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Similar biologics: A field concern

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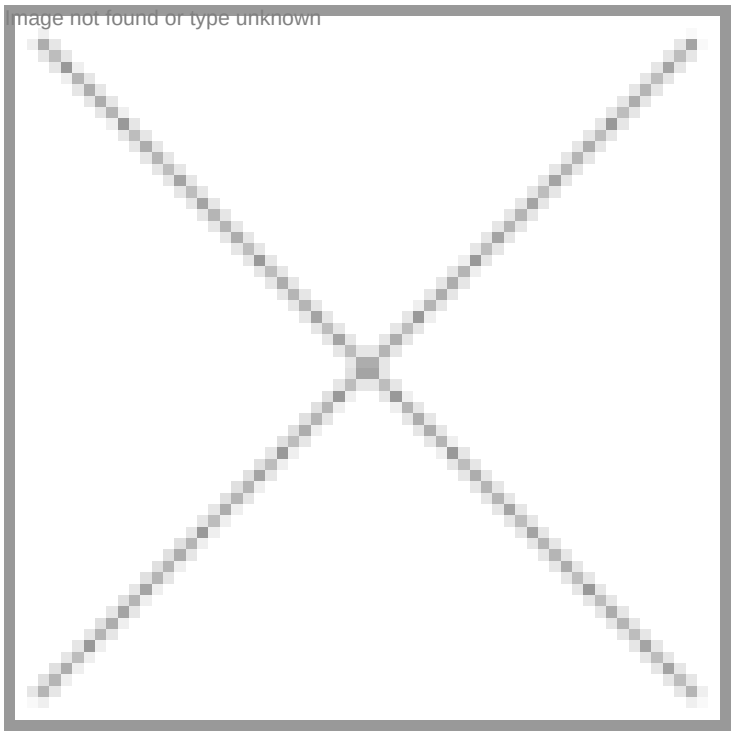

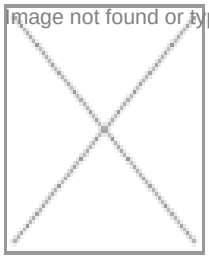

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Pharmaceutical companies protect their innovative molecules of either chemical or biological origin through patent to ensure the market exclusivity. Once the patent is expired, the molecule is open for manufacturing and marketing by any pharma or biotech company other than the one who discovered it. Such off-patented drugs of chemical origin are called as ‘generics’, while those of biological origin are popularly designated as ‘biosimilars’.

Worldwide, biosimilars have many synonyms such as ‘Follow-on-biologics, in the US’, ‘Subsequent entry biologics, in Canada’ and so on. In India, the off-patented biologics produced via genetic engineering will be termed as ‘Similar biologics’ as proposed by the Review Committee on Genetic Manipulation (RCGM), Department of Biotechnology. In India, similar biologics are expected to have $1 billion market by 2020.

In general, the biopharmaceuticals are mainly proteins having considerable therapeutic and structural diversity. Generics are easy to manufacture and standardize as the quantitative analysis is enough to ensure their bioavailability and bioequivalence. The manufacturing of biologics is affected from several process and product variations while producing them in a living cell. One of the major sources of these variations is that manufacturer of the similar biologics does not have access to the original manufacturer process even after expiry of the patent. Therefore, homogenous production of similar biologics would be difficult as a result of possible variations introduced due to several factors such as host cell, vector, fermentation medium, protein folding, post-translational modifications, and protein stability. These subtle differences may affect either the efficacy or tolerability or both of a product.

Similar biologics are approved for marketing based on the data which shows 'high similarity' to the reference innovator product in terms of quality, safety and efficacy. No regulatory authority in the world including the US Food and Drugs Administration (FDA) and European Medicines Agency (EMA) defined the range of similarity between a similar biologic and the respective innovator reference product. FDA indeed approved few products on the basis of bioequivalency when a similar biologic has its 90 percent confidence interval between 80-125 percent with respect to the reference innovator product.

FDA also introduced a separate labeling requirement to differentiate between the innovator original product and itsbiosimilar. The proper labeling provides an easy route for the physicians in the US to easily record the lower efficacy or unexpected outcome of a biosimilar product. Simultaneously, the interchangeability or the substitution of an innovator original product with biosimilar may be regulated smoothly.

EMA states that the physicians should specify the International Non-proprietary Name (INN) or brand name. This hinders generic prescribing and substitution. In India, Drug and Cosmetics Act, 1940 does not have any special labeling requirement for distinguishing between a similar biologic and innovator reference product. Therefore, physicians and patients will find it hard to distinguish between a similar biologic and the reference product. The problem will further aggravate in the absence of an adequate and effective mechanism to regulate the safety as well as efficacy of approved similar biologics on-field. Also, the possible unwanted clinical outcome of a similar biologics as a result of pharmacogenomics variation in an Indian population will be extremely tough to assess. Such outcomes may be extremely severe either locally or at larger scale.

Another related on-field concern is after getting the market authorization; the pharmaceutical companies might dilute the quality of a similar biologics. There is a fear that companies might push such substandard similar biologics in remote areas having no surveillance machinery and even the media does not have good penetration. On the top of that, the greed for greater margin will help in pushing such substandard drugs. The continuous exposure to sub-standard drugs might lead to the development of either tolerance or resistance at a faster pace than expected. Therefore, India needs to consider all these negative traits and their possible harmful consequence.

To tackle such issues, we require a very well-defined pathway to regulate the quality, safety and efficacy of similar biologics after market authorization and also to ensure the benefits of their lower price to the consumers. In other words, strong pharmacovigilance program is desirable. The million dollar question is that does the government have the machinery to execute this mammoth task? The Central Drugs Standard Control Organization (CDSCO) has initiated a national Pharmacovigilance Program of India (PvPI). The program will be completed by 2013 in three phases. The program will operate through routine collection of clinical data for drugs of chemical and biological origin at local medical colleges and pooling the data at a nodal center i.e., AIIMS, New Delhi, for final evaluation and decision-making. The post-marketing monitoring of similar biologics may be facilitated under the same program.

The guidelines for similar biologics will come into effect this year, so there is a gap of at least two years till the PvPI may contribute in real terms. Meanwhile, the companies may take profitable advantage of this gap. Therefore, the Indian regulatory authority should make provision for random testing of market authorized similar biologics in any national laboratory. Such measures will certainly reduce the ambiguity, confusion and apprehensions about the similar biologics among the medical practitioners and their clients.

(The views expressed by the author in this article are personal and have no relation with the official position of the Department of Biotechnology, Ministry of Science and Technology, New Delhi)