HOUSE OF REPRESENTATIVES
FINAL BILL ANALYSIS

BILL #:	CS/CS/HB 365	**FINAL HOUSE FLOOR ACTION:**	
SPONSOR(S):	Health & Human Services Committee; Health Quality Subcommittee; Hudson; Jones, S. and others	116 **Y's**	1 **N's**
COMPANION BILLS:	(CS/CS/SB 732)	**GOVERNOR'S ACTION:**	Approved

SUMMARY ANALYSIS

CS/CS/HB 365 passed the House on April 17, 2013, and subsequently passed the Senate on April 30, 2013. The bill provides for the regulation of biosimilar biological products when they are substituted for other biological products.

A biological product is a virus, therapeutic serum, vaccine, protein, blood component, or other product used to prevent, treat, or cure a disease or condition in human beings. A biological product is made by using a living system or organism to essentially "grow" or create the product, which causes variation in composition of the biological product. This differs from the manufacture of a chemical drug, which is created by combining various chemicals in an easily replicated manner to produce the desired therapeutic effect.

A biosimilar biological product is highly similar to another biological product, known as a reference product, with minor differences in clinically inactive components. There are no clinically meaningful differences between a biosimilar biological product and its reference product that impact the safety, purity, and potency of the product. Biosimilar biological products have been approved and sold in Europe since 2006, as well as in other parts of the world. There is no biosimilar biological product market currently in the United States.

The Biologics Price Competition and Innovation Act (BPCIA) was enacted as part of the Patient Protection and Affordable Care Act on March 23, 2010. The BPCIA creates a pathway for approval of biosimilar biological products by the federal Food and Drug Administration (FDA), which, if determined to be interchangeable, can be substituted for more expensive reference products and thereby lower health care costs.

CS/CS/HB 365 permits Florida pharmacists to substitute biosimilar biological products for prescribed biological products, unless the prescriber requests the prescribed biological product not be substituted or the patient rejects the substitution. Substitution is only permitted if the biological product to be substituted appears on a list developed and maintained by the FDA as biosimilar to and interchangeable with the prescribed biological product. This list must be maintained on the Board of Pharmacy's public website.

The bill also includes certain recordkeeping and patient notification requirements.

The bill appears to have an undetermined, positive fiscal impact on state and local governments.

The bill was approved by the Governor on May 31, 2013, ch. 2013-102, L.O.F., and will become effective on July 1, 2013.

I. SUBSTANTIVE INFORMATION

A. EFFECT OF CHANGES:

Present Situation

"Brand Name" Chemical Drugs and Generic Chemical Drugs

A "brand name" chemical drug is manufactured with simple chemical ingredients that have uniform, predictable structures which are easy to characterize and replicate. The potency of a "brand name" chemical drug is determined by a defined chemical process. A generic chemical drug has the identical active substance and biological effect as its "brand name" counterpart. A generic chemical drug differs from a "brand name" chemical drug by inactive ingredients contained in the chemical structure and the rate and extent of absorption by the human body.

The Federal Food, Drug and Cosmetic Act, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act), established the Abbreviated New Drug Application process, creating a pathway for approval of generic medications, primarily for chemical drugs.[1] Since 1984, the federal Food and Drug Administration (FDA) has approved more than 8,000 generic drugs, which has resulted in hundreds of billions of dollars in cost savings to consumers.[2] In 2009, almost 75% of pharmaceutical prescriptions dispensed in the U.S. were generic medications.[3]

Biological Products and Biosimilar Biological Products

A biological product (biologic), in contrast to a chemical drug, is a large and complex protein, generally produced using a living system or organism.[4] It is heterogeneous and difficult to characterize. The effectiveness of a biologic is expressed in a biological system, meaning the biologic interacts with the human body, or an animal's body, to produce the desired effect. A biologic can be manufactured through a biotechnological process, derived from natural sources, or completely synthesized in a laboratory setting.[5]

A biosimilar biological product (biosimilar) has a similar, but not identical, active substance to another biologic. The biological activity of a biosimilar may vary as compared to another biologic. Because of the variable nature of a biosimilar, it is critical to identify the differences and determine which differences matter clinically. The determination of clinically meaningful differences between a biologic and its biosimilar can be exhibited through animal studies that measure toxicity, clinical studies on humans, and other scientifically accepted metrics.

In 2011, roughly 25% of the $320 billion spent on drugs in the U.S., was spent on biologics.[6] Each year, patients in the U.S. receive over 200 million vaccinations, 29 million transfusions of blood and

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[1] The Federal Food, Drug and Cosmetic Act, s. 505(b)(2); 21 U.S.C. 355(b)(2).
[2] U.S. Dept. of Health and Human Services, Food and Drug Administration, Regulatory Information, *Fact Sheet: New "Biosimilars" User Fees Will Enhance Americans' Access to Alternatives to Biologic Drugs*, July 16, 2012, available at www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm311121.htm. (last viewed on May 7, 2013).
[3] Kozlowski, S., Woodcock, J., et al., *Developing the Nation's Biosimilar Program*, N Engl J Med 365:5, 385 (August 4, 2011).
[4] U.S. Dept. of Health and Human Services, Food and Drug Administration, Sherman, M.D., Rachel, *Biosimilar Biological Products-Biosimilar Guidance Webinar*, February 15, 2012, slide 3, available at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm292463.pdf.
[5] Id.
[6] IMS Health, *Top Therapeutic Classes by U.S. Spending-2011*, available at www.imshealth.com/portal/site/ims/menuitem.5ad1c081663fdf9b41d84b903208c22a/?vgnextoid=fbc65890d33ee210VgnVCM10000071812ca2RCRD&vgnextfmt=default

blood components, and 1.6 million transplants of musculoskeletal tissue, all of which require the use of biologics.[7]

There is no existing market for biosimilars currently in the U.S.[8] Twelve biologics with global sales exceeding $67 billion will lose patent protection by 2020, and will be open to biosimilar competition.[9] By 2015, sales of biosimilars worldwide are expected to reach between $1.9 billion and $2.6 billion, up from $378 million in the first half of 2011.[10] The U.S. is forecast to be the largest opportunity for biosimilar sales by 2020, with a market value between $11 billion and $25 billion, which represents a 4% to 10% share of the total biologics market.[11] Biosimilars are forecast to comprise up to 50% of the off-patent biological market by 2020, with an assumed price discount between 20% and 30% when compared to biologics.[12]

The U.S. Federal Trade Commission predicts that the availability of biosimilars will significantly reduce the cost of biologics and increase their accessibility.[13]

The Biologics Price Competition and Innovation Act of 2010

The Biologics Price Competition and Innovation Act (BPCIA) was enacted as part of the Patient Protection and Affordable Care Act on March 23, 2010.[14] The BPCIA amends the Public Health Service Act and other statutes to create an abbreviated licensure pathway for biologics demonstrated to be biosimilar to or interchangeable with a reference biologic.[15] The BPCIA establishes the requirements for an application for a proposed biosimilar and an application for a proposed interchangeable product.[16]

The application must include information demonstrating biosimilarity, based on data derived from, among other things, "analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,"[17] animal studies that include an assessment of toxicity,[18] and a clinical study or studies sufficient to establish safety, purity, and potency of the biosimilar.[19] Biosimilarity means that a biologic is highly similar to the reference biologic, even when considering the differences in clinically inactive components, and that there are no clinically meaningful differences between the biologic and the reference biologic in terms of safety, purity, and potency.[20]

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[7] U.S. Dept. of Health and Human Services, Food and Drug Administration, *About FDA*, available at www.fda.gov/AboutFDA/CentersOffices/ucm193951.htm. (last viewed on May 7, 2013).
[8] One product exists in the U.S. that may meet the current definition of "biosimilar" contained in the BPCIA. Omnitrope, a form of synthetic human growth hormone used to treat long-term growth failure in children and adult onset growth deficiency, and manufactured by Sandoz, was approved for sale in the U.S. under a special ruling from FDA in 2007.
[9] Genetics and Biosimilar Initiative, *US$67 billion worth of biosimilar patents expiring before 2020*, June 29, 2012 (on file with the Health Quality subcommittee staff).
[10] IMS Health, *Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape*, December 2011, page 1, available at www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Documents/Biosimilars_White_Paper.pdf.
[11] Id. at pages 3 and 6.
[12] Id. at page 6.
[13] U.S. Federal Trade Commission, *Emerging health care issues: follow-on biologic drug competition*, 2009, available at www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.
[14] PPACA (Pub. L. 111-148), title VII, subtitle A, §§7001 to 7003.
[15] A reference product is an existing biological product against which another biological product is compared to determine biosimilarity and interchangeability.
[16] S. 351(k) of the PHS Act (42 U.S.C. 262(k)).
[17] 42 U.S.C. §262(k)(2)(A)(i)(I)(aa).
[18] 42 U.S.C. §262(k)(2)(A)(i)(I)(bb).
[19] 42 U.S.C. §262(k)(2)(A)(i)(I)(cc).
[20] 42 U.S.C. §262(i)(2).

The FDA will use a totality-of-the evidence approach in reviewing biosimilar applications, meaning all available data and information submitted in support of biosimilarity and the proposed biosimilar will be evaluated before a determination is made regarding biosimilarity and interchangeability.[21] To meet the standard of interchangeability, an applicant must provide sufficient information to demonstrate biosimilarity, and also demonstrate that the biologic can be expected to produce the same clinical result as the reference product in any given patient. In addition, an applicant must demonstrate that, if the biologic is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biosimilar and the reference product is not greater than the risk of using the reference product without an alternation or switch in products.[22]

Pending FDA Rules on Biosimilars and Interchangeability

On February 9, 2012, the FDA issued three draft guidance documents regarding biosimilars and interchangeability. The documents, referenced as *Guidance for Industry*, answered questions regarding implementation of the BPCIA[23] and detailed scientific and quality considerations to be addressed in demonstrating biosimilarity.[24] The guidance documents have not yet been finalized by the FDA.

The Federal Food, Drug, and Cosmetic Act, as amended by the Biosimilar User Fee Act of 2012 (BsUFA), authorizes the FDA to assess and collect fees for biosimilars from October 2012 through September 2017.[25] The FDA dedicates these fees to expediting the review process for approval of biosimilars. The FDA has determined that biosimilars represent an important public health benefit, with the potential to offer life-saving or life-altering benefits at reduced cost to the patient. According to the FDA, BsUFA facilitates the development of safe and effective biosimilars for the American public.[26]

The FDA is currently meeting with sponsors of proposed biosimilars, receiving 50 requests for meetings and fulfilling 37 of those requests.[27] In addition, the FDA has approved 14 Investigative New Drug applications (INDs) for clinical development of proposed biosimilars.[28] The FDA has also noted that they are in active discussions with many sponsors at the pre-IND stage, indicating further clinical development of biosimilars in the near future.[29] The FDA also does not expect to diverge greatly from

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[21] U.S. Dept. of Health and Human Services, Food and Drug Administration, *Biosimilars Fact Sheet: Issuance of Draft Guidances on Biosimilar Products*, available at www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm291197.htm .

[22] 42 U.S.C. §262(i)(3).

[23] U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, *Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, February 2012, available at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm259797.htm. (last viewed on May 7, 2013).

[24] U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, *Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* and *Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*, February 2012, both documents available at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm. (last viewed on May 7, 2013).

[25] Biosimilar User Fee Act of 2012, Pub. L. 112-144, title IV, ss. 401-408 (21 U.S.C. 379j-51 through 53).

[26] U.S. Dept. of Health and Human Services, Food and Drug Administration, *For Industry: Biosimilar User Fee Act (BsUFA)*, available at www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm. (last viewed on May 7, 2013).

[27] Comments of Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration, at Bloomberg State of Health Care 2013 Summit, February 11, 2013 (video available at www.bloomberg.com/video/fda-sees-more-breakthrough-drugs-woodcock-says-~Obd9FUMQ7qWka0CfYq3dg.html) (last viewed on May 7, 2013).

[28] Id.

[29] Id.

the policies established by the European Medicines Agency for approval of biosimilars for sale in the European Union and other specific countries.[30]

Biosimilars in Europe

The European Medicines Agency (EMA) is a decentralized agency of the European Union (EU), located in London, England. It is the scientific body of the European Commission (EC).[31] The EMA's primary responsibility is the "protection and promotion of public and animal health through the evaluation and supervision of medicines for human and veterinary use."[32]

The EMA is responsible for the scientific evaluation of applications for EU marketing authorizations for human and veterinary medicines governed by the "centralised procedure."[33] Under the "centralised procedure," pharmaceutical companies submit a single marketing-authorization application to the EMA.[34] Medicines are then approved by the EC based on the positive scientific opinion of the EMA and its expert committee, the Committee on Human Medicinal Products.[35] Once granted by the EC, a centralized marketing authorization is valid in all EU Member States, as well as Iceland, Liechtenstein and Norway.[36] By law, a company can only market a medicine once it has received a marketing authorization.[37]

The "centralised procedure" is mandatory for:

- Human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases;
- Veterinary medicines for use as growth or yield enhancers;
- Medicines derived from biotechnology processes, such as genetic engineering;
- Advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines; and
- Officially designated medicines used for rare human diseases.[38]

Biologics and biosimilars fall within the mandatory "centralised procedure" for approval and marketing within the EU and other specified European countries.

In 2003, the EMA created a new pathway for approving biosimilar medicines.[39] The central feature of the evaluation process is the comparison of the biosimilar with its reference product to show that there are no significant differences between them.[40] The EMA further explains the evaluation process to determine biosimilarity, which is very similar to the proposed pathway process in the U.S.:

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[30] Id.
[31] European Generic Medicines Association, *EGA FACT SHEET on generic medicines, FAQs about Biosimilar Medicines*, July 2011, available at www.egagenerics.com/index.php/biosimilar-medicines/faq-on-biosimilars. (last viewed on May 7, 2013).
[32] European Medicines Agency, *What we do*, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42. (last viewed on May 7, 2013)
[33] Id.
[34] Id.
[35] *See supra*, FN 23.
[36] Id.
[37] Id.
[38] European Medicines Agency, *Central authorization of medicines*, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47. (last viewed on May 7, 2013).
[39] European Medicines Agency, *Questions and answers on biosimilar medicines (similar biological medicinal products)*, available at www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf. (last viewed on May 7, 2013).
[40] *See supra*, FN 38.

> The relevant regulatory authority applies stringent criteria in their evaluation of the studies comparing the quality, safety and effectiveness of the two medicines. The studies on quality include comprehensive comparisons of the structure and biological activity of their active substances, while the studies on safety and effectiveness should show that there are no significant differences in their benefits and risks, including the risk of immune reactions.

One critical difference between the approval process established by the EMA and the proposed pathway outlined by the FDA is that the EMA does not make recommendations on whether a biosimilar can be used interchangeably with its reference product.[41] The FDA will determine interchangeability, which in turn will determine whether or not a biosimilar can be substituted for a prescription biologic by a pharmacist.

The EMA published general guidelines on biosimilars in 2005 and approved its first biosimilar in 2006.[42] As of February 2012, the EMA had approved 14 biosimilar products,[43] with reference products including filgrastim,[44] epoetin,[45] and somatropin.[46]

Pharmacist Substitution in Florida

In general, a pharmacist in Florida is required to substitute a less expensive generic medication for a prescribed brand name medication.[47] The presenter of the prescription may specifically request the brand name medication.[48] Also, the prescriber may prevent substitution by indicating the brand name medication is "medically necessary" in writing, orally, or, in the case of an electronic transmission of the prescription, by making an overt act to indicate the brand name medication is "medically necessary."[49] The pharmacist must inform the presenter of the prescription that a substitution has been made and advise the presenter that he or she may refuse the substitution and request the brand name medication.[50]

Each pharmacy is required to establish a formulary of brand name medications and generic medications which, if selected as the drug product of choice, pose no threat to patient health and safety.[51] The Board of Pharmacy and the Board of Medicine are required to establish a formulary which lists brand name medications and generic medications that are determined to be clinically different so as to be biologically and therapeutically inequivalent.[52] Substitution of the drugs included in this formulary would pose a threat to patient health and safety.[53] The boards are required to distribute the formulary to licensed and registered pharmacies and pharmacists.[54] Each board that regulates practitioners licensed by the state to prescribe medications must incorporate the formulary into its

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[41] *See supra*, FN 39.
[42] European Medicines Agency, *Guideline on similar biological medicinal products*, 2005, available at www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf .
[43] *See supra*, FN 4 at slide 23.
[44] A white blood cell booster used to reduce infection risks in persons receiving strong chemotherapy treatment.
[45] Also known as EPO, it treats anemia caused by chronic kidney disease in dialysis patients by promoting red blood cell production.
[46] Synthetic human growth hormone (hGH).
[47] S. 465.025(2), F.S.
[48] Id.
[49] Id.
[50] S. 465.025(3)(a), F.S.; *see also* Rule 64B-16-27.530, F.A.C.
[51] S. 465.025(5), F.S.; *see also* Rule 64B-16.27.520, F.A.C.
[52] S. 465.025(6), F.S.; *see also* Rule 64B-16.27.500, F.A.C.
[53] Id.
[54] S. 465.025(6)(b), F.S.

rules.[55] No pharmacist may substitute a generic medication for a brand name medication if either medication is included in the formulary.[56]

There is no provision in Florida law regarding substitution for biosimilars.

Effect of Changes

The bill allows a pharmacist to substitute a biosimilar for a prescribed biologic if the biosimilar has been determined by the FDA to be interchangeable with the prescribed biologic and the prescribing health care provider does not express a preference against substitution in writing, orally, or electronically. The ability of a pharmacist to substitute a biosimilar for a prescription biologic is permissive; substitution of a generic chemical drug for brand name chemical drug is mandatory under Florida law.[57]

The bill requires the pharmacist to notify the person presenting the prescription that he or she has substituted a biosimilar for the prescribed biologic. The pharmacist must retain a written or electronic record of the substitution for at least 2 years.

The presenter of the prescription has the right to reject the substitution and request the prescribed biologic. This is identical to current law regarding generic chemical drugs, which permits a presenter of a prescription for a brand name chemical drug to reject substitution and request the brand name chemical drug.

The bill requires a Class II institutional pharmacy to add biological products, biosimilars, and biosimilar interchangeables to its institutional formulary system. Adding these products to the formulary will permit an institutional pharmacist to substitute a biosimilar and interchangeable biological product for another biological product in the same manner provided in the retail pharmacy setting. Also, the bill allows a pharmacist who practices in a Class II or modified Class II institutional pharmacy to comply with the bill's notification requirements by entering the substitution into the institution's medical record system.

The bill directs the Board of Pharmacy (board) to maintain a list on its website of biological products that the FDA has determined to be biosimilar to and interchangeable with other biologics. The board must update the list on its website whenever the FDA changes its list of biosimilar and interchangeable biologics.

Lastly, the bill adopts the definitions of the terms "biological product," "biosimilar," and "interchangeable" as they appear in the federal Public Health Service Act.[58]

II. FISCAL ANALYSIS & ECONOMIC IMPACT STATEMENT

A. FISCAL IMPACT ON STATE GOVERNMENT:

1. Revenues:

None.

[55] Id.
[56] Id.
[57] *See supra*, section I(A), Background, *Pharmacist Substitution in Florida*.
[58] 42 U.S.C. §262(i)(1), (2), and (3).

2. Expenditures:

   While a biosimilar market does not currently exist in the U.S., it is anticipated that once biosimilars are approved by the FDA and deemed interchangeable with prescription biologics, Medicaid and the State Group Insurance program may realize cost savings due to substitution of less expensive biosimilars for prescription biologics. The estimate of cost savings is undetermined.

B. FISCAL IMPACT ON LOCAL GOVERNMENTS:

1. Revenues:

   None.

2. Expenditures:

   While a biosimilar market does not currently exist in the U.S., it is anticipated that once biosimilars are approved by the FDA and deemed interchangeable with prescription biologics, cities and counties that are self-insured or pay a portion of employees' prescription drug insurance coverage may realize cost savings due to substitution of less expensive biosimilars for prescription biologics. The estimate of cost savings is undetermined.

C. DIRECT ECONOMIC IMPACT ON PRIVATE SECTOR:

The bill provides a pathway to establish a market for biosimilars in Florida. Companies that manufacture biosimilars for treatment or prevention of disease or conditions will be permitted to sell such products in Florida.

D. FISCAL COMMENTS:

None.