EDITORIAL

Biosimilars in the Caribbean – Key Considerations

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INTRODUCTION

Biotechnology is the use of living organisms and processes to manufacture large quantities of complex molecules for medicinal purposes known as biopharmaceuticals. Diseases, that were once almost impossible to treat, are now treatable because of biotechnology. Some examples of these diseases are diabetes, chronic anaemia, multiple myeloma and some lymphomas (1).

Although biosimilars are marketed for the same indications as innovator biopharmaceuticals, the manufacturing processes for the products are unique and complex (2). Additionally, there is much disquiet about issues of safety, efficacy, substitutability and interchangeability of the products (3, 4). Proprietary challenges also exist between innovators and generic drug manufacturers (4). Unlike chemical drug molecules, biopharmaceuticals, including biosimilars, are a relatively new and complex area. Without adequate regulatory measures, automatic substitution between innovator and some non-innovator biopharmaceuticals could cause harm (5). Many countries have developed a separate regulatory pathway for these products (6, 7), due to the complex nature of the molecules and safety considerations. This paper seeks to analyse some of the pertinent issues that regulators could take into consideration for developing guidelines or laws for the registering, prescribing, and dispensing of biosimilars in the Caribbean.

Keywords: Biopharmaceuticals, biosimilars, biotechnology, Caribbean, non-innovator biological, substitutability

Definition

A clear definition provided by the European Medicines Agency (EMA) of biosimilars is *"*biological medicine that is similar to another biological medicine that has already been authorized for use" (8). The authorized reference product must be available on the market for at least 10 years in Europe prior to a biosimilar submission (8). In the United States of America (USA), the Food and Drug Administration (FDA) allows 12 years of exclusivity for innovators based on the Biologics Price Competition and Innovation Act of 2009 (9).

Comparability tests

The common recommendation of the EMA, World Health Organization (WHO) and FDA (4, 9, 10) is a vigorous comparability exercise between the authorized reference biopharmaceutical and the product seeking approval as a biosimilar. This comparability exercise includes consideration of both clinical and nonclinical studies. These studies should prove safety, efficacy and quality of non-innovator products (4, 9, 10). The exercise seeks to identify any anomalies in the process of manufacture that may yield impurities, whether the efficacies are the same using the same doses, strengths and routes of administration (substitutability) and if there are signs of immunogenicity (4, 9, 10).

Unlike chemical generic drugs, applications for approval of biosimilars cannot piggyback on the clinical data of its reference product. Manufacturers should provide clinical trial data for each submission made to regulatory agencies (4). These parameters are significant because of possible life-threatening complications that could arise (3). Two examples of potential complications with biopharmaceuticals are the withdrawn application for Marvel insulins from the EMA, and pure red cell aplasia (PRCA) associated with Eprex (3).

Safety and substitutability issues with non-innovator biologicals

Marvel insulins. The EMA conducted a comparability exercise on a batch of insulin from Marvel Pharmaceuticals, submitted for approval based on comparison to Humulin Soluble (3). The EMA discovered that the insulin from Marvel could lower blood sugar levels 45% more than Humulin Soluble within the first hour of administration (3). Marvel insulin manufacturers withdrew their applications (3). This withdrawal not only highlighted the need to have vigorous assessment of the quality of products by regulators, but raised the concern of substituting biological products in the same manner as generic chemical moieties. In this illustration, the same dose, route of administration and product type did not yield same results. Certainly, the Marvel insulin incident could have been an anomaly, but it should

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not be overlooked as it relates to substitution between biopharmaceuticals.

The crux of the generic market is substitutability. The challenge, however, is that there is no consensus on substitution of biopharmaceuticals worldwide. The US FDA discriminates between biosimilars that are substitutable without the consent of the physician (automatic substitution) and those that are not (9). Some European jurisdictions such as France forbid substitution without the consent of the physician (11). The recommendation has been made that biosimilars should have unique nomenclature for the molecules, distinguishing them from the established names given to reference products (11, 12). The suggestion is that if the names differ, automatic substitution would be deterred (11, 12). This has been rejected by WHO experts, however, who state that the international nomenclature of drugs should not be changed for biosimilars but that the substitutability of biopharmaceuticals should be relegated to national regulatory bodies (13).

Eprex. The example of Eprex indicates that minor changes in a product can yield significant problems even with the same manufacturer. Eprex is an innovator biosynthetic erythropoietin used in the treatment of anaemia. The manufacturer of Eprex changed an inactive component of the product. The result was PRCA, a life threatening complication where the body abolishes erythropoiesis by creating destructive antibodies against the body's own red blood cells (3). The manufacturers eventually made the connection between the product change and the reaction after several years of the modified product being on the market. A corrective modification of the product yielded incident-free results thereafter (3). Eprex highlighted the need for vigorous pharmacovigilance of all biologicals.

Implications for the Caribbean

A survey conducted in 2008 revealed that the Caribbean and Latin American countries have legislations for handling biological products. However, the process used for registering non-innovator biopharmaceuticals was unclear (7). Regulatory authorities in Latin American and Caribbean countries such as Cuba, Costa Rica, Panama and Mexico have developed guidelines and/or legislations for similar biopharmaceuticals, but a majority of the English-speaking Caribbean countries have not done so (Personal Communication, June 2012). Jamaica and Trinidad and Tobago recognize non-innovator products as stand-alone drugs and register them *via* the same route used for all new drugs (Personal Communication, June 2012). Technical expertise in evaluating biological products, however, remains a common problem (7).

Are these biosimilars?

One product currently registered in the Caribbean is Reditux, a copy version of Rituxan, a monoclonal antibody made by Hoffman La Roche (7). Sources have implied that although these two products have similar amino acid sequencing, they differ in quality and may not qualify for the classification of biosimilars based on WHO standards (7). Recently, Dr Reddy's Laboratories, manufacturers of Reditux, entered an agreement with Merck Pharmaceuticals to further develop the drug for the European market. It was noted that Dr Reddy's Laboratories would develop the drug to phase one level and Merck would manufacture and conduct later stage trials (14). This comes five years after the drug was launched in India and has been available in the Caribbean (14). Although no reports of adverse events were identified for Reditux, there should be concern over whether the quality issues mentioned earlier are valid. If there were good clinical and non-clinical data to prove biosimilarity, why would Merck need to conduct further trials in pursuit of the European market?

Another non-innovator product of concern is a brand of insulin called Wosulin that is currently registered in Jamaica. Although widely available, regulators have not stated whether or not this brand of insulin is substitutable with any of the established innovator brands in the country, namely Humulin or Novolin. In 2006, an Indian news channel reported a withdrawal of all Wosulin brands of insulin from the market because of consumer complaints (15). The manufacturer of Wosulin, Wockhardt Pharmaceuticals, makes a brand of erythropoietin named Wepox, which is also available in the Caribbean. In 2008, a case of PRCA was reported in a 57-year old male who was administered Wepox (16). The issues with the Wockhardt products could be incidental and may not imply that the products are bad but is cause for concern regarding the need to conduct quality assessments and post-market pharmacovigilance. Binocrit is another non-innovator brand of erythropoietin available for sale in Jamaica. This brand, however, seems to be one of the few products that has been approved by the EMA. It is officially recognized as a biosimilar to the innovator brand Eprex. Without a clear identification of which products are biosimilar, the challenge that remains for clinicians and pharmacists is how to treat non-innovator biopharmaceuticals. It is not certain if automatic substitution between brands is permitted. It is important, therefore, for Caribbean countries to implement national legislations for defining, qualifying, and substituting of biosimilars. This could prohibit the marketing of non-innovator biopharmaceuticals as being similar to innovator products when they have not proven this *via* clinical trials and head-to-head comparisons as recommended by the WHO (4).

The main implication of marketing a non-innovator as similar to an innovator product without regulations or guidelines in place to prove such similarity, is that health professionals could blindly substitute on an unfounded premise which has no legal support (5). In the unfortunate instant of an adverse event, a health professional could be liable for negligence (5). This is because of the foreseeable safety issues that exist with similar biological products (5). A

consideration for national regulatory authorities to avoid potential liability issues is to not register non-innovator biopharmaceuticals as stand-alone products (7). National health authorities would also need to communicate to health professionals on whether or not they can substitute between innovator and non-innovator biopharmaceuticals.

CONCLUSION

It is therefore necessary for Caribbean health professionals to take seriously the various issues associated with non-innovator biopharmaceuticals. Although the biosimilar market is advantageous from a cost-saving perspective, evidence must be available to health professionals that the products are safe, effective and the relevant authorities conducted the requisite evaluations. Guidelines and legislation should also be implemented especially in the English-speaking Caribbean. This would ensure that substitutability between innovator and non-innovator biopharmaceuticals is clear and the level at which this may be allowed. Furthermore, pharmacovigilance measures should be implemented for the monitoring of all biopharmaceuticals, particularly those originating from countries with lax regulatory measures.

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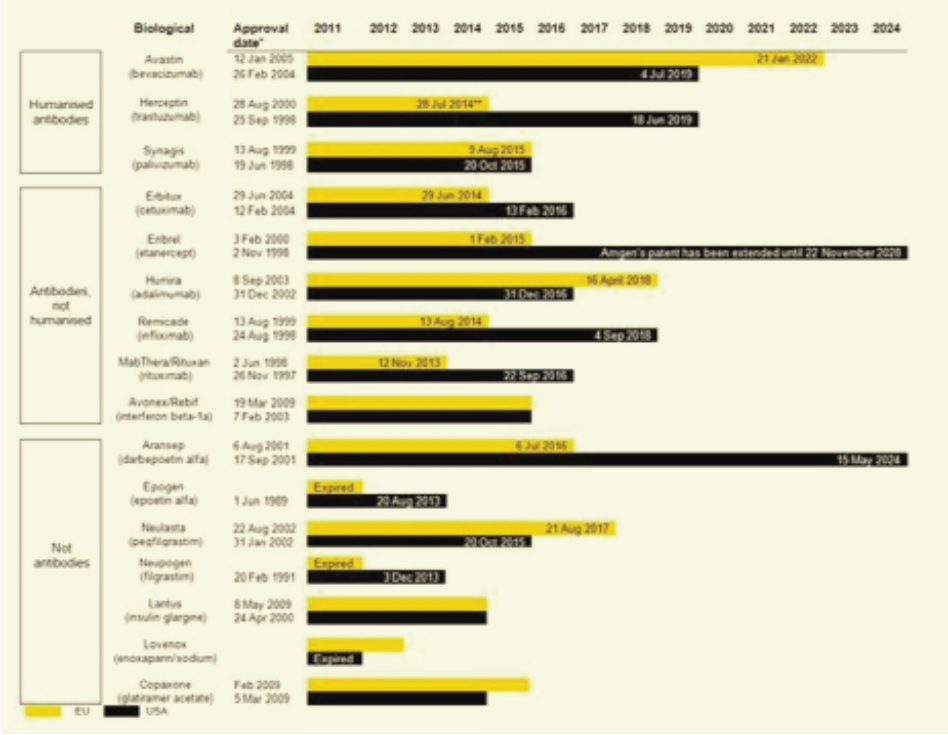
Appendix



Expiry dates for major patents on best-selling biologicals.
Source: Generics and Biosimilars Initiative 2012 (17).