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GUEST EDITORIAL

India to power the more widespread use of biosimilars?

All of us have been kept alive by various drugs that we have taken over the years. Most, if not all, of these were generic drugs, i.e. they were in every way identical copies of the original molecule. The patent on the original drug may have expired, enabling other manufacturers to make these copies at low cost. Alternatively, some countries, including India, did not recognize product patents; and therefore, low-cost generics could be made by other manufacturers legally, even when the product was covered by a valid patent in other countries.

A relatively recent example of the kind of price difference between the original, on-patent, and off-patent generic drug is that of Sofosbuvir or Sovaldi for hepatitis C. Each tablet costs \$1000 in the US, but only \$4 in India (<https://www.chicagotribune.com/business/ct-drug-price-sofosbuvir-sovaldi-india-us-20160104-story.html>). In India, most of the drugs that we take have a low molecular weight and therefore are called small molecule drugs (SMDs). These molecules are produced in a chemistry laboratory. The discussion above refers to these SMDs.

There is another category of drugs called biologics. Although insulin is a good example of such a molecule, it has been in use for almost a century, and most other biologics are of much more recent origin. These are much larger molecules which are produced in a living organism, i.e. a bacterium, a cell culture, an animal or a plant. Examples of various categories of biologics include enzymes, monoclonal antibodies (MABs) and vaccines. Not only are biologics much larger than SMDs, they are also much more complex. So, for example, the core of a MAB is a protein, which may be linked to several carbohydrate chains. Let us assume that an MAB is being manufactured in a particular cell culture. Because it is produced in a living system, there are likely to be slight variations in the composition and structure of the carbohydrate chains even when the MAB is produced in a different batch of the same culture.

These small variations have caused big debates. For many years, there were heated discussions on what the 'generic' version of an original biologic should be called. This would be an off-patent version, usually made by a different company. As mentioned above, the generic form of an SMD is identical to the original, even if produced by a different company. However, in the case of biolo-

gics, it would almost always be the case that there would be some differences. This led to the following suggestions for the naming of the 'generic' biologic: bio-generic, biosimilar, subsequent entry biologic, follow-on biologic and so on.

Why is this word-smithing important? As seen above, when a generic enters the market the price can drop drastically. If it could be shown that biologics are so complicated that a generic could never be identical; then anyone wanting to produce a bio-generic would have to undertake more expensive studies, including clinical trials, to prove that the bio-generic is efficacious. The high cost of running such trials would deter potential competitors. Therefore, this view came to prevail, and in due course the term 'biosimilar' came to rule. Any bio-generic would not be identical to the original and therefore could only be a biosimilar. In this situation, 'similar' emphasized the difference.

The World Health Organization (WHO), which uses the terms 'reference biotherapeutic product' (RBP) for the original product, and 'similar biotherapeutic product' (SBP) for a biosimilar (https://www.who.int/biologicals/BS.2018.2352_QA_for_SBPs_26_July_2018.pdf), came out with guidelines on biosimilar drugs in 2009 (<http://www.twn.my/title2/health.info/Article/Memo%20on%20-WHO%20Guidelines%20on%20SBPs.pdf>). Some of the key points in the guidelines were as follows: (i) biologics are large and complex molecules, difficult to characterize, and therefore an approval pathway similar to that for generic SMDs is not possible; (ii) the manufacturing process leads to variations in the biologic, and this can lead to significant changes in the chemistry, bioavailability, and efficacy of the SBP, and (iii) a company wanting to make an SBP will not have access to the materials or protocols of the originator company, and therefore clinical trials will be necessary to establish similar efficacy of the originator molecule and that of the new SBP, which will undoubtedly be structurally different from the molecule manufactured by the originator.

About ten years have passed since the guidelines were issued. A well-known scientist from The Netherlands, who has worked on biologics for many years, has led a group of concerned scientists in preparing a note about the need to rethink the international guidelines about

SBPs. The group has now submitted this note to the WHO (<http://www.twn.my/title2/health.info/Article/Memo%20on%20WHO%20Guidelines%20on%20SBPs.pdf>). These scientists believe that the concerns raised a few years ago are no longer valid, and we summarize their arguments here. (a) Scientists now have some decades of experience with manufacturing biologics. Processes have been standardized and expertise gained. (b) Most manufacturers source material(s) from a small number of suppliers; so anyone wishing to manufacture an SBP can use the same sources. (c) Analytical techniques have evolved and it would be unlikely that differences between an RBP and an SBP would be missed today. (d) Although immunogenicity is the oft-cited safety concern for SBPs, such incidents have been related to the processing, packaging or handling of the drug, and not the biologic per se. Further, if an SBP is immunogenic, it is highly likely that the originator molecule is equally immunogenic. (e) There are 12 years of experience with SBPs in Australia, Canada, Europe, and so on, and in the European Union alone there are 35 biosimilars available in the market, with medical experience of about 700 million patient years. There have been no major safety alerts so far.

The scientists go on to suggest that instead of clinical trials, which are long and expensive, and which therefore delay or deny patient access, it should be possible to determine whether or not an SBP can be marketed based on analytical criteria alone. In fact, this has already happened. In October 2018, it was reported that two SBPs were found not to be equivalent to the originator molecule herceptin in clinical studies, but were cleared by the European Medicines Agency based on their laboratory analytical characterization alone (<https://www.centerfor-biosimilars.com/conferences/dia-2018/the-clinical-trials-landscape-is-evolving-in-biosimilar-development>).

Why is this discussion important? We have lived well enough all these years without much help from RBPs or SBPs, so why should we care? There are several reasons to do so. First, many of these new drugs are expensive. It is reported that biologics – largely originators – account for 40% of all prescription-based drug spending in the US, although only about 2% of the American population uses them (<https://www.statnews.com/2018/07/18/fdas-gottlieb-slams-drug-makers-for-stalling-release-of-biosimilars/>). Yet, many of the biologics currently available in the market are not as effective as their high price may indicate. In fact, the average increase in life-span brought about by the latest 71 new drugs for advanced cancer was two months (Anon., *Nature Biotechnol.*, 2015, **33**, 9). However, with the large number of biologics in clinical trials, one can hope that more effective drugs will come to the market in future. Second, as the number of older people increases, there will be increasing co-morbidities. The chance of drug–drug interactions, always a fear for SMDs, is much less for biologics. Third, India has been a powerhouse in the production of generic SMDs and

vaccines, doing much for the world's health. Could it not aim to do the same in the case of SBPs? Indian companies would flourish, with the attendant benefits of building a knowledge-based industry.

India has a history of taking good decisions related to the issue of drug prices. Through the Patent Act of 1970, the country took a bold step in denying product patents. Much more recently, it made changes in its patent laws which, while being compliant with international requirements that countries tighten up their intellectual property laws, set a high bar on patenting (<http://apps.who.int/medicinedocs/documents/s17761en/s17761en.pdf>). This high standard has been implemented to some extent. Ali and Rajagopal reported that over about a decade, some 1000 patent applications have been rejected in India because they did not meet the country's threshold of patenting (<https://www.thehindu.com/opinion/op-ed/biologics-patents-and-drug-prices/article22682251.ece>). To be granted a product patent, the new drug would have to show efficacy that is superior to the original, and a combination drug would have to show synergy of the constituent molecules. These provisions lay the ground to permit biosimilars, and indeed several biosimilars are available now in India.

Let us return to the point about India taking a lead in the production of SBPs. An interesting TED Talk in 2014, by a policy advisor, entitled 'Which country does the most good for the world?' (<https://www.youtube.com/watch?v=1X7fZoDs9KU>), mentions how, in order to prosper in the world, each country depends on its reputation. Because of this, each government cares tremendously about its country's image. India has won many friends due to its affordable generic drugs and vaccines. Although their importance remains undiminished, those were achievements of the past. Can we not think of a new kind of success? It takes a certain amount of self-confidence for a country to be a pioneer. In turn, it undoubtedly helps build this self-confidence further when much of the world appreciates such actions and may even copy them. This happened when India struck down the patent on the drug Glivec in 2013, an action that became the subject of editorials in prominent newspapers around the world, in many languages. To be a pioneer is often as much a question of attitude as of ability. Many may have the ability, but a country's determination to follow a certain path could see it having a big impact on its own people and those elsewhere in the world. The country has the skills, and the world has large medical needs for which biosimilars could be solutions. India should not hesitate to demonstrate leadership on this issue.

Gayatri Saberwal

Institute of Bioinformatics and Applied Biotechnology,
Bengaluru 560 100, India
e-mail: gayatri@ibab.ac.in