

ABPI position on biosimilar medicines



Introduction

Biological medicines: This paper sets out the ABPI position on biological and biosimilar medicines. The use of biotechnology to develop medicines is rapidly growing and it is estimated that biological medicines are likely to become the biggest selling medicinal products by 2016.¹ Global Industry Analysts Inc. (GIA) forecast that the global market for biosimilars is expected to reach \$18 billion by 2017.² Driven by the passing in the US Congress of the 2010 Biologics Price Competition and Innovation Act (BPCI) it is also suggested that the US will surpass Europe over the analysis period to become the world's largest market for biosimilars in the near future.

Biotechnology uses proteins, enzymes, antibodies and other substances that are produced in the human body to create biological medicines. Living organisms are also used in the production of these medicines, including plant and animal cells, bacteria and viruses. Biological medicines are much more complex than conventional medicines, which are comparatively simpler chemical molecules.³

Regulatory framework: Granting marketing authorisations (MA) for biotechnology products falls under the authority of the European Medicines Agency (EMA) and the European Commission (EC) in the European Union (EU). However, once authorised through these channels, individual Member States (MS) must develop processes regarding the prescription, delivery and use of biological and/or biosimilar products. These processes vary widely across the EU MS. In the UK, health technology assessment (HTA) and NHS procurement processes need to take into account the specific requirements and assessment needs of biosimilar medicines.

After patent expiry of an originator medicine, biopharmaceuticals can be developed and marketed by other manufacturers which must demonstrate similarity to a reference product. Since biosimilars can never be exact copies of their reference product every biosimilar is in effect a new biological medicine. 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.

¹ Pharmaphorum, 2012 (using data sourced from EvaluatePharma). *Biosimilars 2012 – what does the current landscape look like?* Available at: www.pharmaphorum.com/2012/03/08/biosimilars-2012-what-does-the-current-landscape-look-like/.

² Global Industry Analysts Inc, 2012. *Biosimilars – a global strategic business report*. Available at: www.strategyr.com/Biosimilars_Market_Report.asp.

³ APG, 2011. *Procurement and prescribing practices for biologics in the UK*, 29 June 2011.



EMA guidance issued in October 2005 makes clear that due to the complexity of biological/biotechnology-derived products they cannot be regarded as generics and therefore the approach used to deal with generic medicines is not scientifically appropriate for these products.⁴

In the UK, the MHRA mandates that all similar biotechnology derived medicines (biosimilars) have a Black Triangle symbol because they are not identical to the originator product and therefore require intensive monitoring for safety and efficacy.⁵ The Black Triangle scheme will be superseded in 2013 by an EU level additional monitoring system which will be mandatory for all biological medicines which were approved after 1st January 2011.⁶

In November 2012, MHRA issued a [Drug Safety Update](#) requesting that brand name and batch number is provided when reporting suspected adverse drug reactions to vaccines and biological medicines to allow them to perform appropriate pharmacovigilance.

MHRA guidance⁷ issued in February 2008 reiterates this position and states that physicians should use the brand name when prescribing biological products to ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist.

The EMA issued a concept note for the revised 'overarching' guideline on similar biological (biosimilar) medicinal products for consultation in early 2012. In addition, the EMA has issued and continue to update product specific biosimilar guidelines which are available on the EMA website.⁸

Since 2006, 13 biosimilars have been granted marketing authorisations in the EU⁹ and the use of these presents challenges for clinical practice that 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 which may not be detectable in conventional clinical trials such as rare adverse drug reactions, especially events

⁴ EMA, 2005. *Guideline on similar biological medicinal products CHMP/437/04*. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf

⁵ MHRA. *New drugs and vaccines under intensive surveillance*. Available at: www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/BlackTriangleproducts/index.htm.

⁶ EMA, 2012. *Guideline on good pharmacovigilance practices - Module X*. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129244.pdf.

⁷ MHRA, 2008. *Drug Safety Update*. Available at: www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084739.

⁸ EMA. *Multidisciplinary: Biosimilar*. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c.

⁹ European biopharmaceutical enterprises. *Biosimilars*. Available at: www.ebe-biopharma.org/index.php?option=com_content&task=view&id=32&Itemid=130.



that are immune mediated. It is this key difference that has influenced the current legislative framework for biosimilars, which treats biosimilars differently to conventional generic medicines.¹⁰

ABPI position

The ABPI makes seven recommendations which cover areas where action is needed by regulators, HTA agencies, NHS commissioners and NHS healthcare professionals who prescribe or dispense these medicines.

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

This is in line with the intention of the EU legislation¹¹ for Member States 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.

The ABPI recommends that biological medicinal products should not be prescribed by INN. In February 2008, the MHRA issued a [Drug Safety Update](#) which recommended doctors should prescribe biologics by brand name (rather than INN) because this “*will ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist*”.¹² Despite a consistent message on these requirements from the EU, legislators and the MHRA, this has not yet been fully implemented in NHS clinical and pharmacy practice. This situation is unsatisfactory and must be addressed.

Recommendation 2: A biologic or biosimilar must only be substituted with the knowledge and consent of the treating physician

Automatic substitution of one biological medicine for another can impact patient safety and makes post marketing surveillance more difficult as stated in section 2.1 of the EMA Guideline on similar biological medicinal products¹³. The guideline states that:

“... by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore, in order to

¹⁰ EBE-EFPIA, 31 Jul 2006. *Position Paper: Inapplicability of automatic substitution rules to biotechnology products, including biosimilar medicinal products: recommendation for addressing unique safety concerns.*

¹¹ Article 102e of Directive 2010/84/EU amending Directive 2001/83/EC.

¹² MHRA, 2008. *Drug Safety Update*. Available at: www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084739.

¹³ EMA, 2006. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues*. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf.



support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.”

Guidance published by the EMA in October 2012¹⁴ 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.”¹⁵

This is further supported by the British National Formulary (BNF) in their general guidance on prescribing¹⁶ and also supported by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Biopharmaceutical Enterprises (EBE).

ABPI 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 any 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). 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

¹⁴ EMA, 2012. *Questions and answers on biosimilar medicines (similar biological medicinal products)*. Available at: www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf.

¹⁵ EMA, 2008. *Questions and answers on biosimilar medicines (similar biological medicinal products)*. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf.

¹⁶ British National Formulary, September 2012. *General Guidance on Prescribing*.



obtained from either from 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 health technology assessment processes in the UK

Biosimilar products should be subject to health technology assessment in order that they can be assessed for clinical and cost effectiveness using the appropriate evidence base. It should be stated clearly in the main section of resultant HTA guidance that is issued that the medicine appraised is a biosimilar.

Biosimilar products should be recorded on [UK PharmaScan](#) by companies as soon as they enter Phase III clinical trials or within three years of their expected launch date so they can be reported upon by the NHS horizon scanning agencies for HTA topic selection purposes.

The Scottish Medicines Consortium (SMC) and All Wales Medicine Strategy Group (AWMSG) (where appropriate) should routinely appraise biosimilar medicines and the NICE topic selection process should be used to identify those biosimilars which should be subject to NICE appraisal.

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 at a local across the NHS to permit physicians to make treatment decisions which are in line with the specific needs of their individual patients. Tenders for biological medicines should where possible not seek to source a single product only 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 to another clinical condition not studied for the biosimilar product.

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.

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.

The ABPI would welcome the opportunity for further dialogue with regulators, healthcare providers, patient groups, HTA bodies 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.

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