Pharmaceutical Association of Malaysia
Persatuan Farmaseutikal Malaysia

PhAMA position on biosimilar medicines

Introduction

Biological medicines: This paper sets out the PhAMA position on biological and biosimilar medicines. Recombinant technology has provided means of producing a variety of therapeutic proteins, allowing biologic medicines to become important therapeutic options[1] as well as revolutionized the treatment of patients for some of the most serious and intractable diseases such as cancer[2], diabetes and rheumatoid arthritis. Biologics or "large molecules" differ from chemical drugs or "small molecules'' with respect to their manufacturing processes, size and complexity as well as origin, composition and nature.
For instance, the development and production of generic-equivalent products is relatively straightforward where all that is required is demonstration that it contains identical chemical composition of the innovator product and only recently in Malaysia[3], bioequivalence is a requirement during registration to demonstrate that the pharmacokinetic properties are similar to its reference products but limited to certain categories of medicines.[3,4]

In contrast, biosimilars are not generic equivalents of the innovator products[4]. This perspective was adopted by the European Medicines Agency (EMEA) and is the basis for its biosimilar approval guidelines[5]. This is because the active ingredients in a biosimilar are not identical to the innovator product. Unlike small molecules, whose active ingredients are generally chemicals synthesized in a laboratory or extracted from natural sources, biologic medicines are manufactured from genetic material of living cell cultures or DNA technologies that require multifaceted manufacturing processes.[6] making it far more complex than small-molecule pharmaceuticals. Unlike conventional pharmaceuticals, there is a strong relationship between the manufacturing processes of biopharmaceuticals and the characteristics of the final product.[7]

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Regulatory framework: Granting marketing authorisations (MA) for biotechnology products in Malaysia falls under the authority of the National Pharmaceutical Control Bureau (NPCB). A guideline entitled "*Guidance document and guidelines for registration of biosimilars in Malaysia*" was published by the NPCB in August 2008.[8]In Malaysia, like in Europe or in other parts of the world, granting MA is only the first step and individual countries must develop processes regarding the prescription, delivery and use of biological and/or biosimilar products.

After patent expiry of an originator medicine, biosimilars can be developed and marketed by other manufacturers which must demonstrate similarity to a reference product. It should be noted that biosimilars can never be exact copies of their reference product. Granting of an MA is therefore subject to strict regulatory approval, but assessments of substitution and interchangeability are not part of the scientific evaluation leading to the granting of a MA.

In Malaysia, the NPCB recognized that the challenges posed by biosimilars for clinical practice are different to those that relate to conventional generic medicines. All biotechnology products, including biosimilars have different starting materials and manufacturing processes which means they have different characteristics that may not be detectable in conventional clinical trials such as rare adverse drug reactions, especially events that are immune mediated.[3] NPCB's guideline on biosimilars noted under the section on interchangeability and substitution[2], that "*Biosimilars are not generic products and cannot be identical to their reference products. Further, the formulations may be different and these can have profound effect on their clinical behaviour. In addition, biosimilars do not necessarily have the same indications or clinical use as the reference products. Therefore, given current science, they cannot be considered interchangeable with the reference product or products of the same class. Automatic substitution (i.e the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) and active substance-based prescription cannot apply to biologicals, including biosimilars. Such an approach ensures that treating physicians can make informed decisions about treatments is in the interest of patients' safety.*"

Taking the European experience where despite the regulatory framework for biosimilars are harmonized, there appears to be marked differences among EU countries in the perception of the value and use of biosimilars. Several factors have been considered as challenges to the wide use of biosimilars such as concerns about their safety and efficacy, pharmacovigilance, interchangeability and substitution, market competition, and extrapolation of indications. A proper knowledge of these issues has been recommended to ensure an appropriate place on the market for these products[9]

PhAMA position

Therefore, PhAMA would like to make seven recommendations which cover areas where action is needed by regulators, HTA agencies, MOH officials and healthcare professionals who prescribe or dispense these medicines to address a number of issues once biosimilars is available in the market.

Recommendation 1: **All biologic/biosimilar prescriptions should be written by brand name and not by International Non-proprietary Name (INN)**

This is in line with the intention of the EU legislation for Member States[10], WHO guidance and the Australia's drug regulatory agency to impose an obligation for healthcare professionals to prescribe biological medicines by brand name in order to facilitate compliance with the patient safety and pharmacovigilance identification and traceability requirements.

PhAMA recommends that biological medicinal products should be prescribed with a unique brand name and not be prescribed by INN. This will help to ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist as recommended by the guidance from NPCB on biosimilars Prescriptions by brand name also facilitates a more rigorous, appropriate and accurate post approval surveillance on the safety and efficacy data for these drugs as it is readily distinguishes between

different biosimilar products and the reference biologic medicines so that is clear which specific product a patient has received. This is aligned to the NPCB guidelines for biosimilars.[8,11,12] This is further supported by the British National Formulary (BNF) in their general guidance on prescribing,[13] and also supported by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Biopharmaceutical Enterprises (EBE).

The importance of post-marketing pharmacovigilance cannot be undermined as highlighted by the experience with epoetins, where the development of antibody-mediated pure red cell aplasia (PRCA) in patients with chronic kidney disease was associated with a formulation change for one product.[14] As previously, differential immunogenic responses have also been observed between similar biologic medicines products (e.g. IFNs, epoetins).[2] A rigorous implementation by all involved parties is paramount to protect patients

The UK and Belgium is recommending prescribing by brand name to avoid substitution[15]

Recommendation 2: A biologic or biosimilar medicine cannot be considered immediately interchangeable and therefore not automatically substituted without the knowledge and consent of the treating physician

Interchangeability includes the choice of a drug between two or more drugs targeted for the same therapeutic or prophylactic purposes. However, many scientific examples have proved that drugs with similar pharmacodynamics properties do not necessarily ensure the same efficacy and safety even with simple molecules.[16,17] Reproduction of a biologic is not possible. Any attempt to reproduce a biologic can come close but cannot be the same. This is why the reproduction of a biologic is called a biosimilar. They are only "similar" and cannot be exactly the same.[2] As described briefly earlier on the complexity of the manufacturing processes, production of an innovator biologic can never be duplicated down to the last detail; a biosimilar is made using different cells and different processes than the original biologic.[2] Like snowflakes and thumbprints, no two biologic molecules are the same down to the last atom. Biosimilars have unique properties and may behave differently as a medicine than the biologics they are trying to mimic.[17]

All biosimilars differ from the innovator biologic and from each other, therefore, PhAMA believes that it cannot be considered as immediately interchangeable and warrants caution in automatic substitution.

Automatic substitution of one biological medicine for another can impact patient safety and makes post marketing surveillance more difficult.

Guidance published by the EMA in October 2012 defines the requirement for the decision to treat a patient with a reference or a biosimilar medicine only to be taken following the opinion of a qualified healthcare professional: "Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional."

It is also important to note that no country has declared biosimilars interchangeable with reference products and in many countries substitution is expressly prohibited i.e. France, Germany and Spain. Canada does not support substitution.[16] In Japan; substitution should be avoided during the post-marketing surveillance

period.[15]

PhAMA recommends that automatic substitution should not apply to any biologic; this includes automatic substitution of a biosimilar for its reference product. Substitution should only ever occur with the knowledge and explicit prior consent of the treating physician.

Recommendation 3: Patients should be kept fully informed about their medication and should be consulted if changes to their treatment are made

Patients have the right to be kept informed about their medications and should be consulted if any changes to their treatment are made (including substitutions) as noted by the recent briefing paper by the International Alliance of Patient's Organizatinon where the physician-patient conversations are crucial to aid a fully informed decision to take a biosimilar.[18] Consultation with their physician will ensure that the patient can be made fully aware of the advantages and disadvantages of any particular medicine not least so that they can be prepared for any adverse reactions which may occur with the treatment.
A switching decision should never be based on cost alone, prescribing physicians must be able to employ appropriate clinical judgment, basing their decision on appropriate evidence and considering the specific therapeutic needs of each patient.

Recommendation 4: The summary of medicinal product characteristics (SmPC) should clearly indicate the source of information contained within it, such as relevant clinical studies or that it has been derived from evidence about the originator product

There are examples where the wording of SmPC sections for a biosimilar and its originator product are identical and we believe the SmPC should clearly show where information was obtained from either studies investigating the biosimilar product or where the data was derived from evidence about the originator product.

Recommendation 5: Biosimilar medicines should be subject to clinical practice guidelines for the management of all relevant diseases where biosimilars exist in the treatment armamentarium

There remains an unmet need for the education of HCPs on the integration of biosimilars into therapy and a number of considerations exist, including the related issues of interchangeability, automatic substitution, immunogenicity, monitoring for adverse events (e.g., through effective pharmacovigilance activities). This helps to identify any emerging safety signals in a timely manner and address them through appropriate risk mitigation strategies, as well as safety issues that may arise from nomenclature considerations. In this respect, PhAMA offers to assist Ministry of Health to co-design and conduct the educational programs on the appropriate use of biologic medicines

PhAMA also strongly encourage relevant medical associations and Health Authorities to include a section on Biosimilar Safety Considerations in Clinical Practice when updating their clinical practice guidelines.

Recommendation 6: Tenders which are undertaken involving biological medicines should not seek to source a single product only.

For the reasons set out above, great care is needed when switching biological medicines between patients and not all biological medicines may be suitable for all patients. Where available, a choice of medicines therefore needs to be available to permit physicians to make treatment decisions which are in line with the specific needs of their individual patients. Hence, PhAMA recommends that tenders for biological medicines where possible should not be limited to source of a single product and must be conducted in a way that is consistent with the specific regulatory and pharmacovigilance requirements of biological medicines.

Recommendation 7: Extrapolation of indications for biosimilar products should be evaluated on a case by case basis

One frequently raised question is whether it should be permissible to extrapolate efficacy data from one clinical condition specifically studied with a biosimilar medicine to another clinical condition not studied for the biosimilar medicine.

Since biosimilars are not identical to the originator, being derived from different cell lines and through different manufacturing processes, it cannot be assumed that they will automatically show the same safety and efficacy in all indications as the originator. In order to gain regulatory approval, the applicant will be expected to provide sufficient scientific justification for extrapolation for each of the claimed indications in which they do not have clinical data on the biosimilar medicine itself. Any such approval then has to be supported by post-authorisation monitoring and PV of the biosimilar in clinical use.

Therefore it is well accepted by regulators that extrapolation of indications should be considered on a case by case basis. There needs to be an appropriate scientific assessment of the totality of evidence for biosimilar products (analytical, non-clinical and clinical) to determine the acceptability of extrapolation depending on the type of product, related nature of the indications, mechanism of action and overall weight of evidence presented by the applicant.

PhAMA would welcome the opportunity for further dialogue with regulators, healthcare providers, patient groups and all other interested stakeholders to contribute to developing a sustainable framework for the use of biosimilars whilst encouraging scientific innovation, maintaining standards and patient safety.

The recommendations on this position paper were built in line and referenced to the Association of British Pharmaceutical Industri Position on Biolosimilar Medicines, May 2014.

List of bibliographies quoted :

1. Reichert JM. **Trends in US Approvals: New Biopharmaceuticals and Vaccines**. Trends Biotechnol 2006; 24: 293–298
2. H. Mellstedt et al, **The Challenge of Biosimilars**. Annals of Oncology 2008; 19: 411–419
3. National Pharmaceutical Control Bureau Malaysia. **Frequent Asked Questions**. Assessed on 22 September 2014. http://portal.bpfk.gov.my/index.cfm?menuid=50
4. Schellekens H, Ryff JC. '**Biogenerics': The off-patent Biotech Products**. Trends Pharmacol Sci 2002; 23: 119–121
5. European Medicines Agency. **Guideline on Similar Biological Medicinal Products**. 2005. Available at: http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf
6. APG, 2011. **Procurement and Prescribing Practices for Biologics in the UK**, 29 June 2011
7. Schellekens H. **Bioequivalence and the Immunogenicity of Biopharmaceuticals**. Nat Rev Drug Discov 2002; 1: 457–462
8. National Pharmaceutical Control Bureau Malaysia**. Guidelines on Registration of Biosimilar**. http://portal.bpfk.gov.my/index.cfm?menuid=90&q=biosimlar
9. Suiz and Carlo. **Similar Biological Medicinal products: Lessons Learned and Challenges Ahead**. Journal of Generic Medicines. The Business Journal for the Generic Medicines Sector 2011 8: 4
10. **Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010** amending, as regards pharmacovigilance, **Directive 2001/83/EC on the Community Code relating to Medicinal Products for Human Use**, Article 102e. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF
11. **Directive 2010/84/EU, Article 102e**. Available at: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF
12. **MHRA, 2012. Drug Safety Update**. Available at: www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON207188
13. **British National Formulary**, September 2012. General Guidance on Prescribing.
14. Bennett CL, Luminari S, Nissenson AR et al. **Pure Red-Cell Aplasia and Epoetin Therapy**. N Engl J Med 2004; 351: 1403–1408
15. Bogaert, P., et. al. **Biosimilar regulation: Important Considerations and Global developments**. Cross-border Life Sciences Handbook. Practical Law Company. http://uk.practicallaw.com/3-500 9862?q=Biosimilar+regulation:+important+considerations+and+global+developments
16. Rumel , D . , de Andrade Nishioka , S . and Mar ç al dos Santos , A . A . (2006) **Drug interchangeability: Clinical approach and Consumer's Point of View** .Revista de Sa ú de P ú blica 40 (5) : 1 – 7 .
17. Furberg CD, Herrington DM, Psaty BM. **Are Drugs within a Class Interchangeable?** Lancet. 1999;354(9185):1202-4.
18. IAPO. 2013 **Briefing Paper on Biological and Biosimilar Medicines**, p 23. http://www.patientsorganizations.org/attach.pl/1763/2086/IAPO%20Briefing%20Paper.pdf