's own erythropoietin, as well as created cross-reactivity reactions to other forms of the biologic. Hence, patients could not produce red blood cells on their own nor through the use of any biologic drugs.

Ultimately, several patients died and others became permanently transfusion-dependent. A combination of high dose immunosuppressive therapy and renal transplantation has been required for clinical remediation. Yet despite continuing research efforts, no clear conclusions have emerged as to why Eprex was associated with immunogenicity reactions whereas Epogen was not. The debate and search continues for the etiology or etiologies underlying the severe reactions associated with the biologic.[24]

These and other examples show the sensitive and complex nature of human reactivity to biologics.[1,25] Importantly, for Epogen/Eprex, the research, testing, and technology supporting assessment of biologics were well known to regulatory authorities and industry partners, and full product reviews had been performed. Yet despite this process, severe clinical problems resulted and have yet to be explained sufficiently.

In emerging markets, these challenges will likely be magnified. Because of cost and access considerations, innovator products may be too expensive for broad use, and follow-on biologics will likely become a progressively greater fraction of the therapeutic strategies used to treat complex and co-morbid disease for patients in these markets. Yet given the presence of immunogenicity, careful consideration of inherent limitations of methods to detect and predict it must be taken into account by public health entities and regulators interested in these treatments for their polity.

In addition, current lack of harmonization regarding naming of biosimilar forms, using only global generic names, and/or using names that do not specifically identify the manufacturer create even greater patient safety risks.[1,26] Because immunogenicity will likely become more common since the products "following on" the branded biologics will not be cooperatively licensed, nor will manufacturing methods be disclosed to the follow-on producer, there may be significant risk that such biologic products may create immunogenicity given its incidence and unexplained etiology even in cooperative licensing situations. Indeed, it is expected that biosimilar manufacturers will use modified and altered manufacturing processes and make other unforeseen changes compared to original production methods used by innovator companies.

Yet due to medical emergent nature of immunogenicity reactions, and difficulties in predicting these adverse effects, rapid identification of the manufacturing source should be systemically incorporated into delivery systems to allow rapid identification and response. Policymakers in these countries therefore must take these considerations into account when designing systems that promote biosimilars for domestic populations in these emerging markets.

EMERGING MARKETS: DOMESTIC NEED AND PRODUCTION

There is tremendous interest in producing biosimilars and follow-on biologics in emerging markets. Growth of demand for drugs in these markets is rapid and increasing. For example, China has experienced a pharmaceutical market expansion of 24% since 2010; India expanded 20.4% in 2010; Brazil has experienced market growth increases of ~20%; and the Russian market has been increasing at 15-18% over the past several years.[3,11,27] As a general matter, "pharmerging" markets now account for 1/3 of global growth in drug demand at the expense of the USA and the EU,[11] and by 2015 will account for 28% of the world's spending (a 55% increase since 2010).[3] Indeed, 8 of the 20 top world pharmaceutical markets are now emerging market countries, with China poised to replace Japan as number 3 behind the USA and EU.[11] In response, infrastructural capacity is being built to produce biologics and biosimilar forms in these countries.[1,11]

However, like all countries, the economic climate and increasing costs for healthcare have driven emerging market policymakers to focus on price, and reimbursement cuts for healthcare have become common, including for pharmaceuticals.[11] In addition, more specialty-based, higher demand biologic drugs such oncology treatments, immunotherapy, and other target therapies, are of more interest because of their public health need and the shift of emerging markets from developing country health concerns (e.g., communicable disease) to developed country needs (e.g., cancer treatments). These factors in combination have resulted in an expanded demand for cheaper biologic treatment forms in these emerging markets.

Emerging market producers have a significant advantage to serve these domestic markets. First, they are local, and hence are facile with the legal and regulatory requirements within these markets. Indeed, local

production, distribution, and other supply support are a necessary condition in these markets for any potential commercial benefits, particularly because many emerging markets have rules that favor local businesses, such as in China, Russia, and Brazil.[11] This includes governments actively investing in local development of biosimilars by domestic companies for their own markets and/or refusal to pay for innovator forms due to high costs.[5] Patent and oversight regulation, as well as local demand characteristics, are also more within the manufacturing context and social structure understood by local producers than multinationals.[11] The rejection of Bayer's version of the biologic sorafenib (Nexavar®) by the Indian patent system, compared with the successful entry by Novartis into Russia that employed local adaptation and partnership with domestic actors, a focus on generics, and commitment to establishing local government relationships, illustrate the importance of attention to local environment and conditions.[11]

Second, emerging market producers focus on their local markets rather than consider them an annex or adjunct to developed country markets as many global pharmaceutical firms do. This represents a key opportunity for emerging market producers. At present, there is severe under-penetration of emerging markets by multinational pharmaceutical entities. In fact, only 3.8% of revenues of the 15 largest global pharmaceutical producers in aggregate result from sales in Brazil, Russia, India, and China—and they are mostly focused upon smaller blockbuster, premium markets therein, not the larger generics market.[11] Even global generics firms have not effectively embraced biosimilars opportunities.[28] As innovation pipelines of multinational drug companies dry up and global drug company revenues decline, the need for biosimilar forms to expand commercial opportunities can result in emerging market producers to be well positioned compared to global firm competitors.

Third, the cost of production in emerging markets is lower in terms of development. This stems from lower overall costs in these countries in general as well as their relatively decreased regulatory structure compared with large, developed markets such as the USA and EU. For example, although still costly compared to traditional solid pill generics, Indian follow-on biologic manufacturers can meet lower regulatory burdens with development costs for drug approval estimated to be an astounding 90% lower than in the EU (and even lower compared with the USA).[29] As such, producers in emerging markets may have a competitive advantage in attempting to serve their domestic markets since they may leverage this cost environment to a greater extent than external producers attempting to gain entry into this market *solum de novo*. They may hence be able to enter in a shorter time, and coupled with lower development costs and local subsidization, may compete effectively against multinational drug companies in these markets.

EMERGING MARKETS: GLOBAL NEED AND PRODUCTION

However, to garner any potential substantive gains due to the high costs of biosimilar development and global markets, emerging market drug companies must obtain access to large, developed country markets such as the EU, Japan, and particularly the USA.[30] Yet the regulatory demands for entering these markets are not only detailed and extensive, biosimilar approvals generally require full clinical trials for each production line as well as a range of animal, immunogenicity, safety, toxicity, pharmacokinetic and pharmacodynamics studies using parallel and cross-over comparative methodologies.[1,13] This is a markedly more expensive and challenging proposition compared with the low cost for generic approval of small molecule, solid pill, which generally requires only a bioequivalence study.[1]

Indeed, it is estimated that a small molecule traditional solid pill generic costs ~$3 million to obtain market approval. However, biosimilars are estimated to cost *at least* 10 times that amount at ~$30 million[11,31] (and by some estimates, up to $100 million) for marketing approval in highly-regulated markets.[30] In addition, laws such as the FDA Amendments Act of 2007[32] and pharmacovigilance mandates in biosimilar regulatory guidance have increased standards for approval that now extend to post-marketing approval periods,[13] reflecting a trend of higher and more regulatory barriers that must be negotiated in order to enter into these markets. Limited adoption of biosimilar forms in developed markets (e.g., only 10% for erythropoietin and human growth hormone biosimilars in the EU) reflects the challenges to successful entry.[28]

These realties reify the notion that follow-on biologic production and sales will require significant attention to regulatory compliance and large capitalization to be successful in highly-regulated markets.[33] At present, there are only a limited number of companies with the relevant characteristics to be fully competitive globally in the biosimilars market.[7,34] Indeed, almost half the entities manufacturing or developing follow-on biologics outside the USA or EU have no prior experience with supplying active pharmaceutical ingredients to these developed country markets and lack manufacturing sites that meet required current Good Manufacturing Practices.[29]

Further, it is apparent that to succeed in the global biosimilar market, biosimilar manufacturers must ensure that there is adequate branding and marketing experience to differentiate one biosimilar version from

another. Because current infrastructural differences between and within systems for naming biosimilars have not adopted unique appellations or designations for each version, and because there is generally no provision for substituting biosimilar forms for original biologic products, it is even more important to have the adequate marketing and sales experience to ensure brand differentiation and loyalty that can promote economic growth and benefit.[1,30]

EMERGING MARKETS: POTENTIAL FOR COOPERATION

Safety

Follow-on biologic use and production in emerging markets represent public health and economic opportunities. The reduced costs and increased access to key, clinically advanced therapeutics in growing markets provides potential joint benefits to society, local producers, and multinational drug firms.

To garner these benefits, several aspects bear noting. First, and foremost, stakeholders in emerging markets must recognize the key safety concern associated with biosimilars: immunogenicity. Because of its medical severity, potential broad negative reactions to biosimilars from any adverse event, as well as costs associated with any needed clinical remediation, proactive prevention and early detection systems should be put into place prior to broad integration of biosimilars into the health delivery system.

Patient safety proposals based upon the USA Institute for Safe Medication Practices ("ISMP") "High-Alert Medications" could be adopted or serve as a foundation to address these public health concerns.[35] By doing so, the patient safety community will be alerted to the importance of monitoring these drug forms.[12]

Several characteristics should be part of such a system. First, all biosimilars should be specifically deemed high-alert medications. Emerging market public health and patient safety advocates and teams should then consider using established ISMP tools for safety systems that avoid preventable error with these medications as well as create systems resilient to its presence. For example, in hospitals, follow-on biologic access should be limited as other high-alert medications are as recommended by ISMP. Use of a locked cabinet and sign-out forms with immunogenicity warnings in combination with education can highlight the importance of immunogenicity risk to providers who dispense and employ the drug in treatment plans.

Second, systems interventions providing professional provider information about these drugs should be put into place. Prominently displayed warnings as to immunogenicity should be posted with the drug in pharmacies, on any physician-order entry (e.g., in hospitals, nursing homes, clinics, and other locales), and on dispensing records. In addition, recurrent in-service training for provider teams should emphasize this adverse event potential for any who handle or use the drug.

Third, consistent with provisions that improve effectiveness by engaging patients as part of the patient safety team, patients who are taking follow-on biologic drugs should also be provided with layperson-comprehensible information as part of informed consent explaining immunogenicity risks with follow-on biologics. In addition, express signs and symptoms that may represent early warnings of an immunogenicity reaction should be outlined and well-disseminated in markets that use biosimilars.

Each of these areas may not be well known to manufacturers, public health authorities, and patients in emerging markets. However, multinational pharmaceutical companies have worked in regulatory environments that have these tools and clinical experiences. This is an important area where global pharmaceutical firms could assist local producers and public health authorities in preparing biosimilars for an important role in these markets.

Working together in public-private partnerships, global companies with developed market experience could bring that knowledge and technical expertise to emerging market countries. Beyond ISMP strategies, this would also include global firm insights as to cooperative design of effective systems of communication with government authorities together with input from local producers. Such a jointly conceived system will allow reports of potential adverse events associated with biosimilar therapies to be addressed rapidly through a streamlined, joint public-private response. Due to their large capitalization, multinationals could also provide partial underwriting or seed funding as part of its contribution to these public-private partnerships efforts.

Further, once basic proactive preventive and reactive reporting, analysis and response structures have been jointly created and established, higher-level safety infrastructures could be considered. For example, the use of auxiliary labels and automated alerts, if local health IT systems could accommodate it, for biosimilar warnings would be beneficial as a safety intervention. An electronic auxiliary label, amended for immunogenicity warnings, that transmits information automatically to the ordering physician could provide safety redundancy through clinical and risk information alerts.

In addition, multinational drug company experience in direct-to-consumer advertising, use of the Internet[15]

and mobile handset technology, could be leveraged to benefit these public-private partnerships. These technologies can be applied as an effective public health tool for biosimilars as well as to address other public health needs, including communication on recalls, potential counterfeit drugs, and disaster warnings.

Finally, standardization of purchase and use of these products is essential. Facilities ordering biosimilars should consider purchasing only one brand to provide prompt identification and forensic analysis of any product that results in immunogenicity. In the alternative, they must have systems in place to clearly and rapidly identify the source and version of the follow-on product used. Similarly, standardized protocols in administration of follow-on products and express notation of immunogenicity potential should be put into place, relevant to the specific disease state. For example, clinical practice guidelines and other recognized therapeutic guidance sources in the local medical community should incorporate immune status as a regular assessment when follow-ons are used. Public health authorities as well as local producers would have greater insight as to the specific epidemiology and potential adverse event profiles of patients in emerging markets compared with global pharmaceutical firms, and hence could contribute this safety expertise to public-private partnerships.

Local markets

It is apparent that emerging markets represent the largest untapped and growing source of global pharmaceutical demand. This can be seen to some extent when viewing recent merger and acquisition activity. For example, Abbott has acquired Piramal Healthcare in India; Amgen purchased Bergamo, an oncology producer in Brazil; Merck has entered into a joint venture with Supera Fama Laboratorios in Brazil; and Sanofi Aventis has purchased Medley, Brazil's third largest pharmaceutical company.[11,36-38] However, despite some cooperative activity in emerging markets, most global drug companies are significantly underexposed and underperforming in pharmerging markets.[11]

As in the safety arena, public-private partnerships here would also provide mutual benefits for all stakeholders. Local producers have tremendous advantages in emerging markets that should be leveraged to promote public health and economic benefits in these countries.

At the outset, of course, local manufacturers have concrete working knowledge of the regulatory structure and the relevant personnel and policies that are involved in gaining entry into these emerging markets. Importantly, however, the formal, as well as perhaps more importantly, the informal means of (and contacts for) the approval process, manufacturing authority, and other legal requirements are and have been the complete focus of these companies in these markets. Multinational drug companies, which generally do not have established on-the-ground presence in these markets, can leverage this extant local knowledge, relationships, and focus to gain access to these markets by partnering with local producers.

Further, cultural competence in these markets cannot be ignored. Marketing blockbuster drugs to western markets is significantly different from marketing biosimilar or generic drugs in emerging markets.[11] Local, culturally-competent marketing is fundamental business knowledge for emerging market companies since it is, in fact, their primary, and in many cases, their only market. Beyond traditional conceptions of cultural competency for patient communications, the unique local producer infrastructure for marketing and distribution that includes local marketing contacts and relationships with healthcare providers, government purchasers, and others is also an area that is sensitive to local cultural conditions about which global pharmaceutical firms generally have only secondary knowledge compared with local producers.

In addition, however, cultural competence is a key public health concern. Attention to it must be a priority to ensure appropriate patient understanding of biosimilar treatment risks and benefits as well as sensitivity to cultural differences that may influence clinical outcomes. Here, multinational companies working in partnership with local manufacturers and government public health and drug regulatory authorities can develop appropriate biosimilar education, culturally-competent communications strategies, and drug monitoring strategies that include relevant cultural characteristics potentially influencing use, compliance, and adverse event potential. Indeed, countries with indigenous peoples and other underserved populations fundamentally require expanded approaches and assessments than highly urbanized environments, and may require specialized protections relating to public health concerns.[39]

Importantly, maturation of such public-private partnerships can result in competitive pressure to improve biosimilar quality in these markets. With technical knowledge and manufacturing that fulfill regulatory hurdles in highly-regulated markets, global pharmaceutical companies can assist local manufacturers to produce drugs at these higher quality levels, regardless if such is required in local markets. In combination with local public health knowledge to reach and protect patients, emerging markets with stakeholders employing these partnerships may provide higher quality biosimilars—approaching highly-regulated market levels—for patients there (as well as in other emerging markets in which they compete). In this case, the competitive bar is raised in

these emerging markets for higher quality biosimilars when employing these public-private partnerships.

Local and global stakeholders that produce higher quality drugs in partnership with government agencies in public health monitoring activities, safety reporting and response, and culturally-sensitive communications, will be best positioned to succeed in these markets, particularly as governments become the primary purchaser of biosimilars. Coupled with the potential for sovereignties to limit biosimilar purchases to few or even one manufacturer as a proactive safety measure, there is even greater potential for economic benefits through these partnerships.

Global drug firms engaging with local producers in partnership with public agencies in emerging markets is therefore key. Indeed, these alliances can transform the market for pharmaceuticals in emerging markets and provide private sector partners with competitive advantages there. Production of these drugs also benefits public health through lower prices and higher quality in these countries, sensitive to local peoples and conditions. With global capital costs at all time lows, stakeholders in these emerging markets have significant opportunities to work together and invest into this strategy for present and future mutual benefits.

Global markets

The significant benefits local biosimilar manufacturers provide in emerging markets keenly depends upon knowledge of the local conditions there. Communication methods, formal and informal processes, unique public health needs, and financial and market advantages available to local producers all contribute to strategic planning and positioning in these local markets.

Yet global success in biosimilar production for local, emerging market firms requires entry into highly-regulated markets to offset the costs of development. Here, global pharmaceutical firms have had significant presence and experience. As with emerging markets, infrastructural processes, methods, means, and contacts (formal and informal) in these developed markets require culturally competent knowledge of the regulatory system for success. Here, global pharmaceutical firms have tremendous advantages over biosimilar producers from emerging markets in negotiating the much more challenging process of approval in developed ones.

Indeed, regulatory authorities such as the USA FDA advise manufacturers seeking biosimilar approval to meet with regulators to present specific development plans and milestones as well as scientific justifications for the particular molecule before actual application. Furthermore, it counsels continued close discussions with the agency during the entire process of development.[13] Review standards and approval will be on a case-by-case basis, using a "totality of the evidence" approach.[13] Global pharmaceutical manufacturers are likely able to leverage longstanding presence, technical knowledge, existing drug regulatory agency relationships, and formal and informal communications channels to engage this process and appropriately interpret any agency guidance more accurately and at lower cost than emerging market producers.

Further, highly-regulated market regulators are demanding expensive clinical trials for biosimilar approval. Clinical trials are complex, requiring significant planning, time, financial and expert human resources, as well as appropriate human subjects protections, oversight, ethics training, and quality assurance mechanisms, all generally outside the experience of emerging market biosimilar producers, but very much within the experience of multinational pharmaceutical firms. The extensive nature of assessment and review of biosimilar molecules for approval in these highly-regulated markets hence places global pharmaceutical firms at a significant competitive advantage over emerging market biosimilar producers.

Yet costs to produce biosimilar drugs in these highly-regulated markets is much greater than in emerging markets. Further, emerging market producers have existing capacity to produce biosimilars, and in combination with their lower costs, can provide a foundation for producing biosimilar forms that ultimately may be used in highly-regulated markets.

Hence, joint benefits from partnerships between global and emerging market manufacturers for biosimilar entry into developed markets can inure through strategic leveraging of global drug company knowledge of highly-regulated markets with the emerging market manufacturer's lower cost of production. By a global drug firm focus upon bringing production quality of emerging market producer partners to highly-regulated market standards, both can benefit from each's strategic advantages.

However, it is important to emphasize that highly-regulated markets have significant concerns regarding quality of biologic drugs entering into their drug supply chain. It is broadly recognized that some emerging markets, including countries such as China and India, are the source of counterfeit and substandard drugs that have appeared in both developing and developed markets.[40] Global public health concerns arising from tainted biologics originating in emerging market countries in recent years, including the heparin case where ~250 patients worldwide died due to falsified materials used in China, has created significant attention to the downsides of sourcing drugs from emerging markets.[40-42]

These challenges present additional opportunities for public-private partnerships. Mechanisms to counter reputational effects as to poor or suspect quality goods can be done on two levels: substantive improvement of quality to developed country standards; and partnership and leveraging of global pharmaceutical reputational branding.

First, emerging market producers in partnership with global pharmaceutical firms should voluntarily subject themselves to developed country drug regulatory authority oversight and inspections on the same level as highly-regulated market manufacturers. These emerging market partners should also agree to subject their goods to potential import alerts, where receiving developed countries hold products from suspect sources at import sites for targeted assessment and review.[43] In contrast to the traditional import alert approach focusing on country of origin or *ex post* identification of problematic manufacturers, public-private partnerships would allow for proactive inspections and quality standards to be determined on emerging market soil for these particular manufacturers and their specific products.

Using this voluntary, cooperative approach, from a commercial perspective global drug manufacturers partnering with emerging market producers that substantively raise their level of manufacturing to highly-regulated market standards can obtain a competitive advantage over other emerging market manufacturers that are attempting to enter developed country markets. From a public health perspective, these partnerships allow developed country drug regulatory authorities to ensure, through use of the same tools and inspection methods applied in their markets, that specific emerging market manufacturers and products meet their higher regulatory standards. Such an approach would avoid the weaknesses of the current system, which has not resulted in improved safety,[40-43] and rewards entities for voluntarily raising their quality levels.

Indeed, simply opening a branch of a developed country drug regulatory agency in an emerging market country will not address drug quality concerns across producers there without provisions for the same level of assessment, including surprise inspections, documentation of current Good Manufacturing Practices, and process control testing as in highly-regulated markets.[41,43] However, by voluntarily entering into public-private partnerships with these regulatory authorities, emerging market producers with their global pharmaceutical firm partners that reach highly-regulated market standards will be significantly better positioned to enter developed markets.

Second, the experience of global pharmaceutical companies in branding could be of great benefit for emerging market producers. With an increasing number of competitors in the biosimilars space, and the current convention of naming that does not allow for easy identification of biosimilar source in developed markets, emerging market producers will be unable to differentiate themselves from others when attempting to enter into developed markets alone. Hence, emerging market manufacturers partnering with global drug firms would be better poised to take advantage of the large pharmaceutical company's longstanding, successful branding efforts—indeed, cultural competency in communications to patients in developed markets—that otherwise would be outside their expertise and experience. Just as important, extant relationships with providers and physicians and reputational effects (including safety profiles) of global pharmaceutical firm products in these markets are also integral to branding emerging market biosimilars. This intangible capital of global pharmaceutical firms can significantly counter emerging market reputational issues.

In addition, and importantly, the challenge to rapidly identify follow-on drug forms that may be the source of immunogenicity (or other adverse reactions) should be addressed through private entity collaboration with drug regulatory agencies. Sourcing, biologic identification, track-and-trace technologies, and other methods for rapid identification of biologic manufacturing source should be employed and tested working with drug regulatory agencies to develop best practices in the context of emerging market production and global pharmaceutical branding. Such an approach has potential to also address global health issues arising from suspect biologics that may be compromised or counterfeit, particularly for biologics in shortage and/or from nontraditional procurement sources such as the Internet.[44,45]

CONCLUSION

Advances in global health have resulted in emerging market countries' medication needs increasingly mirroring those of developed nations. Biologic drugs to treat high level diseases are therefore increasingly demanded in these markets. Yet the same cost dynamic of developed countries exist in emerging markets, and the demand for low cost forms has created a significant push for follow-on biologics and local industry to produce these drugs. Access to lower cost forms of these cutting-edge drugs hence can benefit public health. However, concerns surrounding immunogenicity represent a significant threat to patient safety, particularly as predicting this clinical emergency is extremely difficult.

Public-private partnerships between global drug firms, emerging market producers, and government authorities have the potential to address safety issues and promote public health assessment and infrastructures.

As well, levering advantages of private sector actors can promote higher quality formulations in emerging markets as well as developed market success in biosimilar production and sales, promoting global health.

Stakeholders in biosimilar production and use must recognize the mutual benefits from cooperation. The future of global health will require that these stakeholders bring appropriate experience, talents, and a forward-looking focus as well as accept the reality that a balance of incentives and voluntary regulatory assessment will be the norm for successful biosimilar market entry. Voluntary governance structures through public-private partnerships and other means to assemble stakeholders on a regular basis should be the new model. In this way, the benefits of biosimilars can inure most quickly for those patients in need, the means for proactive and reactive patient safety interventions can be effectively planned and implemented, and the highest quality biosimilar producers globally will win at the competitive game.

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