FOR INTERNAL USE

Biosimilars: policy position statement — September 2015

Arthritis Research UK funded research at the Kennedy Institute where anti-TNF biological therapies were pioneered in the 1990s. We welcome the continued development of new biologic medicines and biosimilars which have the potential to bring greater choice of treatment to people with inflammatory arthritis.

Biological therapies have innate variability and it is essential that these medicines are proportionally regulated, accurately prescribed and effectively monitored to develop a full evidence base of their safety and efficacy in the long-term.

Arthritis Research UK is working to ensure that people who choose to use biosimilars have the information and support they need to make informed decisions about these treatments.

What are biological and biosimilar medicines?

Biological medicines are medicines derived or manufactured from a living biological system.*[1,2] They are fundamentally different from chemical medicines. Instead of being small molecules made chemically, biologics are grown in and isolated from natural sources (human, animal or microorganism) and are complex protein molecules. The way that they are produced means that biological medicines are intrinsically more variable than chemical medicines – although they are strictly regulated, the characteristics of different batches will not be exactly identical, but determined by the individual process and the materials used. Biological medicines are used to treat a range of diseases including inflammatory arthritis, asthma, diabetes, multiple sclerosis and some forms of cancer.[3]

A biosimilar is a new biological product that has been developed to be similar to an existing biological product.†[,4] Unlike *generics*, which are exact copies of chemical medicines and can be shown to be identical to the product they are based on (the reference medicine) biosimilars cannot be exact replicas of their reference medicines. The World Health Organization's guidance states that similar biotherapeutic products (biosimilars) are similar in terms of *quality, efficacy* and *safety* to an already licensed reference ... product.[5] European guidance states that the active substance of a biosimilar must be 'essentially the same biological substance' as its reference but it is accepted that there may be 'minor differences due to their complex nature and production methods. Like all biologics, biosimilars have a degree of natural variability.'[6]

What biosimilars are currently approved for treatment of arthritis?

A range of biologic medicines are approved for the treatment of some types of arthritis and other inflammatory diseases.[7] These medicines have several different ways of working (for example they block different parts of inflammatory pathways) and structures (for example some are monoclonal antibodies, others are fusion proteins). A well-known group of biologics (anti-TNFs) inhibit a molecule called tumour necrosis factor alpha that drives the inflammatory aspect of joint disease.

* Biological medicines may be referred to as biologic therapies, biologics, biologic agents, biologic drugs, biological products, biopharmaceuticals, or biologic interventions.
† Biosimilars may be referred as similar biological medicinal products, similar biotherapeutic product or biosimilar medicines.

To date, just two biosimilars have been approved in Europe for the treatment of inflammatory forms of arthritis.* These are both based on the reference medicine infliximab† (sold under the brand name Remicade) and are sold under the brand names Inflectra (by Hospira) and Remsima (by Celltrion healthcare and under license by Napp Pharmaceuticals in the UK) (see table 1). These biosimilars were approved in 2013 by the European Medicines Agency (EMA) and came onto the market in the UK in 2015.[8,9] Other biosimilars for inflammatory forms of arthritis are in development, in Europe and in other countries, and manufacturers will aim to market these as the original biologic drugs on which they are based reach the end of their patent periods.[10]

Table 1: Biosimilar medicines currently authorised in Europe for treatment of arthritis and other inflammatory diseases.[11]

Product Name	Active Substance	International non-proprietary name (INN)	Indications	Authorisation date (EMA)	Marketing Authorisation Holder	Availability in the UK
Inflectra	Infliximab	Infliximab	o Psoriatic arthritis o Rheumatoid arthritis o Ulcerative colitis o Crohn disease o Psoriasis o Ankylosing spondylitis	10/09/2013	Hospira UK Limited	From February 2015
Remsima	Infliximab	Infliximab	o Psoriatic arthritis o Rheumatoid arthritis o Ulcerative colitis o Crohn disease o Psoriasis o Ankylosing spondylitis	10/09/2013	Celltrion Healthcare Hungary Kft. Marketed in the UK by Napp pharmaceuticals under license from Celltrion	From February 2015

How are biosimilar medicines regulated and monitored?

The EMA is responsible for approving biosimilars for use across Europe, including in the UK.[12,‡] The regulatory process is different to that for *generic* drugs, which must establish the same structure and bioequivalence§ to their reference products. For biosimilars, *quality, efficacy* and *safety* must all be demonstrated to be similar to the reference product.

The assessment process for regulating biosimilars is different to the process for completely new biological medicines as, according to EMA regulations, 'some studies carried out with the reference medicine may not need to be reproduced'. For a new biological drug, studies must show that the product is safe and effective for every indication that it will be used to treat. For a biosimilar, studies including laboratory analyses and studies in patients, must show that there are no clinically significant differences between the biosimilar and the reference medicine.[13,14]

Biological medicines are often used to treat more than one disease. European guidance on biosimilars suggests that the extrapolation of efficacy and safety data to indications that are not specifically studied during the development of a biosimilar is possible, but should be decided on a case by case basis.[15] In other words, the studies used to establish similarity for a biosimilar may be conducted in people with one type of disease, but the biosimilar may then, on a case by case basis, be licensed for any of the indications of the reference medicine.

* Biosimilar medicines are also available to treat other types of disease, including some forms of cancer. For further information see Bennett C et al. (2014). Bennet Regulatory and clinical considerations for biosimilar oncology drugs. Lancet Oncol.15(13) e594–e605.
† Infliximab is a monoclonal antibody anti-TNF therapy.
‡ Other agencies regulate biosimilars in different countries, e.g. the Food and Drug Administration (FDA) has this role in the USA.
§ Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same (European Medicines Agency, 2000).

European pharmacovigilance* law covers the way that medicines are monitored once they are on the market, including the way that unexpected side effects (adverse drug reactions, [ADRs]) are reported. All medicinal products with a new active substance and biological medicinal products (including biosimilars) approved after 1 January 2011 must be subject to additional monitoring for at least five years to support detection of any rare side effects.[16] An inverted black triangle must be included on the product label, packaging leaflet and in key regulatory documents† during this time. Manufacturers must also consider including biosimilars in relevant disease registries.[17]

Cost and access

Biological drugs are generally far more costly than conventional medicines, because of the complexity of their manufacture and distribution, with estimates in rheumatology indicating that they can cost up 20 times more than conventional (small molecule) therapies.[18] Data suggest that biosimilars may become available at 75% of the cost of biologics or less, due to reduced development costs and market competition.[19, 20]

All biosimilars are prescription only medicines (POM). In Europe, the ways in which biosimilars are prescribed, delivered and used are determined by processes in each member state. In England, the National Institute for Health and Care Excellence (NICE) undertakes technology appraisals and publishes commissioning guides and information.‡,[21] NICE guidance typically recommends the use of biologics for people with active and severe forms of an inflammatory condition, who have contraindications or who do not respond to conventional treatments.§,[22] The Medicines and Healthcare products Regulatory Agency (MHRA) also has a role in issuing drug safety alerts and guidance.

Current concerns – and hopes

Concerns and hopes about the introduction and use of biosimilars have been raised by people with arthritis and the organisations which represent them:[23]

- Safety: People are concerned that the subtle differences between a biosimilar and its reference medicine may mean that biosimilars carry greater risk of adverse drug reactions (ADRs), or that biosimilars may have different side-effect profiles to their reference medicines. In comparison to chemical medicines, all biological medicines have a greater potential to induce immune responses (immunogenicity) and this property might also vary between a biosimilar and its reference medicine. However, it is also important to recognise that batches of a reference medicine differ, and variation between biosimilars and reference medicines should be considered in the wider context of variation between batches of a reference medicine. As with all new medicines, it is possible that some ADRs will not be fully recognised until biosimilars are in widespread use. Effective pharmacovigilance, including reporting of ADRs and longitudinal research is important to develop a clear evidence base around biosimilars.

- Switching and substitution: Individual people respond differently to different medications and people may try a range of treatments before finding one which works for them. There is concern that the introduction of biosimilars may result in people being transitioned onto biosimilars from their existing medication without their consent – either inadvertently, or to reduce costs.[24] *Switching* is used to describe a 'decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment'.[25] This could include, for example, transfer from a reference product to a biosimilar or between

* Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
† The summary of product characteristics (SmPC).
‡ The Scottish Medicines Consortium (SMC) and Scottish Intercollegiate Guidelines Network (SIGN) and All Wales Medicines Strategy Group (AWMSG) have comparable roles.
§ Clinical guidelines differ for the use of biologics in specific conditions.

different biosimilars. *Substitution* is used to describe the 'practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.'[26] In simple terms, this could mean that a pharmacist dispenses a biosimilar in place of another biosimilar or a reference medicine without the knowledge of the prescribing physician. These processes are not regulated by the EMA but governance processes should be in place at a national level.

- Medicine labelling and reporting: Biosimilars made by different manufacturers can be based on the same active biological substance, but will have subtly different characteristics. Brand names (and not international non-proprietary names, INN) are the most effective way of identifying biologics including biosimilars (see table 1). Consistent use of the brand name is essential for prescription of biologics including biosimilars, with batch numbers also being used for ADR reporting.

- Choice and availability: There are expectations that the development of new biosimilars will increase the choice of treatments available, and that the lower costs will make them more affordable to health systems and so more widely available. However, it is possible that biosimilars will not be significantly cheaper than existing biological medicines, thresholds for value in NICE technology assessment will not be reached and availability will remain unchanged.

- Awareness and information provision: People need to be able to take fully informed decisions about the benefits and risks of the medicines they use or prescribe. A key concern of patient organisations is the low level of awareness and information available about biosimilars for people using them and for the healthcare professionals who prescribe and dispense them.[27]

How is Arthritis Research UK involved?

Arthritis Research UK funded research at the Kennedy Institute where anti-TNF biologics were pioneered in the 1990s. Biosimilar products have innate variability and it is essential that these medicines are proportionally regulated, accurately prescribed and effectively monitored to develop a full evidence base of their safety and efficacy in the long-term.

- Arthritis Research UK is working to ensure that people who choose to use biosimilars have the information and support they need to make informed decisions about these treatments.

Recommendations

Regulation

1. Medicines regulators including the European Medicines Agency (EMA) should continue to evaluate the extrapolation of indications for biosimilars on a case by case basis.

2. Regulatory documentation for biosimilars, including the summary of product characteristics (SmPC) should identify the source of all data as belonging to either the reference biologic or the biosimilar.

3. Medicines regulators including the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) should be alert to the development of new biosimilars from outside Europe and to the potential of cross border availability.

Availability

4. Biosimilar medicines should be subject to appropriate health technology assessment, using the brand name in all documentation. The National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) should share information on assessments. Biosimilar medicines should be recorded on the UK Pharma

Scan database as soon as they enter Phase III clinical trials, or within three years of their expected launch to enable timely assessment.[28,29]

5. Local tenders and NHS formulary agreements should be designed and conducted to ensure local availability of biologic medicines including biosimilars across the NHS, so that prescription is based on clinical need and patient choice, unaffected by the local supply of specific products.

Prescription and use

6. Decisions to use biological medicines including biosimilars should be made by the person involved and the prescribing clinician in discussion and collaboration.

7. Prescription of biological medicines including biosimilars should be made on the basis of clinical need and the choice of the person involved, and not on cost.

8. **Biological medicines including biosimilars should be prescribed by brand name. This is essential in supporting pharmacovigilance and helps to prevent substitution.**

9. Switching of biological medicines including biosimilars should only occur under the supervision of a prescribing physician and with the informed consent of the person using the medication. Decisions to switch biological medicines, including biosimilars, should not be made by others (e.g. pharmacists) or be based on cost.*

Pharmacovigilance, evidence base, research and data

10. Healthcare professionals and people using biological medicines including biosimilars should be aware of the process for reporting adverse drug reactions using both brand name and batch number.

11. People using biosimilar medicines, including those switching from reference medicines should be registered with the BSR Biologics Registers to enable data capture on treatment and outcomes.

12. Longitudinal research studies should be supported to develop the evidence base around the long term safety and efficacy of biosimilars, including in people who initially use these medicines at different stages of the treatment pathway, or as a switched medicine.

13. Data on the prescription of biological medicines including biosimilars should be collected and collated and reported nationally by the Health and Social Care Information Centre (HSCIC).

Awareness and information

14. There is a need for up-to-date and accessible information about biosimilars for people with arthritis, health care professionals including pharmacists, and commissioners. Activities to raise awareness of biosimilars should be jointly undertaken by organisations including charities, NHS-England, Public Health England, NICE, the MHRA and EMA and professional representative bodies.

Laura Boothman
September 2015

* Initially, it is likely that biosimilars will only be prescribed for people starting a new biological therapy, rather than switching from a reference medicine to a biosimilar.

External review:

- Professor John Isaac | *Professor of Clinical Rheumatology, Newcastle University & Chair, Arthritis Research UK Adult Inflammatory Arthritis Clinical Studies Group (CSG)*
- Dr Virginia Acha | Executive Director, Research, Medical & Innovation, Association of the British Pharmaceutical Industry
- Miguel Souto | *Head of Policy, British Society for Rheumatology (BSR)*
- Federico Moscogiuri | *Chief Executive Officer, Arthritis and Musculoskeletal Alliance (ARMA)*

References

1 Medicines and Healthcare products Regulatory Agency (2012). Drug Safety Update. https://www.gov.uk/drug-safety-update/reporting-suspected-adverse-drug-reactions-to-vaccines-and-biological-medicines
2 For further information see: International Alliance of Patient Organisations (2013). Briefing Paper on Biological and Biosimilar Medicines. https://www.iapo.org.uk/sites/default/files/files/IAPO%20Briefing%20Paper.pdf
3 National Institute for Health and Clinical Excellence (2012). Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology. Commissioning guide.
4 Medicines and Healthcare products Regulatory Agency (2008). Drug Safety Update. https://www.gov.uk/drug-safety-update/biosimilar-products
5 World Health Organization (2009). Guidelines on evaluation of similar biotherapeutic products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
6 European Medicines Agency (2012). Questions and answers of biosimilar medicines (similar biological medicinal products). http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf
7 Smolen et al (2014). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014; 73: 492-509.
8 European Medicines Agency. European public assessment reports accessed on-line a http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars
9 Financial Times (2015) accessed on-line http://www.ft.com/cms/s/0/ebfba63c-bc3d-11e4-a6d7-00144feab7de.html
10 Scheinberg M et al. (2013). Biosimilars in rheumatology: perspective and concerns. *What all rheumatologists should know?* Rheumatology 2014;53:389-39.
11 European Medicines Agency. European public assessment reports accessed on-line a http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars
11 Financial Times (2015) accessed on-line http://www.ft.com/cms/s/0/ebfba63c-bc3d-11e4-a6d7-00144feab7de.html
12 http://www.ema.europa.eu/ema/
13 European Medicines Agency (2012). Questions and answers of biosimilar medicines (similar biological medicinal products). http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf
14 Weise et al (2014). Biosimilars: the science of extrapolation. Blood 124 (22). http://www.bloodjournal.org/content/124/22/3191
15 European Commission (2013). What you need to know about biosimilar medicinal products.
16 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. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf
17 European Medicines Agency. Pharmacovigilance legislation accessed online at http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp&mid=WC0b01ac058058f32d
18 National Institute for Health and Clinical Excellence (2012). Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology. Commissioning guide.
19 Grabowski H et al. (2014). Biosimilar Competition: Lessons from Europe. Nature Reviews Drug Discovery, Vol. 13, No. 2, 2014, 99–100.
20 IMS Institute for healthcare informatics (2014). Assessing biosimilar uptake and competition in European markets. http://www.imshealth.com/imshealth/Global/Content/Corporate/IMS%20Health%20Institute/Insights/Assessing_biosimilar_uptake_and_competition_in_European_markets.pdf
21 National Institute for Health and Clinical Excellence (2015). Introducing biosimilar versions of infliximab: Inflectra and Remsima http://www.nice.org.uk/guidance/htta329
22 National Institute for Health and Clinical Excellence (2012). Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology. Commissioning guide.
23 eular (April 2015). Biosimilars: What do patients need to consider? http://www.eular.org/myUploadData/files/Biosimilars_2015.pdf
24 National Institute for Health and Clinical Excellence (2015). Introducing biosimilar versions of infliximab: Inflectra and Remsima http://www.nice.org.uk/guidance/htta329
25 European Commission (2013). What you need to know about biosimilar medicinal products.
26 European Commission (2013). What you need to know about biosimilar medicinal products.
27 eular (April 2015). Biosimilars: What do patients need to consider? http://www.eular.org/myUploadData/files/Biosimilars_2015.pdf
28 The Association of the British Pharmaceutical Industry (2015). Position on biosimilar medicines. http://www.abpi.org.uk/our-work/library/Documents/ABPI%20position%20on%20biosimilar%20medicines.pdf

Additional sources and references:

29 British Society for Rheumatology (2015). Position statement on biosimilar medicines. http://www.rheumatology.org.uk/about_bsr/press_releases/bsr_supports_the_use_of_biolsimilars_but_recommends_measures_to_monitor_safety.aspx

Annex: internal recommendations

Recommendations for our communications team

1. Produce a supporter Q&A for use until more detailed information resources are produced. The Q&A should include signposting to other sources of information.
2. Consider awareness raising pieces for people taking biosimilars e.g. through AToday and on-line channels.

Recommendations for our health promotion team

3. In addition to information on biosimilars already included in new revision of Infliximab leaflet to be distributed from November 2015 (see below) work with communications team on the best methods for communicating key messages around biosimilars.

   Key messages should include:
   - Check that your prescription is prescribed by brand name, and challenge any non-brand prescription.
   - Make informed choices about the medicines you are taking – and discuss any changes with your doctor.
   - Complain if you think you are being forced to switch medicines.
   - Report any adverse drug reactions.
   - Consider taking part in clinical trials.

   New wording inserted into Infiximab leaflet: *"Infliximab was originally available only under the brand name Remicade. More recently, two drugs called Inflectra and Remsima have become available. These newer drugs are referred to as 'bio-similars' because they're made to act in the same way as the original drug. Because these drugs are newer, we don't yet know as much about them in terms of safety and effectiveness in all the situations described in this leaflet."*

4. Consider producing information leaflets or articles aimed at HCPs (inc AHPs) to raise awareness (scope what RCGP/BMA/BSR have produced already). E.g. Topical review/Hands On/Synovium.

Recommendations for our research team

1. Consider a spot light for research calls on biosimilars using the BSR biologics registry in future.