

# ABPI position on biologic medicines, including biosimilar medicines



## Introduction

**Biologic medicines:** This paper sets out the ABPI position on biologic medicines, including biosimilar medicines. The use of biotechnology to develop medicines is rapidly growing and it is estimated that biologic medicines are likely to become the biggest selling medicinal products by 2016.<sup>1</sup> Global Industry Analysts Inc. (GIA) forecast that the global market for biosimilar medicines is expected to reach \$18 billion by 2017.<sup>2</sup>

Biotechnology uses proteins such as hormones, enzymes, and antibodies, as well as other substances that are produced in the human body to create biologic medicines. Living organisms are also used in the production of these medicines, including plant and animal cells, bacteria and viruses. Biologic medicines are much more complex than conventional medicines, which are comparatively simpler chemical molecules.<sup>3</sup>

**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 biologic medicines, including biosimilar medicines. 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 biologic medicines, including biosimilar medicines.

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

EMA guidance issued in October 2005 and revised in October 2014 makes clear that due to the complexity of biological / biotechnology-derived medicines, they cannot be regarded as generics

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<sup>1</sup> 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/](http://www.pharmaphorum.com/2012/03/08/biosimilars-2012-what-does-the-current-landscape-look-like/).

<sup>2</sup> Global Industry Analysts Inc, 2012. *Biosimilars – a global strategic business report*. Available at: [www.strategyr.com/Biosimilars\\_Market\\_Report.asp](http://www.strategyr.com/Biosimilars_Market_Report.asp).

<sup>3</sup> What you need to know about Biosimilar Medicinal Products (European Commission), section 20. Available at: [http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars\\_report\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf)



and therefore, the approach used to deal with generic medicines is not scientifically appropriate for these products.<sup>4</sup>

All biotechnology products, including biosimilar medicines, 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 that are immune mediated. It is this key difference that has influenced the current legislative framework for biosimilar medicines, which treats biosimilar medicines differently to conventional generic medicines.<sup>5</sup>

The EMA has completed a revision of its 'overarching' guidelines on similar biologic (biosimilar) medicinal products regarding quality<sup>6</sup>, non-clinical and clinical issues<sup>7</sup>. In addition, the EMA has issued and continues to update product specific biosimilar medicines guidelines which are available on the EMA website.<sup>8</sup>

Since 2006, over 20 branded biosimilar medicines have been granted marketing authorisations in the EU,<sup>9</sup> and the use of these presents challenges for clinical practice that are different to those that relate to conventional generic medicines.

**Pharmacovigilance:** The EU pharmacovigilance (PV) legislation mandates that all new medicinal products (small molecule and biologic medicines, including biosimilar medicines) approved after the 1 January 2011 are subject to closer monitoring for safety, also called additional monitoring. Medicines under additional monitoring have a black inverted triangle displayed in their labelling, the package leaflet and the summary of medicinal product characteristics (SmPC). A short sentence in the labelling explains that the triangle highlights it is a new product and encourages both prescribers and patients to report suspected adverse drug

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<sup>4</sup> EMA, 2014. *Guideline on similar biological medicinal products CHMP/437/04*. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/10/WC500176768.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf)

<sup>5</sup> 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*.

<sup>6</sup> EMA, December 2014. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)*. Available at: [http://www.ema.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentId=WC500167838](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500167838)

<sup>7</sup> EMA, December 2014. *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/ema/pages/includes/document/open\\_document.jsp?webContentId=WC500180219](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500180219)

<sup>8</sup> EMA. *Multidisciplinary: Biosimilar*. Available at: [www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000408.jsp&mid=WC0b01ac058002958c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c).

<sup>9</sup> Updated information available at European Medicines Agency, European public assessment reports: [http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar\\_search.jsp&menu%2Fmedicines%2Fmedicines.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&ReadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&menu%2Fmedicines%2Fmedicines.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&ReadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit)



reactions.<sup>10</sup> Additional monitoring lasts for five years or until certain conditions have been fulfilled. Furthermore, inclusion of biosimilar medicines in relevant disease registries should be considered by manufacturers.

The Medicines and Healthcare Products Regulatory Agency (MHRA) issued a Drug Safety Update in February 2008 stating that physicians should use the brand name when prescribing biologic medicines to ensure that automatic substitution of a biosimilar medicine does not occur when the medicine is dispensed by a pharmacist.<sup>11</sup> In line with the EU PV legislation, MHRA also issued a Drug Safety Update in November 2012<sup>12</sup> requesting that brand name and batch number is provided when reporting suspected adverse drug reactions to vaccines and biologic medicines to allow them to perform appropriate PV. This facilitates the identification of the suspect drug in an adverse drug reaction to a biologic medicine, resulting in effective safety monitoring. Should automatic substitution without the prescribers knowledge take place, there is a chance that the incorrect product could be recorded thus delaying or preventing any remedial measure.

The BioIndustry Association (BIA) has also produced a concept paper with specific PV considerations for biologic medicines including biosimilar medicines.<sup>13</sup>

Effective identification and traceability of biologic medicines, including biosimilar medicines, is needed at all stages of patient care covering prescribing, dispensing, recording and reporting of any adverse reactions. The need for appropriate safety monitoring and compliance with the EU PV legislation underpins the recommendations in this position paper.

## ABPI position

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

### **Recommendation 1: All biologic medicines, including biosimilar medicines should be prescribed by brand name and not by International Nonproprietary Name (INN)**

This is in line with the intention of the EU PV legislation<sup>14</sup> for Member States to impose an obligation for healthcare professionals to prescribe biologic medicines by brand name in order to facilitate compliance with the patient safety and PV identification and traceability requirements.

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<sup>10</sup> Regulation (EU) No 1235/2010, Article 23 and Directive 2010/84/EU, Article 11 amending Regulation (EU) No 726/2004 and Directive 2001/83/EC respectively. Available at: [http://ec.europa.eu/health/human-use/pharmacovigilance/index\\_en.htm](http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm)

<sup>11</sup> MHRA, 2008. *Drug Safety Update*. Available at: [www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084739](http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084739).

<sup>12</sup> MHRA 2012, *Drug Safety Update*. Available at: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON207188>

<sup>13</sup> *Specific Pharmacovigilance Considerations for Biological Medicinal Products and Biosimilar Medicinal Products*. BioIndustry Association (BIA) Concept Paper. June 2012. Please contact the BIA directly for a copy.

<sup>14</sup> 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



The ABPI recommends that biologic medicines should not be prescribed by INN. In February 2008, the MHRA issued a Drug Safety Update which recommended doctors should prescribe biologic medicines 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*”.<sup>15</sup> Despite a consistent message on these requirements from the EU, legislators and the MHRA, this requirements has not yet been fully implemented in NHS clinical and pharmacy practice. This situation is unsatisfactory and must be addressed.

**Recommendation 2: Automatic substitution is inappropriate for biologic medicines, including biosimilar medicines. A biologic medicine, whether an originator medicine or biosimilar medicine, must only be substituted under the direct supervision and with the consent of the treating physician**

Automatic substitution<sup>16</sup> of one biologic medicine for another can impact patient safety and makes post marketing surveillance more difficult as clear identification of the specific medicinal product is needed for appropriate PV monitoring.<sup>17,18</sup>

This is further supported by the British National Formulary (BNF) in their general guidance on prescribing,<sup>19</sup> and also supported by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Biopharmaceutical Enterprises (EBE).

The ABPI recommends that automatic substitution must not apply to any biologic medicine; this includes automatic substitution of a biosimilar medicine for its reference biologic medicine, or a biosimilar medicine for another biosimilar medicine where both have the same reference product. Substitution should only ever occur under direct supervision and consent of the treating physician and patients should be encouraged to speak to their doctor to address any questions about changes to their treatment.

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

A 2013 consensus paper from the European Commission states that: “*It is important that patients have a thorough conversation with their prescribing doctor about all the available therapeutic options, their safety, benefits and risks, and the differences between the medicines, before*

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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>

<sup>15</sup> MHRA, 2008. *Drug Safety Update*. Available at: [www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084739](http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084739).

<sup>16</sup> Automatic substitution is defined as the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber. *European Commission. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products.*

<sup>17</sup> Directive 2010/84/EU, Article 102e. Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF>

<sup>18</sup> MHRA 2012, *Drug Safety Update*. Available at: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON207188>

<sup>19</sup> British National Formulary, September 2012. *General Guidance on Prescribing*.



*coming to a decision concerning treatment*<sup>20</sup>. 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 the International Alliance of Patients' Organizations (IAPO) noted in its briefing paper on biologic medicines, including biosimilar medicines: "As for any medicine, being able to make a fully informed decision to take or prescribe a biologic or biosimilar medicine is important for patients, doctors, nurses and pharmacists."<sup>21</sup>

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. Clear information about the medicine (including noting if it is a biosimilar medicine or originator biologic medicine) in the package information leaflet and other materials directed to patients and their carers is essential.

A switching decision should never be based on cost alone. Prescribing physicians must be able to employ appropriate clinical judgment without undue influence, basing their decision on appropriate evidence and considering the specific therapeutic needs of each individual patient. Prescribers are encouraged to seek further treatment guidance for biologics, including biosimilars, from their professional societies.

#### **Recommendation 4: Biosimilar medicines should be subject to appropriate health technology assessment processes in the UK**

Biosimilar medicines should be subject to appropriate health technology assessment processes 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 HTA guidance that is issued (including both health technology assessments and evidence summaries for new medicines) that the medicine appraised is a biosimilar medicine, and the guidance should also state the brand name of the medicine. NICE published its position statement on biosimilar medicines in January 2015, the Scottish Medicines Consortium (SMC) has an existing position statement which is presently being reviewed and the All Wales Medicine Strategy Group (AWMSG) has an existing process for the appraisal of biosimilar medicines.<sup>22 23 24</sup>

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<sup>20</sup> What you need to know about Biosimilar Medicinal Products (European Commission), section 20. Available at: [http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars\\_report\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf)

<sup>21</sup> IAPO. 2013 *Briefing Paper on Biological and Biosimilar Medicines*, p 23. Available at: <http://www.patientsorganizations.org/attach.pl/1763/1987/IAPO%20Briefing%20Paper.pdf>

<sup>22</sup> NICE, January 2015. *NICE's Biosimilars Position Statement*. Available at: <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/biosimilars-statement.pdf>

<sup>23</sup> SMC, *Biosimilar Medicines*. Available at: [https://www.scottishmedicines.org.uk/About\\_SMC/Policy\\_Statements/Biosimilar\\_Medicines](https://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Biosimilar_Medicines)

<sup>24</sup> AWMSG, *Decision Process for Full & Limited Submissions*. Available at: <http://www.awmsg.org/docs/awmsg/appraisaldocs/inforandforms/AWMSG%20decision%20process%20for%20full%20&%20limited%20submissions.pdf>. Accessed 17 February 2015.



Biosimilar medicines 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 SMC and AWMSG should where appropriate appraise biosimilar medicines and the NICE topic selection process should be used to identify those biosimilar medicines which should be subject to NICE appraisal.

#### **Recommendation 5: Tenders and framework agreements involving biologic medicines should not seek to source a single product only**

For the reasons set out earlier in this position paper, great care is needed when switching a patient's biologic medicine and not all biologic medicines may be suitable for all patients. A choice of medicines therefore, needs to be available at a local level across the NHS to permit physicians to make treatment decisions which are in line with the specific needs of their individual patients. Tenders for biologic medicines should 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 biologic medicines. This also applies to any local and regional NHS formulary agreements which in addition to the inclusion of specific regulatory and requirements, should be developed in a way which safeguards clinical choice.

#### **Recommendation 6: Extrapolation of indications for biosimilar products should be evaluated by regulators 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 biosimilar medicines are not identical to the originator biologic medicine, 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 medicines in clinical use.

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

#### **Recommendation 7: The SmPC for a biosimilar medicine should clearly indicate the source of information contained within it, such as relevant data from its clinical development programme and clinical data derived from the originator or reference biologic medicine**



It is important that prescriber readily identify in the SmPC, the data upon which the approval has been given and for which product (the reference or the biosimilar medicine) the data have been generated. Biosimilar medicine approval is based primarily on comparative quality/ non-clinical evidence, but it is also important for the prescriber to be fully informed about data from comparative safety and efficacy equivalence trials involving the biosimilar medicine as well as data from the pivotal safety and efficacy trials for the reference biologic medicine.

Whilst this approach has been implemented by SwissMedic in their biosimilar medicine guidelines,<sup>25</sup> labelling for biosimilar medicines in Europe is not consistent in this regard. Moreover, there has only been limited engagement with prescribers and pharmacists to understand what information about the biosimilar medicine would be appropriate.

In order to present clear information to the prescriber, ABPI believe the SmPC should describe the biosimilar medicine's basis of approval and include details of where information has been obtained; either from studies investigating the biosimilar medicine or from evidence relating to the originator biologic medicine. Moreover, ABPI recommends that this is matched by continuing education and dialogue on biosimilar medicine concepts to help healthcare professionals, patients and other stakeholders to better understand biosimilarity and to make best use of product information relating to biosimilar medicine, such as the SmPC.

The ABPI would welcome the opportunity for further dialogue with regulators, healthcare providers, clinicians, patient groups, HTA bodies and all other interested stakeholders to contribute to developing a sustainable framework for the use of biosimilar medicines whilst encouraging scientific innovation, maintaining standards and patient safety.

**ABPI contacts:** Dr Virginia Acha, Executive Director - Research, Medical and Innovation (RM&I) (vacha@abpi.org.uk) and Dr Paul Catchpole, Value & Access Director (pcatchpole@abpi.org.uk).

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<sup>25</sup> SwissMedic, January 2014. *Administrative Ordinance / Instructions: Authorisation of similar biological medicinal products (Biosimilars)* Article 6.9 Product Information.