



What is a Biosimilar Medicine?

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The National Health Service Commissioning Board was established on 1 October 2012 as an executive non-departmental public body. Since 1 April 2013, the National Health Service Commissioning Board has used the name NHS England for operational purposes.

The following organisations, listed alphabetically, have partnered with NHS England in developing this document. It should be noted that MHRA has only commented on regulatory aspects of the paper. NICE has only provided comment on section 3.3.2 of this paper.

- Association of the British Pharmaceutical Industry (ABPI)
- BioIndustry Association (BIA)
- British Generic Manufacturers Association (BGMA)
- Medicines and Healthcare Regulatory Agency (MHRA)
- The National Institute for Health and Care Excellence (NICE)
- Royal Pharmaceutical Society (RPS)

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

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1 Executive Summary

The aim of this document is to provide an update for key clinical and non-clinical stakeholders about the developing role of biosimilar medicines in the NHS in England and to support the safe, effective and consistent use of all biological medicines, including biosimilar medicines, to the benefit of patients.

Key messages:

- Biological medicines are medicines that are made or derived from a biological source and as such are complex, with inherent variability in their structure. [\(see 3.1\)](#)
- A biosimilar medicine is a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the originator biological medicine in terms of quality, safety and efficacy. [\(see 3.2\)](#)
- Biosimilar medicines are not considered generic equivalents to their originator biological medicine because the two products are similar but not identical. However, they will have met regulatory requirements in terms of comparative quality, safety and efficacy. [\(see 3.2 and 3.3\)](#)
- Where NICE has already recommended the originator biological medicine, the same guidance will normally apply to a biosimilar of the originator. [\(see 3.3.2\)](#)
- Continuing development of biological medicines, including biosimilar medicines, creates increased choice for patients and clinicians, increased commercial competition and enhanced value propositions for individual medicines. [\(see 4.1\)](#)
- The decision to prescribe a biological medicine for an individual patient, whether an originator or biosimilar medicine, rests with the responsible clinician in consultation with the patient. [\(see 4.3\)](#)
- At the time of dispensing, a biosimilar medicine should not be automatically substituted for the originator by the pharmacist. [\(see 4.5\)](#)
- In line with MHRA guidelines, biological medicines, including biosimilar medicines must be prescribed by brand name to support on-going pharmacovigilance of the individual products. [\(see 4.6\)](#)
- NHS England supports the appropriate use of biosimilars which will drive greater competition to release cost efficiencies to support the treatment of an increasing number of patients and the uptake of new and innovative medicines.

Key terms are highlighted in **grey** throughout the document and are explained in more detail in the [glossary](#).

2 Background

Biological medicines have revolutionised patient treatment by offering new and effective medicines for acute and chronic conditions including neutropenia, cancer, a wide range of inflammatory and autoimmune diseases, and enzyme or hormone deficiencies. As the patent expires for individual originator medicines, **biosimilar medicines** can be introduced to provide additional options for patients and the NHS.

Q: How long have they been around?

A: The first biosimilars, both somatropins, received their marketing authorisation from the European Commission in 2006. By mid-2015, twelve biosimilar molecules marketed as 19 brands have been used by patients across Europe. But this list continues to grow, and the latest information can be found on the EMA website, a link is provided in 5.2 *Where can additional information and support be found?*

Biosimilar medicines have been used in the NHS for many years as treatments for growth hormone replacement, neutropenia and anaemia related to chronic renal failure or cancer. So why are they receiving so much attention now?

The answer can be found in the increasing range of biosimilar medicines in development. Since 2013, the European Commission, on the advice of the European Medicines Agency, has authorised biosimilar medicines for infliximab (the first biosimilar monoclonal antibody), insulin glargine and follitropin alfa, to add to those already approved; somatropin, filgrastim and epoetin alfa.

Further biosimilar medicines are in development or under review for approval as originator biological medicines come off patent. More and more NHS staff will be involved in prescribing, administering, supplying and monitoring these biosimilar medicines and many more patients will be eligible for treatment with a biosimilar medicine.

3 Key facts

3.1 What is a biological medicine?

Biological medicines are derived from living cells or organisms and consist of large, highly complex molecular entities which may be difficult to characterise. Due to the variability of the biological system and the manufacturing process, biological medicines may show a certain degree of variation, even between batches of the same product.¹

3.2 What is a biosimilar medicine?

A biosimilar medicine is a biological medicine that is developed to be highly similar and clinically equivalent to an existing biological medicine.² A biosimilar contains a version of an active substance of an already approved biological medicine, which is referred to as the '**reference medicine**' or 'originator medicine'. Similarity to the reference medicine in terms of quality, structural characteristics, biological activity,

safety and efficacy must be established based on a comprehensive scientific comparability exercise such that they do not have any clinically meaningful differences from the reference medicine in terms of quality, safety and efficacy.³ Comparability is a well-established concept. Biosimilar medicines are not the same as generic medicines, which contain simpler chemical structures and are identical, in terms of molecular structure, to their reference drugs.⁴

3.3 How are biosimilar medicines authorised for use?

3.3.1 European licensing

In the European Union, marketing authorisation applications for biotechnology-derived medicines, including biosimilar medicines, are by law reviewed centrally by the European Medicines Agency (EMA).⁵ The resulting marketing authorisation, issued via a decision by the European Commission, is valid in all EU Member States.⁶

Biosimilar medicines require distinct regulatory pathways from those applied to generic medicines as they are not exact replicates of the originator (reference) medicine. The shortened and simplified regulatory approval process used for generic medicines is not sufficient to demonstrate similarity.⁷

In 2003, the EU adopted a specific regulatory pathway that provides a robust regulatory process through overarching⁸, quality⁹, non-clinical and clinical¹⁰, and product class-specific¹¹ scientific guidelines for biosimilar medicines. The main part of the evaluation is a detailed head-to-head comparison of the biosimilar medicine with its reference medicine to show that there are no clinically significant differences between them.¹² The biosimilar pathway does not seek to demonstrate safety and efficacy for each indication of the biosimilar medicine, as this is done by reference to the originator product, which has already satisfied these requirements.¹³

Q: Why are there changes?

A: Biological medicines change in ways that chemically-manufactured medicines don't. You may hear terms like batch to batch variability, manufacturing change and biosimilarity, and it is important to understand what each means. For details, please see [4.1 Glossary](#) and [5.2 Where can additional information and support be found?](#)

All biologics may exhibit batch to batch variability which is controlled and maintained within defined and approved limits. Manufacturing changes can occur in both originator biological medicines and biosimilar medicines. These changes are evaluated by the regulator to ensure that any changes do not impact the quality, safety and efficacy of biological medicines. The scientific basis for this regulatory pathway is the same as that used for manufacturing changes.¹⁴

Depending on the evidence provided for regulatory assessment of the biosimilar medicine, it will typically have all of the therapeutic indications established by the reference medicine. Although there may not be comparative clinical data (phase III studies) in all of these indications for the biosimilar, the data package submitted when considered in totality will provide sufficient assurance for the EMA to allow extrapolation of the biosimilarity assessment to additional indications. Extrapolation of indications is not automatically

awarded to the biosimilar, but must be scientifically justified. Once a product has been authorised as a biosimilar by the regulators, it should be considered by the prescriber as therapeutically equivalent in its authorised indications.

Since the approval of the first biosimilar (Omnitrope®, a somatropin biosimilar to Genotropin®) in 2006, until mid-2015, twelve biosimilar medicines have been authorised under 19 brand names in six types of product: somatropin, filgrastim, epoetin alfa, infliximab, follitropin alfa and insulin glargine.¹⁵ Once authorised by the European Commission, biosimilars are subject to the same level of post-authorisation regulatory scrutiny as originator (reference) products and will pursue their own development (e.g. new indications) and manufacturing changes as any other biological medicine.

3.3.2 Do biosimilars require a health technology assessment?

In England, NICE produced a position paper on biosimilar medicines in 2015.¹⁶ NICE will consider biosimilar medicines notified to it by the National Institute for Health Research Horizon Scanning Centre for referral to the Technology Appraisal topic selection process.

If appraised, biosimilars will usually form part of a Multiple Technology Appraisal (MTA) alongside their reference products, in the indication under consideration.

The Department of Health in England has confirmed that a technology appraisal remit referred to NICE enables NICE to decide to apply the same remit, and the resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market.¹⁷ Therefore, where NICE has already recommended the reference medicine, that same guidance is likely to apply to the biosimilar medicine.

There may be some occasions where a review of the evidence for the biosimilar medicine is deemed necessary, and in that case, NICE will consider producing a quality-assured summary of the evidence via an 'Evidence summary: new medicine' (ESNM). NICE has indicated that ESNMs will use the brand names of the medicines because substitutability and interchangeability cannot be assumed. ESNMs are not formal NICE guidance and so do not make recommendations.

The decision regarding the choice of biosimilar or originator biological medicine for an individual patient rests with the responsible clinician in consultation with the patient.¹⁸

NICE technology appraisal guidance often recommends treatment with the least expensive drug where there are a number of choices available, taking into account for example administration costs, dosages, mode of administration and treatment schedules.

4 Key considerations for the NHS

4.1 Why should biosimilar medicines be used in the NHS?

Competition between different biological medicines, including biosimilar medicines, creates increased choice for patients and clinicians, and enhanced value propositions for individual medicines.¹⁹ This is particularly relevant in the context of Future Focused Finance which is looking at how the NHS can be supported to take value based decisions.²⁰ There are additional benefits, such as further sources of supply.

Biosimilar medicines are more challenging and expensive to develop than generic medicines.²¹ Whilst they cannot offer the same percentage price reductions as traditional generic medicines, nevertheless, there are significant savings associated with increased competition between biological medicines, including biosimilar medicines.

Recent research has given clear evidence that the additional competition is bringing value and opportunity to widen access for patients in some circumstances.²² However, this research also demonstrates that biosimilar medicine uptake across Europe to date shows very different patterns, depending on the class of biological medicine and the procurement measures in place.

Further research²³ has emphasised that making the most of biosimilars in our healthcare systems requires investment: investment in education around biosimilars, investment in experience and use, investment in establishing sustainable and appropriate procurement, and investment in transparent and clear decision-making frameworks.

4.2 What considerations should inform a purchasing decision?

Biosimilar medicines are approved to be therapeutic equivalents to the reference medicine, establishing that the previously proven safety and efficacy of that medicine also applies to the biosimilar.²⁴ As with any biological medicine, the biosimilar medicine will have details of its licensed indications included in the British National Formulary.

Those making decisions about whether to purchase a biosimilar should consider the following questions:²⁵

- Is the biosimilar licensed for all the indications and routes of administration required?
- Is the biosimilar available in suitable strengths and presentations?
- Is the administration device acceptable to the patient and are product-associated support services available?²⁶

4.3 How should treatment decisions be made?

Treatment decisions should be made first on the basis of clinical judgement for individual patients and secondly on the basis of the overall value proposition offered by individual medicines.

The role of the physician in treating patients with these complex medicinal products is particularly important.²⁷

Patient consultation, which takes into account their needs, preferences and values, is also an essential part of evidence-based medicine. Clinicians should seek to use all available evidence to guide decisions about the care of the individual patient.²⁸

4.4 Can a patient already established on an originator biological medicine be switched to a biosimilar medicine?

There is growing practical NHS experience that demonstrates the safety and efficacy of biosimilars in clinical practice. The evidence regarding interchangeability is still developing. Guidance across some EU Member States currently recommends that switching between a reference product and its biosimilar (and indeed amongst biosimilar medicines) should be managed at the discretion of the individual prescriber in partnership with the patient, with appropriate monitoring in place.²⁹ Evolving evidence and treatment guidance³⁰ should be made available to patients and prescribers to support them in their decision-making.

4.5 Is automatic substitution permitted?

Automatic substitution, defined here as the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber,³¹ is not appropriate for biological medicines, including biosimilar medicines and is not permitted at this time. Prescribers, of course, are always able to switch treatments for a given patient, provided it is safe to do so and there are appropriate monitoring arrangements in place.

As biosimilar medicines often use the same international non-proprietary name (INN) as their reference product, the main way to ensure automatic substitution does not take place is through brand name prescribing.³² Brand name prescribing should be adhered to by all prescribers for biological medicines, including biosimilar medicines, and is in line with recommendations from the MHRA³³ and NICE, as well as being enshrined in EU law.³⁴

UK prescribers are taught to prescribe using the INN, or 'generic' name, and this is established practice within the NHS for most products. It is important to ensure that prescribers are aware of the different requirements associated with biological medicines, including biosimilar medicines (as well as some other products). Measures should be taken to ensure all those involved in the prescribing and dispensing of such medicines abide by these requirements, such as brand name prescribing.

4.6 What is important about monitoring biological medicines, including biosimilar medicines?

4.6.1 Pharmacovigilance

Q: Where can I find further information on safety of biological medicines?

A: MHRA and the EMA provide more explanations on how medicines safety is monitored across Europe. The MHRA Drug Safety Updates are a core resource. It is worth noting that by mid-2015, no safety signals different to the reference medicine have been identified for biosimilars. Please see 5.2 *Where can additional information and support be found?*

All medicinal products in the EU are subject to strict testing and assessment of their quality, efficacy and safety before being authorised. Once placed on the market they continue to be monitored by all relevant stakeholders to assure that any aspect which could affect the safety profile of a medicine is detected and assessed and that necessary measures are taken. This monitoring is called **pharmacovigilance**. In the UK reports of side effects to medicines should be reported to the MHRA Yellow Card scheme.³⁵ In addition, the companies marketing biosimilars may have further post marketing commitments, in line with requirements for the reference product; for example, to include their biosimilar products in relevant registries which gather data on the safety and effectiveness of the medicine in clinical practice.³⁶

4.6.2 Additional monitoring by brand and batch number

EU pharmacovigilance legislation mandates that any medicine with a new active substance and all biological medicines, including biosimilar medicines, approved after 1 January 2011, are subject to closer monitoring for safety. This is also called additional monitoring.³⁷ Medicines under additional monitoring have a black inverted triangle (▼) in their labelling. The triangle highlights it is a new product and encourages both prescribers and patients to report suspected adverse drug reactions (ADR).³⁸

In accordance with European pharmacovigilance legislation, the MHRA requests those reporting a suspected ADR to a biological medicine to provide the brand name and specific batch number on any ADR report.³⁹ The MHRA also asks that this information is provided to patients and carers when the product is administered, to help them report an issue more accurately.⁴⁰

An inability to attribute any safety concerns to the correct product, manufacturer and batch could prevent a root-cause determination and may put patients at risk.⁴¹

5 Appendices

5.1 Glossary

A glossary of key terms associated with biosimilar medicines has been included for ease of reference.

- **Active substance:** an active ingredient or molecule which goes into a specific medicine and which provides this medicine with properties for treating or preventing one or several specific disease(s).⁴²
- **Automatic substitution:** the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.⁴³
- **Batch to batch variability:** Because biological medicines, including biosimilars, are derived from living organisms and produced using complex manufacturing processes, there is intrinsic variability from batch to batch. This variation is kept within strict acceptable limits, which is monitored by the manufacturer and approved by the regulator, known as 'release specifications'.
- **Biological medicine:** a medicine that contains one or more active substances made by or derived from a biological source. Some of them may be present in the human body and examples include proteins such as insulin and growth hormone. Active substances in biological medicines are larger and more complex than those of non-biological medicines.⁴⁴
- **Biosimilarity:** biosimilars are an alternative for a given biological medicine (the originator) and are developed to be highly similar to the originator biological medicine. A candidate molecule is designed, produced and compared with several batches of the reference (originator) medicine using advanced analytical techniques to assess its structure and function. It must be shown to match or be highly similar to the key characteristics of the molecular structure and biological activity, and will be expected to have similar function and clinical outcome. Any differences will be expected to have no meaningful clinical impact on the safety and efficacy of the medicine for patients.
- **Biosimilar medicine:** a biological medicine that is developed to be highly similar to an existing biological medicine.⁴⁵
- **Biotechnology:** any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. An example is the reproduction of human hormones like insulin.⁴⁶
- **Cell line:** a well-established, living system of cultured (grown in a laboratory) cells that will continue to grow and produce new cells indefinitely, so long as the cells receive nourishment and have space to develop.⁴⁷
- **Extrapolation of indications:** the decision whether to extend the efficacy and safety data from an indication (a medical condition, disorder or disease) for which the biosimilar has been clinically tested to other conditions for which the branded product is approved, is known as "extrapolation".⁴⁸

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The decision to extrapolate is based on the entire data package submitted ie European Public Assessment Reports (EPAR), of which the selected clinical studies are only part. Extrapolation then follows if the totality of evidence provides assurance. Much of the data in the EPAR is not clinical patient data but does provide assurance in the other indications to which the product is intended to be extrapolated.

- **International Non-proprietary Name (INN):** the unique name which identifies pharmaceutical substances or active pharmaceutical ingredients. Also known as a 'generic' name.⁴⁹
- **Interchangeability:** the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.⁵⁰
- **Manufacturing change:** during the commercial lifecycle of all biological medicines, planned changes occur to the manufacturing process, generally minor (such as a change in filter supplier) but sometimes substantial (such as a new manufacturing site). The manufacturer must ensure the process is controlled and the variability remains within release specifications approved by the regulatory authority. The assessment for any manufacturing change is done via a comparability exercise, informed by the historical manufacturing, non-clinical and clinical data available to the manufacturer. Depending on the scale of the change and the potential impact to the product, the regulator may ask for additional analytical data, non-clinical and clinical data, but the aim is to ask only for what is needed to make an assessment.
- **Molecule:** the smallest particle of a substance that has all of the physical and chemical properties of that substance. Molecules comprise two or more atoms held together by strong chemical bonds. If they contain more than one atom, the atoms can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins, can be made up of many thousands of atoms.⁵¹
- **Pharmacovigilance:** science and safety control procedures to which medicines are subject before, during and after their approval by regulatory authorities with the aim of detecting, assessing and understanding the benefit: risk profile of a medicinal product.⁵²
- **Reference product:** a medicinal product which has been granted a marketing authorisation by a Member State or by the European Commission on the basis of submitted quality, pre-clinical and clinical data, to which the application for marketing authorisation for a generic or a biosimilar product refers.⁵³

5.2 Where can additional information and support be found?

5.2.1 Key reading

#	Document Name	Publication Date	Publication Organisation
1	Guideline on Similar Biological Medicinal Products	23-Oct-14	European Medicines Agency
2	Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	01-Dec-14	European Medicines Agency
3	Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)	01-Dec-14	European Medicines Agency
4	Questions and answers on biosimilar medicines (similar biological medicinal products)	27-Sep-12	European Medicines Agency
5	What you need to know about Biosimilar medicinal products: Consensus Information Paper	2013	European Commission
6	NICE Biosimilars Position Statement	06-Jan-15	National Institute for Health and Care Excellence

5.2.2 Additional information

#	Document Name	Publication Date	Publication Organisation
1	Multidisciplinary: Biosimilar	18 May 2015 (accessed date)	European Medicines Agency
2	Biosimilar medicines with marketing authorisation from EMA	Regularly updated	European Medicines Agency
3	Drug safety update: reporting suspected adverse drug reactions to vaccines and biological medicines Drug Safety Update - GOV.UK	22-Nov-12	Medicine and Healthcare products Regulatory Agency
4	Drug Safety Update: Biosimilar Products	01-Feb-08	Medicine and Healthcare products Regulatory Agency
5	Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes	2015	National Institute for Health and Care Excellence
6	Biosimilar medicines – NICE's approach	03-July-15	National Institute for Health and Care Excellence
7	Biosimilar medicines: a national prescribing framework	19-May-15	Healthcare Improvement Scotland
8	MEB position on prescription of "biosimilar medicinal products"	31-March-15	Medicines Evaluation Board

5.3 References and footnotes

- ¹ Blood Journal: [Biosimilars: what clinicians should know](#), 2012
- ² European Medicines Agency: [Questions and answers on biosimilar medicines](#), 2012
- ³ European Medicines Agency: [Guideline on similar biological medicinal products](#), 2014
- ⁴ European Medicines Agency: [Questions and answers on biosimilar medicines](#), 2012
- ⁵ Note: Although this is correct, not all biosimilars are made by recombinant technology and thus centrally regulated; low molecular weight heparins can be approved through decentralised procedures only in some countries.
- ⁶ European Commission: [What you need to know about biosimilar medicinal products](#), 2013
- ⁷ European Medicines Agency: [Guideline on similar biological medicinal products](#), 2014
- ⁸ Ibid.
- ⁹ European Medicines Agency: [Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues](#) (revision 1), 2014
- ¹⁰ European Medicines Agency: [Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues](#), 2014
- ¹¹ European Medicines Agency: [Product-specific biosimilar guidelines](#).
- ¹² European Medicines Agency: [Questions and answers on biosimilar medicines](#), 2012
- ¹³ Blood Journal: [Biosimilars: the science of extrapolation](#). 2014
- ¹⁴ ICH Expert Working Group: [ICH harmonised tripartite guideline: Comparability of biotechnological/biological products subject to changes in their manufacturing process](#). 2004
- ¹⁵ As of June 2015. Please refer to the [European Medicine Agency's website](#) for the latest list of biosimilars authorised in Europe, as there are many other biosimilar products in development.
- ¹⁶ National Institute for Health and Care Excellence: [NICE's biosimilars position statement](#), 2015
- ¹⁷ Ibid.
- ¹⁸ Ibid.
- ¹⁹ European Commission: [What you need to know about biosimilar medicinal products](#), 2013
- ²⁰ Future Focused Finance. www.futurefocusedfinance.nhs.uk
- ²¹ Ibid.
- ²² IMS Institute for Health Informatics. [Assessing biosimilar uptake and competition in European Markets](#), 2014
- ²³ GFK: [Factors supporting a sustainable European biosimilar medicines market](#), 2014
- ²⁴ Committee for Medicinal Products for Human Use (CHMP), [Guideline on Similar Biological Medicinal Products](#). European Medicines Agency, 23 October 2014CHMP/437/04
- ²⁵ UK Medicines Information: [What are biosimilar medicinal products?](#), 2015
- ²⁶ Drug and Therapeutics Bulletin: [What are biosimilars and are they important?](#), 2013
- ²⁷ European Commission: [What you need to know about biosimilar medicinal products](#), 2013
- ²⁸ National Institute for Health and Care Excellence: [Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes](#), 2014
- ²⁹ Healthcare Improvement Scotland, [Biosimilar Medicines: A National Prescribing Framework](#), 2015; Medicines Evaluation Board, ["Biosimilar Medicines"](#), 2015
- ³⁰ London Medicines Evaluation Network Review: [Answers to commonly asked questions about biosimilar versions of infliximab](#), 2015
- ³¹ European Commission: [What you need to know about biosimilar medicinal products](#), 2013
- ³² [Medicines Act 1968: Chapter 67 \(as amended\)](#). 1968
- ³³ Medicines Healthcare Products Regulatory Agency: [Biosimilar medicines](#), 2008
- ³⁴ European Union: [EU directive \(2012/52/EU\)](#), 2012
- ³⁵ MHRA: [Yellow Card Scheme](#). 2015
- ³⁶ European Commission: [Medicinal products for human use](#) webpage, accessed June 2015
- ³⁷ European Union: [Regulation \(EU\) No 1235/2010](#), 2010
- ³⁸ European Union: [Directive 2010/84/EU](#), 2010
- ³⁹ Ibid.
- ⁴⁰ Medicines Healthcare Products Regulatory Agency: [Reporting suspected adverse drug reactions to vaccines and biological medicines](#), 2012
- ⁴¹ BioIndustry Association: [Pharmacovigilance Specific Considerations for Biological Medicinal Products and Biosimilar Medicinal Products](#), 2012
- ⁴² European Commission: [What you need to know about biosimilar medicinal products](#) 2013
- ⁴³ Ibid.
- ⁴⁴ European Medicines Agency: [Questions and answers on biosimilar medicines](#), 2012

⁴⁵ From this point until the end of the document, all definitions are sourced from: European Commission: [What you need to know about biosimilar medicinal products](#) 2013