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Copies of biotechnology-derived medicinal products (“biosimilars”): the European Medicines Agency (EMA) makes a timid shift towards a more pragmatic approach

Submission of comments on 'Draft guideline on similar biological medicinal products' (EMA/CHMP/437/04 Rev. 1)

Comments from:

Name of organisation or individual

International Society of Drug Bulletins (ISDB)

The International Society of Drug Bulletins, founded in 1986, is a worldwide Network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of pharmaceutical industry. Currently ISDB has around 80 members in 41 countries around the world. More info: www.isdbweb.org.
Contact: press@isdbweb.org.

Medicines in Europe Forum

Launched in March 2002, the Medicines in Europe Forum (MIEF) includes more than 70 member organizations from 12 Member States representing the four key players on the health field, i.e. patient groups, family and consumer bodies, social security systems, and health professionals. It is a testament to the importance of European medicines policy. Medicinal products are not merely consumer goods, and the European Union represents an opportunity for European citizens to seek further guarantees of efficacy and safety.
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Copies of biotechnology-derived medicinal products (“biosimilars”): the European Medicines Agency (EMA) makes a timid shift towards a more pragmatic approach

In their joint response to the European Medicines Agency (EMA) consultation on its draft revised guideline on biosimilars, the Medicines in Europe Forum (MiEF) and the International Society of Drug Bulletins (ISDB) argue that the costly requirements imposed on biosimilars primarily serve to defend companies’ intellectual property, not public health.

Key points:

- The context surrounding the current discussions on “biosimilars”, i.e. copies of biotechnology-derived medicinal products, is one of pharmaceutical companies pushing for greater protection of their intellectual property. Companies that market novel originator medicinal products are striving to prolong their monopoly for as long as possible, thereby delaying the market introduction of cheaper competing copies.
 - All biological medicinal products exhibit variation related to their methods of production, even between different batches of the same originator product. Drug regulatory agencies should therefore impose the same requirements on companies manufacturing an originator product (for example when the manufacturing process or manufacturing site is changed) as on companies manufacturing biosimilars.
 - The comparability of an originator medicinal product and a copy can usually be assessed using analytical methods and, if necessary, in bioequivalence studies. This is after all the method routinely used to assess the comparability of two batches of the same proprietary medicinal product.
 - The main argument put forward both by pharmaceutical companies selling originator products and drug regulatory agencies to justify the requirement to conduct clinical and preclinical studies before a biosimilar can be marketed is the risk of differing immunogenicity between the biosimilar and the originator, for example due to differences in their glycosylation profiles. Yet in the vast majority of cases, these slight differences in immunogenicity will have no clinical impact: their efficacy and adverse effect profile will be similar.
 - Specific preclinical and clinical studies provide a false sense of security. The results obtained will always be the same: the two medicinal products have equivalent harm-benefit balances and can be used for the same purposes as long as one remains attentive to the emergence of any safety signals, as with any medicinal product.
 - In France, biosimilars are about 20% to 30% cheaper than the reference product. Their uptake is held back by various systemic barriers in Member States: some require biological medicinal products to be prescribed by their brand names, most do not allow pharmacists to substitute biological medicinal products with a biosimilar, etc.
 - Ten years after the invention of “biosimilar” status in Europe, it remains an unattractive prospect for pharmaceutical companies and is having little impact on Member States’ spiralling healthcare costs.
 - As of 2013, the EMA’s guidelines on biosimilars seem to be shifting towards a more pragmatic approach, dispensing with certain clinical trials that rather than help demonstrate “biosimilarity” are, in reality, used to delay the market introduction of copies.
 - The EMA could also encourage the development of useful biosimilars by upholding the integrity of the international non-proprietary name (INN) system; by adopting a responsible policy on access to data; by creating a centralised list of groups of biosimilar medicinal products; and by developing proactive pharmacovigilance.
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Copies of biotechnology-derived medicinal products (“biosimilars”): the European Medicines Agency (EMA) makes a timid shift towards a more pragmatic approach

In their joint response to the European Medicines Agency (EMA) consultation on its draft revised guideline on biosimilars (1), the Medicines in Europe Forum (MiEF) and the International Society of Drug Bulletins (ISDB) argue that the costly requirements imposed on biosimilars primarily serve to defend companies’ intellectual property, not public health.

In May 2013, the European Medicines Agency (EMA) released for public consultation a draft revision of its guideline on the general principles to be applied for “biosimilars”, i.e. copies of biotechnology-derived medicinal products (1). To make a worthwhile contribution to this consultation, one must be aware of the context in which the concept of “biosimilar medicinal product” was created almost 10 years ago, as well as the current context. Our response therefore outlines this then context, followed by a number of concrete proposals to encourage the development of useful biosimilars, which would improve patient care.

1. Foreword - A context of constant pressure for greater protection of intellectual property

Stakeholder number	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>The prices agreed by Member States for pharmaceutical companies’ new (i.e. “originator”) medicinal products are generally very high relative to the real costs of research and development, even for medicinal products that offer no advantage over existing therapies (2), making the pharmaceutical industry one of the most profitable sectors (3).</p> <p>The prices agreed for biotechnology-derived medicinal products are particularly exorbitant (4,5). In the 1990s, the justification given for the high price of biotechnology-derived medicinal products was the need to enable innovative start-ups developing biotechnology-derived medicinal products to generate rapid returns on their research and development investments, as in contrast to pharmaceutical multinationals these small and medium-sized enterprises had no income from products already on the market (4). But the situation has changed since then: the profitable</p>	

start-ups have been absorbed by multinationals. In 2013, the biotech market is highly concentrated: 10 of the largest multinationals account for 70% of the market (6).

Copies of medicinal products: competition helps improve access to healthcare.

Copies of medicinal products that are brought to the market without the need for new clinical trials and with smaller promotional budgets offer savings that enable Member States' health systems to fund healthcare access for more people. For example, in France, generic medicines are on average 60% cheaper than their originator counterparts (6). This competition also leads to the price of originator medicinal products being reduced in order to maintain sales (6). The existence of copies also ensures that alternatives are available in the event of a shortage of a particular medicinal product (e.g. due to a problem with pharmaceutical quality or an interruption in manufacturing) (7).

Constant pressure for increased protection of intellectual property to delay copies.

In order to preserve their monopoly, which allows them to impose high prices, it is in pharmaceutical companies' interests to slow down the development of copies, in particular through increased protection of their intellectual property (a).

In Europe, during the overhaul of the regulatory framework of medicinal products in 2004, lobbying by pharmaceutical companies selling originator drugs led in particular to two measures to increase the protection of intellectual property: the invention of "biosimilars" (see below); and longer protection for regulatory data on originator medicinal products (8,9).

"Protection of regulatory data" means that, for a specified time, the company that holds the marketing authorisation (MA) on an originator medicinal product retains exclusive rights to use the data it provided in support of its MA application for the originator product (clinical trial results, details of the manufacturing process), which means that they cannot be used by generics manufacturers without specific consent. The aim is to impose dissuasively high additional costs on manufacturers of copies: they must either wait until the data from the MA dossier are publicly available or conduct their own clinical trials in order to obtain a MA (8,9).

In 2004, the period during which regulatory data on medicinal products is protected was increased to 8 years in all Member States, and an additional 2 years during which generics

a- In addition to increased protection for intellectual property, other practices are used to slow down the development of copies: campaigns to discredit generic drugs (refs 30,31); illegal agreements between companies that market originator products and those that market generic medicinal products in order to delay the market introduction of copies (refs 32); and all-out lobbying against transparency of clinical-trial and pharmacovigilance data, including bringing legal action against the EMA to prevent the results of certain clinical trials being sent to competing companies wishing to develop biosimilars (ref 33).

manufacturers can start to compile their abridged applications based on data from the MA dossier of the originator but do not have the right to apply for a MA for their copy (generics producers can only apply for a MA for their copy 10 years after the MA was granted for the originator drug) (b).

2. General comments – “Biosimilars”: costly requirements, too often unjustified from a public health perspective

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	<p>In 2004, although the European Directive of 1986 had already defined the concept of “essentially similar proprietary medicinal products” including “high-technology medicinal products” (10), the notion of a biological medicinal product that is “similar” to a reference medicinal product was invented to denote copies of medicinal products manufactured using biotechnology (8). The aim was to distinguish these “biosimilar” copies from generics, with the term “generic” being reserved for medicinal products presented as having a “simple” structure and mainly produced by chemical synthesis (8).</p> <p>A biosimilar is defined in French law (our translation) as “(...) <i>any biological medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as a reference biological medicinal product (...) which cannot be considered a generic medicinal product (...) owing to differences relating in particular to the variability of the raw material or to the manufacturing processes, requiring additional preclinical and clinical data to be produced (...)</i>” (11).</p> <p>This definition implies that, for a biotechnology-derived medicinal product, the same active substance produced using a different biotechnology-based manufacturing process cannot be considered as a straightforward generic version. A company that wishes to market a biosimilar cannot simply submit an abridged application demonstrating the same level of pharmaceutical quality and bioequivalence with the originator product, as is the case for generic medicinal products (7,12). Instead, it must submit specific preclinical and clinical tests (c).</p> <p>Demonstrating similarity between biological medicinal products: physicochemical and</p>	

b- This 10-year period of de facto market exclusivity for originator products can be extended by an additional year of protection for regulatory data, as an incentive to companies to engage in certain types of development (to develop orphan medicinal products or medicinal products for paediatric use, to switch a product from prescription-only to over-the-counter status, or to obtain within the first 8 years a new indication that brings a significant clinical benefit in comparison with existing therapies, etc.) (ref 9).

c- According to recital 15 of ref 29, “When a biological medicinal product does not meet all the conditions to be considered as a generic medicinal product, the results of appropriate tests should be provided in order to fulfil the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both.”

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	<p>biological characterisation and pharmacokinetic and pharmacodynamic studies often suffice. The pharmaceuticals sector has long been using manufacturing methods in which reproducibility is an issue, including variability between batches (e.g. extraction from natural sources (plants) or fermentation (antibiotics)) and the presence of residues (e.g. for certain vaccines). And all biological medicinal products exhibit variation related to their production method, even between different batches of the same proprietary pharmaceutical product.</p> <p>Yet there is no requirement to conduct clinical trials to evaluate the efficacy and adverse effect profile of each new batch.</p> <p>Advances in analytical techniques mean that there is often no more need to perform preclinical or clinical studies to demonstrate similarity between biological medicinal products than when demonstrating the similarity of two batches of an originator product. As of 2013, when the manufacturing site or manufacturing process of a medicinal product is changed — as they frequently are —, the “comparability” of two batches is generally assessed using a few appropriate, complementary analytical methods (demonstration of the pharmaceutical quality), and confirmed using pharmacokinetic and pharmacodynamic studies (13-15).</p> <p>Specific clinical and preclinical studies to demonstrate “biosimilarity”: a disproportionate requirement. Biotechnology-derived medicinal products are often proteins, administered by injection. Proteins have a complex structure and a high molecular weight, which means that the body may identify them as foreign and mount an immune response (for example, by producing antibodies) against them (6,7). If the biosimilar is produced using a different manufacturing process to the originator product, the main argument advanced by originator companies and drug regulatory agencies to justify the need for clinical and preclinical studies before market introduction of the biosimilar is the possibility that it may be more immunogenic than the originator product (d) (16).</p> <p>Yet in the vast majority of cases, these slight differences in immunogenicity have no clinical impact: their efficacy and adverse effect profiles are similar. For example, a possible causal relationship between</p>	

d- Differences in the manufacturing process can of course result in differences in immunogenicity, for example a higher level of glycosylation (addition of carbohydrate groups to the sequence of amino acids that make up the protein) can make the protein more immunogenic. However, such differences in glycosylation and other post-translational modifications are also observed between different batches of the same medicinal product, including originator medicinal products. It is also possible for a copy to be less immunogenic than the original (ref 17).

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	<p>rare adverse effects associated with various epoetins (erythroblastopenia) and their method of production was suggested, but the same adverse effects were later reported with all of the epoetins on the market (17,18). An additional clinical trial before the market introduction of the copies would have made no difference: to rule out an excess incidence of a rare adverse effect, clinical trials have to include a very large number of participants.</p> <p>Conducting and repeating limited, short-term clinical trials before authorisation provide a false sense of security but cannot demonstrate complete similarity between two medicinal products that contain the same active substance, nor detect potential differences between them. The results obtained will always be the same: the two medicinal products have equivalent harm-benefit balances and can be used for the same purposes as long as one watches for the emergence of any safety signals, as with any medicinal product (12).</p> <p>Requiring manufacturers of biotechnology-derived copies of medicinal products to conduct new clinical trials serves only to protect manufacturers of originator products. It also involves enrolling patients into trials that offer them no prospect of benefiting from a therapeutic advance, which is ethically questionable, and investing substantial human and financial resources to generate inconsequential results (12).</p> <p>All in all, the argument that biosimilars may be more immunogenic is reminiscent of the long-running controversy over the possible risks of generic medicinal products because they contain a different salt or ester of the active substance (e).</p> <p>The European biosimilars market remains underdeveloped. In Europe, 15 products with biosimilar status were authorised between 2006 and early October 2013, corresponding to five active substances, all proteins: <i>epoetin alfa</i> and <i>epoetin zeta</i>, a haematopoietic growth factor (5 products); <i>filgrastim</i>, a granulocyte colony-stimulating factor (7 products); <i>somatropin</i>, a growth hormone (1 product); and <i>infliximab</i>, a monoclonal antibody that was authorised in July 2013 for its various therapeutic indications by extrapolation from the demonstration of similarity to the reference product in rheumatoid arthritis (2 products) (19,20). A “twin” copy of <i>interferon beta-1b</i> was also marketed in 2009, but without biosimilar status because it is produced using the same manufacturing methods (the originator company</p>	

e- It has since been specified in the definition of a generic medicinal product: “(...) The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.” (ref 29, Article 10)

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	<p>released all the data from the MA to the company marketing the copy, as ought to happen in every case) (21). Marketing authorisation for a biosimilar of <i>interferon alfa-2a</i> for use in chronic hepatitis C was refused in 2006 (12).</p> <p>The assessment reports the EMA has released do not specify exactly how the manufacturing method of the biosimilar differs from that of the originator product; nor do they explain why it imposed clinical evaluation prior to authorisation (12,22). Similarly, because no quantitative data or details about the endpoints used were provided, we do not know precisely what led the EMA's Committee for Medicinal Products for Human Use (CHMP) to issue a negative opinion on June 2006 on a MA application for a biosimilar version of <i>interferon alfa-2a</i> (12).</p> <p>However, as data protection for several monoclonal antibodies and long-acting human insulin analogues is about to expire, the number of MA applications for biosimilars is bound to rise over the coming years (6,7).</p> <p>Member States: systemic barriers to wider uptake of biosimilars. In 2012, sales of biosimilars in France totalled about 60 million euros and accounted for less than 15% of sales of the three classes of medicinal products concerned (f) (6,7). The uptake of biosimilars has been slow in the United Kingdom too, despite the widespread use of generics (g) (22).</p> <p>According to the principle of subsidiarity, the situation regarding the information to be included on prescriptions and the substitution of prescribed medicinal products is a matter for Member States to decide (h). In France, by 2015 it will be compulsory to prescribe all medicinal products, including biosimilars, by their international non-proprietary name (INN) (6). However, the French drug regulatory agency, ANSM (our translation) <i>“recommends that a given patient should be treated as far as possible with a single product, without making changes within a family of biosimilars, and that if the attending physician decides on a change in treatment, traceability should be ensured and the patient should be monitored</i></p>	

f- In France, in 2012, biosimilars account for about 10% of the growth hormone market, about 5% of the epoetin market, and about 25% of the growth factor market (ref 6).

g- In the United Kingdom, in 2009, biosimilars of growth hormone accounted for less than 1% of an already saturated market comprising 6 other growth hormone products; biosimilars only accounted for about 1% of the epoetin market (although the percentage has been increasing since it was demonstrated that all epoetins have a similar harm-benefit balance), while biosimilars accounted for about 20% of the filgrastim market (ref 22).

h- As part of the implementation of the Directive on cross-border healthcare adopted in 2011 (Directive 2011/24/EU), the European Commission has been tasked with developing proposals for enabling the recognition of prescriptions issued in another Member State, including the use of INNs (ref 34).

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	<p><i>appropriately</i>" (7). A large majority of European Union Member States have refused to officially allow biosimilar substitution by pharmacists (6). The British drug regulatory agency (MHRA) has even recommended that biological products should be prescribed by their brand name to <i>"ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed"</i> (22).</p> <p>These "precautions" appear scientifically unjustified, because the same variability can be observed between two batches of a given biological medicinal product as between one batch of an originator biological medicinal product and its biosimilar. Three Member States, Germany (for products from the same manufacturer) (23), Denmark and Bulgaria, have authorised the substitution of biotechnology-derived medicinal products by their biosimilar (6,23).</p> <p>The traceability argument does not hold up either: all that would be required to make it possible to detect a problem associated with an injudicious change in the manufacturing process, for example, would be to include the product's INN, brand name and batch number and the name of the manufacturer when recording pharmacovigilance reports (24).</p> <p>"Biosimilar" is not the same as "interchangeable" in the United States either. The European Union passed legislation on copies of biotechnology-derived medicinal products back in 2003, creating the "biosimilar" concept. The United States of America made up for lost time with its 2010 Patient Protection and Affordable Care Act, creating its own abridged MA for biosimilars (abbreviated approval pathway under section 351(k)). The US drug regulatory agency (FDA) also has the authority to designate a biosimilar as interchangeable with its reference product (the originator product). In practice however, the guidelines developed by the FDA do not currently provide for automatic interchangeability (25).</p> <p>Biosimilar status is an unattractive prospect for companies, with major consequences for the sustainability of health systems. As of 2013, it is estimated to take 6 years to bring a biosimilar to the market (22). One practice shows how unappealing biosimilar status is for pharmaceutical companies when bringing copies of biotechnology-derived medicinal products to the market. Because biosimilar status requires them to conduct preclinical tests and sometimes even clinical trials, pharmaceutical companies may as well position their copy as a "new active substance" in order to benefit from at least 8 years of protection of their regulatory data, while also avoiding becoming the target of campaigns by originator companies to discredit the copy, as has occurred with generic medicines. Often, the first step to obtaining</p>	

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	<p>new active substance status for a copy is to attempt to obtain an INN that is distinct from that of the originator drug (by arguing for example that the copy has a different glycosylation profile) (i) (15,17).</p> <p>In practice, in France, biosimilars are currently only about 20% to 30% cheaper than the originator product (6,7). In addition, the fact that in most Member States pharmacists are not permitted to substitute a biosimilar for an originator product (automatic interchangeability) limits the uptake of biosimilars and prevents potential savings in healthcare expenditure that would help ensure the sustainability of Member States' health systems (j).</p> <p>The EMA's "biosimilar" approach: a pragmatic but timid development. In its draft guideline of May 2013, the EMA stresses the importance of physicochemical and biological characterisation (1, line 83). The EMA notably proposes applying the same requirements on companies that manufacture an originator medicinal product and on companies that manufacture biosimilars by basing the "comparability exercise" on the methods used routinely by companies that manufacture originator medicinal products to assess the impact of changes to the manufacturing process (ICH Q5E guideline).</p> <p>One of the welcome developments in the draft guideline is that the chosen reference medicinal product can be a medicinal product not yet authorised in Europe, provided that it has been authorised in another country that participates in the International Conference on Harmonisation (ICH) (1, line 132, section "3.2. Choice of Reference Product").</p> <p>The EMA also specifies that differences that may represent an advantage by reducing the incidence of adverse reactions (for example, if the biosimilar contains lower levels of impurities or is less immunogenic than the originator) <i>"should be explained, but may not preclude biosimilarity"</i> (1, line 154, section "3.3. Principles of establishing biosimilarity"). The EMA should also include these explanations in the assessment report it produces in support of its recommendation to grant or refuse marketing authorisation.</p> <p>Finally, the EMA states that clinical trials are not necessary in all cases, particularly for</p>	

i- A recent example that illustrates this trend is lipegfilgrastim, a me-too of pegfilgrastim, which was authorised as a "new active substance" on the basis of a full MA dossier in July 2013, rather than with biosimilar status. Like pegfilgrastim, lipegfilgrastim is a pegylated form of filgrastim. The only difference between these two proteins is the nature and position of the bond between the polyethylene glycol (PEG) moiety and filgrastim, the role of PEG being to decrease renal clearance to enable less frequent drug intake than with the non-pegylated form. Both products are supplied as a solution containing 6 mg of filgrastim, have the same authorised indications (reduction in the duration of neutropenia), and their harm-benefit balances appear similar (refs 35,36).

j- Even so, given the exorbitant price of certain biotechnology-derived medicinal products, biosimilar prescribing saved 12 million euros in France in 2012 (ref 6).

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	<p>biotechnology-derived medicinal products with a relatively simple structure, for which physicochemical and biological characterisation and pharmacokinetic and pharmacodynamic studies could predict that the efficacy and adverse reaction profile of the biosimilar product are similar to those of the reference product (1, lines 167 to 172, section “3.3. Principles of establishing biosimilarity”).</p> <p>In another guideline on biosimilar development, the EMA developed the principle of extrapolation to other indications based on the demonstration of similarity in one indication, provided that the mechanism of action is the same (for example, in the case of a monoclonal antibody the mechanism must involve the same active sites of the medicinal product and same receptors of the target cells) and that the harm-benefit balance is similar in the various indications (14).</p>	

3. General comments – Concrete proposals to encourage the development of useful biosimilars

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	<p>The EMA already plays a central role in the development of biosimilars: they can only be authorised through a centralised procedure (6,7).</p> <p>We also suggest that the EMA should use other means to encourage the development of biosimilars that are useful in patient care. Our suggested modifications to the wording of the EMA’s draft guideline are given in appendix 1.</p> <p>Uphold the integrity of the international non-proprietary name (INN) system. For nearly 60 years, the World Health Organization has been assigning international non-proprietary name (INNs) to drugs as part of its role in international standardisation, resulting in the development of a consistent, coherent language. The INN system gives drugs meaningful names, by including informative common stems shared by all INNs of drugs belonging to the same group (k) (26).</p>	

k- The common stem indicates either the drug’s mechanism of action, origin, chemical or biochemical group, or therapeutic class. The WHO INN programme applies the same principles to all pharmaceutical substances, whether they are produced by chemical synthesis or biotechnology (ref 26).

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	<p>The standardised, informative nature of INNs is essential to the organisation of national health systems. Thanks to the INN system, it is possible to identify medicinal products that contain the same drug. The INN is therefore the cornerstone of national lists that group reference medicinal products with their copies (27).</p> <p>Pharmaceutical companies are well aware of this: in order to prevent their new medicinal product from being considered a copy of a previously authorised medicinal product or from being too easily copied, they apply for a specific INN on the grounds of a minor difference (e.g. a slight structural difference such as the product's glycosylation profile) without providing evidence that this alters the its efficacy or adverse effect profile (15).</p> <p>There is no justification for giving a biosimilar a different INN from the originator product unless a difference in its efficacy or its adverse effect profile has been demonstrated. The first part of the name at least, i.e. the name of the pharmaceutical substance, must be the same. INNs are not intended to enable users to identify the method used to manufacture a biotechnology-derived medicinal product.</p> <p>In order to uphold the integrity and intelligibility of the INN system, we urge the EMA, and in particular its Name Review Group (NRG) in charge of assessing the proposed names of medicinal products, to systematically consult the WHO INN programme when authorising a name for a biosimilar (28).</p> <p>Facilitate the authorisation of biosimilars by adopting a responsible policy on access to data. The updates to the EMA's guidelines on biosimilars show that it has learned from the experience acquired in recent years and that it is adopting an increasingly rational approach, based in particular on identifying potential risks before imposing costly clinical trials that would provide only a false sense of security and would delay the market introduction of copies.</p> <p>We would also ask the EMA to apply the same requirements on companies that manufacture originator biotechnology-derived medicinal products as on companies that manufacture biosimilars.</p> <p>In addition, because the EMA archives the marketing applications reviewed by its departments, the EMA is well placed to facilitate access to the data in the MA dossier of originator medicinal products for manufacturers of copies, including data on the manufacturing process (module 3 (quality) of the Common Technical Document), once the period of regulatory data protection has expired. Such a policy would be particularly valuable from a public health perspective: it could reduce variability between originator</p>	

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	<p>products and copies by enabling biosimilars to be manufactured using the same process as the originator.</p> <p>Create a centralised list of groups of biosimilar medicinal products. In accordance with the principle of subsidiarity, it is up to Member States to decide whether or not to allow the substitution of biological medicinal products (interchangeability between an originator product and a biosimilar or between two copies of the same originator product). However, the Member States’ health authorities, health professionals and European patients ought to be able to benefit from the expertise of the EMA and its Biosimilar Medicinal Products Working Party in these matters. In addition, it is part of the EMA’s coordination role to make centralised tools available to Member States, so eliminating the need to replicate the same work in each state.</p> <p>We urge the EMA to set up a non-prescriptive centralised list of groups of biosimilar medicinal products that, on entering the INN, would give access to the names of authorised products (the reference medicinal product and copies with biosimilar status), possibly specifying any differences in excipients known to have a recognised action or effect and in their indications.</p> <p>Monitoring of biosimilars: develop proactive pharmacovigilance. Since the Directive adopted in 2004, Member States are required to ensure the traceability of biotechnology-derived medicinal products (29, Article 102e). And since the new Directive on pharmacovigilance, biosimilars must be systematically included in the centralised list of medicinal products subject to “additional monitoring”. They are identified by a black equilateral triangle pointing downwards, displayed in the package leaflet and the summary of product characteristics (29). Strengthening the surveillance of adverse reactions to all newly-marketed medicinal products, both originator products and copies, is completely justified, to find out more about these reactions and thereby allow prompt decision-making and better protection of patients.</p> <p>Prospective pharmacovigilance (through epidemiological studies for example), as opposed to a wait-and-see approach, would in particular help determine whether certain categories of copies should be singled out for special evaluation, simply because of the manufacturing method employed.</p>	

4. Conclusion

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>More transparency in EMA documents on biosimilars (particularly assessment reports on applications for marketing authorisation or for variations) will be needed in order to convince the public of differences that justify clinical trials to compare medicinal products which, to all intents and purposes, appear to be no more than copies.</p> <p>In practice, for health professionals and patients, after having decided to use a given treatment, the choice between using the original or one of its copies will depend above all on their convenience and cost. Patient safety would be better served if health professionals could concentrate on each patient's clinical situation (e.g. by adapting the dose for patients with impaired renal or hepatic function) rather than having to waste time remembering various brand names and subtle, scientifically unfounded differences in their indications aimed at encouraging the use of the originator product over copies.</p>	

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5. Annex: Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
1.2. Scope Line 59		<p><i>“The Agency’s evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine”</i></p> <p>Comment:</p> <p>We understand that this statement refers to the subsidiarity principle whereby Member States are responsible for the organisation of their health systems.</p> <p>However, health authorities in Member States as well as health professionals and the public rely on the EMA and on the expertise of its Biosimilar Medicinal Products Working Party.</p> <p>Moreover, the EMA should fulfil its coordination role by setting up a non-prescriptive list of groups of biosimilar medicinal products (in which differences in excipients known to have a recognised action or effect and in their indications compared with the reference medicine could be highlighted) (see for example the French “Répertoire des groupes génériques” at http://ansm.sante.fr/Mediatheque/Publications/Listes-et-repertoires-Repertoire-des-medicaments-generiques)</p> <p>Proposed change (if any):</p> <p>Add the text in bold:</p> <p><i>“The Agency’s evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine.</i></p> <p>However, the Agency shall publish detailed information in the assessment reports to substantiate the need to conduct comparative preclinical and clinical tests and the results of these tests so that health authorities in Member States as well as health professionals</p>	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		<p><i>and the public can make informed choices. Moreover, the Agency shall set up a non-prescriptive list of groups of biosimilar medicinal products”.</i></p>	
<p>3.1. Application of the “biosimilar approach” Line 77-78</p>		<p>Comment: In the context of biosimilars, preclinical and clinical tests rarely provide any added value.</p> <p>Proposed change (if any): A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.</p>	
<p>3.1. Application of the “biosimilar approach” Line 86</p>		<p>Comment: The statement <i>“The standard generic approach (...) is in principle not appropriate to biological/biotechnology derived products due to their complexity”</i> is too strong.</p> <p>Article 10(4) of Directive 2001/83/EC consolidated states “Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, (...)” implying that there are cases in which a biological medicinal product which is similar to a reference biological product meets the conditions in the definition of generic medicinal products.</p> <p>Proposed change (if any): “The standard generic approach (...) is in principle in some cases not appropriate to biological/biotechnology derived products due to their complexity”</p>	