

REPORT 1 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-11)
An Abbreviated Approval Pathway for Biosimilars
(Reference Committee K)

EXECUTIVE SUMMARY

Objective. The existence of a biosimilar approval pathway raises several questions related to the requirements for approval, drug efficacy and patient safety, potential cost savings, clinical acceptance, substitution practices, off-label uses, naming and pharmacovigilance, and the educational needs of prescribers. This report reviews the current status of biosimilar implementation in the U.S., examines the preceding issues in this context, and refines current AMA policy in this area.

Methods. English-language reports were selected from a PubMed and Google Scholar search from 2005 to August 1, 2011 using the MeSH terms “biological products/*economics/therapeutic use,” “therapeutic equivalency,” and “drug approval/*legislation,” and using the text terms “biosimilar(s),” or “follow-on biologics.” Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the U.S. Food and Drug Administration (FDA), the United States Adopted Names Council, the World Health Organization, and the European Medicines Agency. Additionally, some verbiage in this report is synonymous with comments previously submitted by the AMA in response to an FDA public hearing regarding the approval pathway for biosimilar and interchangeable biological products held on November 2, 2010.

Results. A two-tiered framework for an abbreviated approval pathway for biological products that are “highly similar” (i.e., biosimilar) to, or further demonstrated to be “interchangeable” with an FDA-licensed biological product has been established in the U.S. General guidance on the specific requirements for a biosimilar application has not been forthcoming from FDA, but is expected by the end of the year. Achieving biosimilarity is a two-part test with products having to demonstrate on a structural basis that they are highly similar and that they exhibit “no clinically meaningful differences” compared with the reference product. The European experience indicates that biosimilarity can be achieved through the use of appropriate preclinical analytical and toxicity studies, product purity and biological activity, results of comparative clinical trials, and monitoring for immunogenicity.

Conclusion. The AMA supports a science-driven, abbreviated approval pathway for biosimilars that prioritizes product efficacy and patient safety and provides FDA with the latitude and necessary authority to determine whether no clinically meaningful differences exist on a case-by-case basis between the proposed biosimilar and reference product in terms of safety, purity, and potency. The European experience indicates that therapeutically equivalent biosimilars can be successfully approved using an abbreviated pathway. Patient safety remains a primary concern including the potential for immunogenicity and the substitution of biosimilar products. General agreement exists that a process must be in place for product-specific safety monitoring of biosimilars and to prevent confusion among prescribers and patients; part of this process will revolve around non-proprietary naming issues. Substitution practices in the outpatient arena should be governed by the same standards that apply to A-rated traditional generic products.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 1-I-11

Subject: An Abbreviated Approval Pathway for Biosimilars

Presented by: Lee R. Morisy, MD, Chair

Referred to: Reference Committee K
(D. Robert McCaffree, MD, Chair)

1 INTRODUCTION

2
3 The Patient Protection and Affordable Care Act contains a subtitle (Biologics Price Competition
4 and Innovation Act of 2009 or BPCI) that establishes an abbreviated approval pathway for so-
5 called “follow-on” biologic drugs or “biosimilars” for existing products whose patent protection
6 has expired.¹ This framework is similar in concept to the Drug Price Competition and Patent Term
7 Restoration Act of 1984 (commonly referred to as the Hatch-Waxman Act), which established an
8 Abbreviated New Drug Application process for generic drugs. Passage of the Hatch-Waxman Act
9 both encouraged the development of new innovator drugs by extending patent rights and
10 established procedures facilitating the approval of low-cost generic drugs. Generic drugs are
11 approved for marketing based on an average bioequivalence approach to assure interchangeability
12 of generic and brand name reference products, thus obviating the need to conduct additional
13 clinical trials.

14
15 The driving force for establishing a science-based abbreviated approval pathway for biosimilars is
16 the recognized benefit, but very high cost of many of these products. However, in contrast to the
17 process for generic drug approval, an abbreviated biosimilar approval pathway will likely require
18 clinical trial data to verify the safety and efficacy of these complex molecules. Therefore,
19 biosimilar development costs are still likely to be substantial and are not expected to generate the
20 same cost savings as small molecule generic drugs. One estimate from the Congressional Budget
21 Office placed the potential cost savings at approximately \$300 billion by 2029.² The European
22 biosimilar market indicates that a 25% cost savings can be expected based on the experience with
23 biosimilar erythropoietin products.³

24
25 Current AMA policy supports the existence of an abbreviated pathway for the approval of
26 biosimilar products, which retains appropriate patent protection for innovator companies but also
27 facilitates the approval of biosimilar products while ensuring patient safety and preserving the
28 authority of physicians to select the specific products their patients receive (Policies H-125.980, D-
29 125.989, AMA Policy Database).

30
31 The existence of a biosimilar approval pathway raises several questions related to the requirements
32 for approval, drug efficacy and patient safety, potential cost savings, clinical acceptance,
33 substitution practices, off-label uses, naming and pharmacovigilance, and the educational needs of
34 prescribers. This report reviews the current status of biosimilar implementation in the U.S.,
35 examines the preceding issues in this context, and refines current AMA policy in this area.

1 METHODS

2
 3 English-language reports were selected from a PubMed and Google Scholar search from 2005 to
 4 September 1, 2011 using the MeSH terms “biological products/*economics/therapeutic use,”
 5 “therapeutic equivalency,” and “drug approval/*legislation,” and using the text terms
 6 “biosimilar(s),” or “follow-on biologics.” Additional articles were identified by manual review of
 7 the references cited in these publications. Further information was obtained from the Internet sites
 8 of the U.S. Food and Drug Administration, the United States Adopted Names Council, the World
 9 Health Organization, and the European Medicines Agency. Additionally, some verbiage in this
 10 report is synonymous with comments previously submitted by the AMA in response to an FDA
 11 public hearing regarding the approval pathway for biosimilar and interchangeable biological
 12 products held on November 2, 2010.

13
 14 BIOLOGICS IN THE U.S.

15
 16 *Biologics--Definition*

17
 18 Biologics comprise a wide range of products including vaccines; blood and blood components;
 19 allergenic extracts and allergen patch tests; somatic cells, human cells or tissue intended for
 20 implantation, transplantation, infusion, or transfer into a human recipient; and recombinant
 21 therapeutic proteins. Biologics are regulated separately from other drugs under federal law. The
 22 Biologics License Application (BLA) is a request for permission to introduce, or deliver for
 23 introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated
 24 under 21 CFR 600–680.

25
 26 Depending on the biologic product category, regulation is under the domain of either the Center for
 27 Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research
 28 (CDER). On June 30, 2003, FDA transferred some of the therapeutic biological products that had
 29 been reviewed and regulated by CBER to CDER.⁴ CBER retains authority over: (1) vaccine and
 30 vaccine associated products; (2) allergen patch tests and allergenic extracts used for the diagnosis
 31 and treatment of allergic diseases; (3) blood, blood components, plasma derived products, blood
 32 substitutes, plasma volume expanders, and polyclonal antibody preparations including radiolabeled
 33 forms, as well as related products such as cell separation devices, blood collection containers and
 34 HIV screening tests that are used to prepare blood products or to ensure the safety of the blood
 35 supply; (4) human cellular and tissue-based products intended for implantation, transplantation,
 36 infusion, or transfer into a human recipient;^a (5) antitoxins, antivenins, and venoms; and, (6) gene
 37 therapy products. Although the FDA has not yet approved any human gene therapy product for
 38 marketing, it regulates products intended to introduce genetic material into the body to correct the
 39 function of faulty, or replace missing, genetic material.

40
 41 Biologic products now regulated by CDER include: (1) monoclonal antibodies for *in vivo* use; (2)
 42 proteins intended for therapeutic use, including enzymes (e.g., thrombolytics), and other novel
 43 proteins including therapeutic proteins derived from plants, animals, or microorganisms and
 44 recombinant versions of these products; (3) immunomodulators (e.g., cytokines, chemokines,
 45 growth factors, and other proteins) acting in an antigen-specific fashion and intended to treat
 46 disease by inhibiting or modifying a pre-existing immune response; and (4) growth factors,
 47 cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter

^a CBER does not regulate the transplantation of vascularized human organ transplants such as kidney, liver, heart, lung or pancreas. The Health Resources Services Administration oversees the transplantation of vascularized human organs.

1 the production of hematopoietic cells *in vivo*. These therapeutic biologic products currently
2 regulated by CDER are the major focus of biosimilar development.

3
4 *Biosimilar Approval Pathway*

5
6 Under the BPCI, a sponsor may seek approval of a “biosimilar” product under new section 351(k)
7 of the Public Health Service Act that establishes an abbreviated approval pathway for biological
8 products that are “highly similar” (i.e., biosimilar) to, or further demonstrated to be
9 “interchangeable” with an FDA-licensed biological product.⁵

10
11 Thus, a two-tiered framework was established as follows:

12
13 Biosimilar products are “highly similar to the reference product notwithstanding minor
14 differences in clinically inactive components” and exhibit “no clinically meaningful differences
15 between the biological product and the reference product in terms of the safety, purity, and
16 potency of the product.”¹ The BPCI Act requires that an application for a proposed biosimilar
17 product include information demonstrating that the proposed product is highly similar to the
18 reference product based on analytical, animal, and/or clinical studies, and that the FDA at its
19 discretion can determine what is necessary to designate such a product as biosimilar (see Table
20 1 for specific statutory requirements).

21
22 In order to meet the higher standard of interchangeability, the sponsor must demonstrate that an
23 interchangeable biologic product “produces the same clinical result as the reference product in
24 any given patient” and the “risk in terms of safety or diminished efficacy of alternating or
25 switching between use of the biological product [biosimilar] and the reference product
26 [originator/brand] is not greater than the risk of using the reference product without such
27 alteration or switch.” Furthermore, the BPCI states that “the [interchangeable] biological
28 product may be substituted for the reference product without the intervention of the health care
29 provider who prescribed the reference product.”

30
31 *FDA Implementation of the BPCI Act*

32
33 General guidance on the specific requirements for a biosimilar application has not been
34 forthcoming from FDA, but is expected by the end of the year. Achieving biosimilarity is a two-
35 part test:

36
37 First, the biosimilar must be “highly similar.” While small molecule drugs and their generic
38 equivalents are chemically synthesized, therapeutic biologics are synthesized by living cells or
39 organisms and are considerably larger in size and more complex in structure. Therapeutic
40 biologics are developed by identifying and cloning the genetic sequence encoding the active
41 protein, inserting the cloned DNA sequence into a unique living cell line that will carry out
42 translation of the biologic protein, expanding and maintaining the cultured cells to support large-
43 scale biologic protein production,^β harvesting and purifying the biologic product, and developing a
44 stable dosage form. In order to be therapeutically active, the proteins must exhibit a specific set of
45 structural features, including their primary amino acid sequence, secondary post-translational
46 modifications (e.g., glycosylation), and tertiary folding native to the specific protein structure.
47 Because biologics are generated from a unique cell line and are harvested through a complex and

^β Approximately 90% of currently approved biologic products are produced using cultured E.coli, yeast, or mammalian cell (e.g., chinese hamster ovary cells) lines.

1 sensitive process, any change to this process could affect the key structural features of the final
 2 product, potentially modifying its pharmacologic effects or immunogenicity.

3
 4 Second, the biosimilar must exhibit “no clinically meaningful differences” compared with the
 5 reference product. This demonstration will require some combination of comparative analytic
 6 characterization, *in vitro* pharmacologic and/or toxicologic assessments and functional assays,
 7 human pharmacokinetic equivalence determinations, and a randomized comparative clinical
 8 trial(s). Meeting the “highly similar” standard may permit some reliance on what is known about
 9 the safety and effectiveness of the reference product (extrapolation), but this should be allowed
 10 only when scientifically justified and the mechanism of action is established.

11
 12 The FDA has indicated that review and approval of a biosimilar application will be a risk-based
 13 exercise relying on the totality of the evidence.⁶ Under this scenario, the amount of clinical data
 14 required will likely be influenced by the complexity of the product, its formulation, and the
 15 intended indications or clinical population (e.g., oncology versus rheumatology). In the meantime,
 16 FDA is not precluded from approving biosimilar or interchangeable products in the absence of
 17 industry guidance. The Agency also is currently negotiating a user fee structure with the industry
 18 for biosimilar applications.

19
 20 *Comparability versus Highly Similar*

21
 22 Pharmaceutical companies that develop and market therapeutic biologics sometimes make
 23 manufacturing-related changes. The International Conference on Harmonization Guideline 5 on
 24 comparability (Quality of Biotechnological Products) notes that after manufacturing changes, the
 25 new product needs to be compared against the old product in a step wise process from chemical-
 26 physical comparability and other analytical/pharmacologic studies to clinical studies, if needed.⁷
 27 After changes in manufacturing, the demonstration of comparability does not necessarily mean that
 28 the quality attributes of the pre-change and post-change products are identical, but that they are
 29 highly similar. Thus, a process already is in place to compare biologics emerging from a revised
 30 production process with an existing product.

31
 32 During the public debate on biosimilars, it has often been stated that due to the complexity of the
 33 manufacturing process for biologics and use of unique cell lines, another manufacturer cannot
 34 create an exact copy. Despite the complexity of biologic production, innovator companies that
 35 changed one or more elements in their manufacturing process have been able to demonstrate
 36 largely through analytic techniques that the resulting product is “comparable” to the original
 37 product. For example, Rituxan®, Herceptin®, and Enbrel® each underwent post-approval changes
 38 in their manufacturing processes (e.g., manufacturing site or cell line) but were not required to
 39 conduct new clinical efficacy trials for each indication.⁸ On the other hand, in some cases,
 40 additional clinical trials have been required to demonstrate that the “new” product retains the safety
 41 and efficacy profile of the original product (e.g., Aranesp®, Epogen®).⁸ When the initial
 42 manufacturing process for Epogen® was replaced with what was thought to represent a more
 43 efficient process, subsequent clinical trials failed to demonstrate comparable efficacy with the
 44 previous product and the new manufacturing process was abandoned.

45
 46 EUROPEAN EXPERIENCE WITH BIOSIMILARS

47
 48 While the abbreviated pathway for approval of biologics is new and as yet untested in the U.S, the
 49 European Union under the aegis of the European Medicines Agency (EMA) has had general
 50 guidance in place since 2005 and has published a number of specific guidance documents on non-
 51 clinical, clinical, and quality issues for biosimilars.⁹⁻¹¹ In Europe, biosimilarity is established by an

1 appropriate comparability exercise that examines preclinical analytical and toxicity studies, the
2 product's purity, physicochemical properties and biological activity, results of comparative clinical
3 trials (usually), and monitoring for immunogenicity. The EMA also has issued guidelines on
4 specific biologic classes, including insulin, somatropin, granulocyte-colony stimulating factor, a
5 draft guidance on monoclonal antibodies, and concept papers on low-molecular weight heparins
6 and interferon alfa. European regulations have no equivalent to the "interchangeable" designation
7 in the BPCI and European countries currently do not allow automatic substitution of a biosimilar.
8 Fourteen biosimilars of three reference products (erythropoietin, filgrastim, somatropin) have been
9 approved by the EMA since 2006 (Table 2).¹²

10 PATIENT SAFETY ISSUES

11 *Immunogenicity*

12
13 Because an exact copy of a biologic cannot be made with current technology, patient safety is a
14 primary concern including the potential for immunogenicity and the substitution of biosimilar
15 products. However, immunogenicity issues are not unique to biosimilars but rather reflect the fact
16 that all biologics have the potential to be immunogenic and human responses cannot be predicted
17 by animal studies. Risk factors for human immunogenic responses to a biologic product include
18 the structure of the biologic, use of the subcutaneous rather than intravenous route of
19 administration, the patient's genotype and immune status, and the duration of exposure. Therefore,
20 risk mitigation strategies for biosimilars should be no different than that of originator products. All
21 biologic products require a sufficient period of human exposure during clinical trials and vigilant
22 post marketing surveillance.
23
24

25 *Pharmacovigilance and Naming*

26
27 General agreement exists that a process must be in place for product-specific safety monitoring and
28 recalls of biosimilars, and to prevent confusion among prescribers and patients. Part of this process
29 involves the name of the drug or biologic. In the U.S., nonproprietary names are issued by the
30 United States Adopted Names (USAN) Council, a tripartite organization headquartered at the
31 AMA and also sponsored by the American Pharmacists Association and the United States
32 Pharmacopeia.¹³ In addition, the FDA cooperates with and is represented on the USAN Council.
33 Using established rules of nomenclature based on chemical structure and class, the nonproprietary
34 (USAN) name eventually adopted by the Council is synonymous with the "generic" name of the
35 drug product. Adopted USANs are submitted to the World Health Organization's International
36 Nonproprietary Name (INN) expert panel for deliberation (including linguistic evaluation) and
37 approval in order to harmonize drug nomenclature internationally.
38
39

40 The naming of biologics is complicated by three issues.

41
42 (1) Several nonproprietary names for biologics were assigned 20 to 30 years ago in the absence of a
43 biosimilar framework. For example several interferons are marketed in the U.S. Interferon was
44 published as an INN in 1962 and the name was revised in the 1980s when human interferon and its
45 variations *alfa*, *beta* and *gamma* were produced by recombinant DNA technology.¹⁴ Arabic
46 numbers are used to distinguish subspecies that differ in primary amino acid sequence but are still
47 considered to be in one of the primary groups, and small lower case numbers are used to subdivide
48 such groups further on the basis of less significant differences, such as post-translational
49 modifications, including glycosylation (e.g., interferon alfa-1a, interferon alfa-2b, interferon alfa-
50 n3, interferon-alfacon-1). Pegylated versions carry the "Peg" prefix. Similar examples exist for
51 botulinum toxin (A or B) and epoetin (alfa, beta, zeta, Darbepoetin).

1 (2) The advent of a biosimilar approval pathway in the European Union prompted the need to
2 distinguish different products. The INN program coordinated by the WHO instructed that
3 biosimilars should have unique brand names but recommended against unique INNs for non-
4 glycosylated products. For the latter, Greek letters are used to indicate differences in glycosylation
5 (See Table 2).
6

7 (3) The BPCI is silent on the topic of naming and FDA Guidance is currently lacking on the
8 requirement for the U.S. abbreviated pathway for biosimilar approval. Up to this point, the USAN
9 Council has harmonized the naming of biologics with the WHO INN Program. Because the BPCI
10 is silent on naming, the USAN Council will have to rely on the FDA to make a determination
11 regarding unique naming conventions for biosimilars in the U.S.
12

13 It also has been argued that assigning unique names to biosimilars would assist in identifying
14 adverse events associated with specific products. However, the USAN (or INN) is only one of
15 several components that together constitute the surveillance system for marketed drugs and
16 biologics, including the product or brand name, the manufacturer, a unique NDC number for each
17 product (even when it is a multisource product) and lot number. The existing system relies on a
18 combination of these markers for initiating recalls linked to a problem with a specific product and
19 has generally worked effectively. For example, in September 2010, there was a recall of Epogen®
20 and Procrit® which was due to a lot-specific problem across multiple manufacturing sites.¹⁵ If the
21 USAN was the seminal unit for analysis, a much larger recall of the entire product off the
22 marketplace would have occurred, not just limited to those specific lots in which the complications
23 were noted. It also is possible that unique naming of biosimilars may introduce confusion by
24 implying that such products are not clinically comparable. Conceptually, biosimilar products that
25 are deemed interchangeable by the FDA should have the same USAN, while products that are not
26 interchangeable but merely biosimilar could be distinguished in some minor way through use of
27 prefixes, Arabic numerals, or Greek letters added to the USAN stem.
28

29 *Substitution*

30
31 Although the BPCI provides that “interchangeable products may be substituted for the reference
32 product by a pharmacist without the intervention of the prescribing health care provider,” the AMA
33 believes that the congressional intent was to treat biosimilars categorized as interchangeable in the
34 same way that traditional A-rated generic medications are managed. With interchangeable A-rated
35 generic medications, physicians in every state have the authority to designate which product
36 (branded or generic) is dispensed. Only when the prescriber is silent on the issue of substitution or
37 proactively authorizes substitution can the pharmacist act independently to dispense A-rated
38 generic drugs.
39

40 Congress did not intend to pre-empt state laws authorizing physicians to make such a designation
41 for biosimilars. Furthermore, physicians cannot be compelled to prescribe a reference biological
42 product, a biosimilar, or an interchangeable biological product. An alternative interpretation of the
43 statute would be inconsistent with basic rules of construction governing preemption and would
44 require a very high regulatory approval bar for deeming a biosimilar as interchangeable given the
45 potential safety risks and medical consequences associated with substitutions between reference
46 biological products and biosimilars. Automatic substitution by a pharmacist in the outpatient
47 setting should not be permissible with biosimilars that do not meet the regulatory standard for
48 interchangeability. On the other hand, pharmacy and therapeutics committees acting under an
49 established formulary system will evaluate, appraise, and select from among the numerous
50 available drug and biological products those that are considered most useful in patient care in the
51 inpatient setting.
52

1 *Off-Label Use*
2

3 It is not established whether the FDA will allow clinical data on the use of a biosimilar in one
4 condition to be extrapolated to all labeled indications for the reference product where the
5 mechanism of action is the same. Thus, the clinical decision to use a biosimilar off-label will be
6 somewhat more challenging than with small molecule generic drugs.
7

8 CONCLUSION
9

10 The AMA supports a science-driven, abbreviated approval pathway for biosimilars that prioritizes
11 product efficacy and patient safety and provides FDA with the latitude and necessary authority to
12 determine whether no clinically meaningful differences exist on a case-by-case basis between the
13 proposed biosimilar and reference product in terms of safety, purity, and potency. A substantially
14 higher hurdle should exist with respect to the data that is required by the FDA for the designation
15 of a biosimilar product as interchangeable. The European experience indicates that biosimilars can
16 be successfully approved using an abbreviated pathway and that they can be therapeutically
17 equivalent in safety and efficacy.
18

19 It is important that the appropriate balance be struck in implementing the BPCI so that the
20 development of biosimilars is encouraged, but regulatory barriers do not unnecessarily impede
21 biosimilar development. The AMA supports an approach that provides exclusivity and patent
22 protections that promote innovation but does not unduly inhibit the competition needed to bring
23 biosimilar products to the market and reduce escalating costs.
24

25 It is important to recognize that the current substitution practices for small molecule generics are
26 regulated at the state level by Pharmacy Practice Acts, all of which permit the pharmacist to
27 substitute a generic equivalent if the prescriber consents to substitution on the prescription (e.g.,
28 may substitute) or remains silent. In each state, however, a mechanism also exists for the
29 prescriber to dictate which product is dispensed (i.e., “dispense as written,” “do not substitute,”
30 etc.). The same situation should apply to biosimilars. Because these products are injectable
31 formulations and many are administered in the hospital or affiliated care centers, Pharmacy and
32 Therapeutics Committees and third party payers will play prominent roles in determining patterns
33 of use in these settings.
34

35 Based on experiences with small molecule A-rated generic drugs, education of physicians and
36 patients on biosimilars will be needed. Despite substantial evidence to the contrary, some
37 prescribers believe that generic drugs are not therapeutically equivalent to the brand name product,
38 especially for narrow therapeutic index drugs. Biosimilars represent an even more complicated
39 scenario, although the extent to which this issue becomes relevant in the outpatient arena remains
40 to be seen. As the FDA develops the necessary guidance to implement the BPCI, the Agency
41 should develop a strategic plan and allocate significant resources to ensure that physicians
42 understand the distinctions between biosimilar products that are merely considered comparable,
43 and those that are deemed interchangeable. The strategic plan should include regular interaction
44 and feedback from medical specialty societies, at a minimum, and include components that
45 facilitate the establishment of partnerships between the FDA, industry, and physicians that promote
46 effective communication on drug and biological product concerns and issues.
47

48 RECOMMENDATIONS
49

50 The Council on Science and Public Health recommends that the following statements be adopted
51 and the remainder of the report be filed:

- 1 1. That Policy H-125.980 “Follow-on Biologic Medications” be renamed “Abbreviated Pathway
2 for Biosimilar Approval” and be amended by insertion and deletion as follows:
3

4 ~~AMA policy is that pharmaceutical companies should be allowed to make follow-on biologic~~
5 ~~biosimilar medications available to physicians and their patients in a reasonable period of time~~
6 ~~with a reasonably predictable pathway to bring them to market., and Our AMA will advocate~~
7 ~~for appropriate FDA Guidance and implementation of the Biologics Price and Competition Act~~
8 ~~of 2009 enactment of federal law that would establish a follow-on biologic to be allowed on the~~
9 ~~market, with two guiding principles: 1) a reasonable time frame for US Food and Drug~~
10 ~~Administration exclusivity and patent expiration with a that: 1) includes a straightforward~~
11 ~~regulatory process for an abbreviated approval pathway for biosimilars; follow-on biologic~~
12 ~~competitors to be brought to market, and 2) places appropriate emphasis on the protection of~~
13 ~~patient safety in both the original branded products and all biosimilar follow-on products that~~
14 ~~are brought to market; and 3) includes planning by the FDA and the allocation of sufficient~~
15 ~~resources to ensure that physicians understand the distinctions between biosimilar products that~~
16 ~~are considered highly similar, and those that are deemed interchangeable.~~
17

- 18 2. That Policy D-125.989 “Substitution of Biosimilar Medicines and Related Medical Products”
19 be amended by insertion and deletion to read as follows:
20

21 ~~Our AMA urges that State Pharmacy Practice Acts and substitution practices for biosimilars in~~
22 ~~the outpatient arena: (1) mirror the current practices for A-rated generic drugs by preserving~~
23 ~~the right of physicians and other prescribers to designate which product is dispensed to their~~
24 ~~patients; (2) limits the authority of pharmacists to automatically substitute only those biosimilar~~
25 ~~products that are deemed interchangeable by the FDA will: (1) monitor legislative and~~
26 ~~regulatory proposals that to establish a pathway to approve follow-on biological products and~~
27 ~~analyze these proposals to ensure that physicians retain the authority to select the specific~~
28 ~~products their patients will receive; and (2) work with the US Food and Drug Administration~~
29 ~~and other scientific and clinical organizations to ensure that any legislation that establishes an~~
30 ~~approval pathway for follow-on biological products prohibits the automatic substitution of~~
31 ~~biosimilar medicines without the consent of the patient’s treating physician.~~

Fiscal Note: Less than \$500

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Table 1. Required Information for U.S. FDA Biosimilar Application¹

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| <p>(I) The biological product is biosimilar to a reference product based upon data derived from--</p> <ul style="list-style-type: none">• analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;• animal studies (including the assessment of toxicity); and,• a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product; <p>(II) The biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product;</p> <p>(III) The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product;</p> <p>(IV) The route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product; and</p> <p>(V) The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.</p> |
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Table 2. Biosimilars Approved in Europe

Name	Active Substance	Therapeutic Area	Date of Authorization	Status
Abseamed	Epoetin alfa	Kidney Failure, Chronic Anemia Cancer	8/28/2007	Authorized
Binocrit	Epoetin alfa	Kidney Failure, Chronic Anemia	8/28/2007	Authorized
Biograstim	Filgrastim	Hematopoietic Stem Cell Transplantation Neutropenia Cancer	9/15/2008	Authorized
Epoetin alfa Hexal	Epoetin alfa	Kidney Failure, Chronic Anemia Cancer	8/28/2007	Authorized
Filgrastim Hexal	Filgrastim	Neutropenia Cancer Hematopoietic Stem Cell Transplantation	2/6/2009	Authorized
Filgrastim Ratiopharm	Filgrastim	Neutropenia Hematopoietic Stem Cell Transplantation Cancer	9/15/2008	Withdrawn
Nivestim	Filgrastim	Hematopoietic Stem Cell Transplantation Cancer Neutropenia	6/8/2010	Authorized
Omnitrope	Somatropin	Turner Syndrome Dwarfism, Pituitary Prader-Willi Syndrome	4/12/2006	Authorized
Ratiograstim	Filgrastim	Neutropenia Cancer Hematopoietic Stem Cell Transplantation	9/15/2008	Authorized
Retacrit	Epoetin zeta	Cancer Anemia Kidney Failure, Chronic Blood Transfusion, Autologous	12/18/2007	Authorized
Silapo	Epoetin zeta	Anemia Blood Transfusion, Autologous Cancer Kidney Failure, Chronic	12/18/2007	Authorized
Tevagrastim	Filgrastim	Neutropenia Cancer Hematopoietic Stem Cell Transplantation	9/15/2008	Authorized
Valtropin	Somatropin	Dwarfism, Pituitary Turner Syndrome	4/24/2006	Authorized
Zarzio	Filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	2/6/2009	Authorized