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ONE HUNDRED FOURTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
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MEMORANDUM

February 2, 2016

To: Subcommittee on Health Democratic Members and Staff

Fr: Committee on Energy and Commerce Democratic Staff

Re: Hearing on "Examining Implementation of the Biologics Price Competition and Innovation Act"

On **Thursday, February 4th, at 10:30 a.m., in Room 2123 of the Rayburn House Office Building**, the Committee will hold a hearing on the implementation of the Biologics Price Competition and Innovation Act (BPCIA).

I. BACKGROUND

According to the Food and Drug Administration (FDA), a "biologic" is a medical product "made from a variety of natural sources and, like drugs, biological products are used to either treat or cure diseases or medical conditions, prevent diseases, or diagnose diseases."[1] These medications differ from traditional medicines in that they are created from a variety of natural sources such as proteins, nucleic acids or even living cells or tissue.[2] Generally, the medications are composed of larger, more complicated compounds compared to the traditional drug market.

Currently, the FDA lists several hundred FDA approved biologic products.[3] These medicines are used for a wide variety of conditions ranging from antidotes for poisonous

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[1] Food and Drug Administration (FDA), *Information for Healthcare Professionals (Biosimilars)* (Aug. 27, 2015) (online at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm).

[2] *Id.*

[3] FDA, *List of Licensed Biologic Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date* (Jan. 4, 2016) (online at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedan

snakebites, to the reversal of life-threatening bleeding for patients on blood thinners, to a variety of vaccinations including Hepatitis B and Human Papillomavirus.

Given the inherent differences between biologic products and traditional medicines, a separate regulatory pathway was created under BPCIA to approve those new biologics that are similar to already existing biologic products.[4] A "biosimilar" is a type of biologic product licensed by the FDA that is highly similar to an already approved biologic product.[5] By definition, biosimilars are not generic drugs. Generic drugs maintain a variety of FDA requirements to ensure they are "copies of brand name drugs." Given that biologics are made of naturally occurring materials, including living cells, biosimilars are allowed certain differences from the reference biologic.

In order to be FDA approved, a biosimilar is required to have the same mechanism of action, route of administration, dosage, form, and strength of another biologic product.[6] In addition, it must match and can only be utilized to treat already approved conditions or indications. Of note, there is an additional FDA classification for "interchangeable biologic products."[7] Interchangeable biologics are products that have not only been deemed biosimilar, but are supported by additional studies that demonstrate safety, purity, potency and other relevant measures.[8]

A. Present State of Biologic Industry

In 2013, U.S. biologic drug sales amounted to over $66.3 billion dollars.[9] Globally, the marketplace has increased significantly over recent years. In 2002, worldwide sales of biologics were $46 billion, representing 11 percent of the global drug market.[10] By 2017, sales of biologics

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dApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM412398.pdf).

[4] Affordable Care Act, *Title VII Subtitle A – Biologics Price Competition and Innovation* (2009) (online at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ucm216146.pdf).

[5] FDA, *Information for Consumers (Biosimilars),* (Aug. 27, 2015) (online at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm).

[6] *Id.*

[7] FDA, *Information for Industry (Biosimilars)* (Aug. 27, 2015) (online at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241720.htm).

[8] *Id.*

[9] Mulcahy AW, Predmore Z, Mattke S, *The Cost Savings Potential of Biosimilar Drugs in the United States*, RAND Corporation (2014) (online at https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf).

[10] Aitken M, *The Trillion Dollar Market for Medicines: Characteristics, Dynamics and Outlook,* IMS Institute for Healthcare Informatics (Feb. 24, 2014) (online at http://www.jhsph.edu/research/centers-and-institutes/center-for-drug-safety-and-effectiveness/academic-training/seminar-series/MUrray%20Aikten.pdf).

are expected to grow to between $205-235 billion, which would comprise approximately 20 percent of the global pharmaceutical marketplace.[11]

Potential growth of the biosimilar marketplace has been cited as an important factor in minimizing rapid rises in U.S. drug expenditures. Biologics have generally been more expensive than traditional drugs due to both the complexity of the drug development and manufacturing as well as the lack of competition. Experts theorize that increased competition in the biologic marketplace through biosimilars has the potential to decrease costs, but likely less of an impact than that seen with non-biologic drugs. For example, in Europe, the first biosimilar entered the marketplace with only a 20-25 percent decrease compared to the original biologic product.[12]

Historically, the European biologics and biosimilar marketplace has held significant historical differences compared to the U.S. market. The European Union approved a regulatory pathway for biosimilars in 2003, earlier than the U.S. and having differing technical requirements than the U.S. approval process.[13] As a result, the European Medicines Agency has approved 20 biosimilars for use since 2006.[14] Consequently, in 2011, biosimilars accounted for 10 percent of the overall European available market. Yet the European Union accounted for 80 percent of the global biosimilar market share.[15]

II. FDA AUTHORITY AND REGULATORY ACTION

A. Overview of the Biologics Price Competition and Innovation Act

BPCIA was signed into law in March 2010 as a part of the Affordable Care Act (ACA). BPCIA added Section 351(k) of the Public Health Service Act (PHS Act) authorizing FDA to establish an abbreviated approval pathway for biological products shown to be "biosimilar to" or "interchangeable with" an FDA-licensed biological products. Through this new abbreviated pathway, a biosimilar may be approved by demonstrating that it is "highly similar to the

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[11] *Id.*

[12] Carpenter L, *Generic substitution and biopharmaceuticals: where are all the follow-onbiologics: and how much money will they save?* National Law Review (Jan. 1, 2010) (online at http://www.natlawreview.com/article/generic-substitution-and-biopharmaceuticals-where-are-all-follow-biologics-and-how-much-mone).

[13] European Medicines Agency, *Questions and answers on biosimilar medicines,* (Sept. 27, 2012) (online at http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf).

[14] European Medicines Agency, *Human Medicines: European public assessment reports (biosimilars)* (online at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&keyword=Enter%20keywords&searchType=name&alreadyLoaded=true&status=Authorised&jsenabled=false&searchGenericType=biosimilars&orderBy=authDate&pageNo=1).

[15] Blackstone EA, Joseph PF, *The economics of biosimilars,* American Health & Drug Benefits (Sept-Oct, 2013) (online at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/).

reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[16] This is in contrast to generic drugs, which must demonstrate that they are the same as the reference product.

An application submitted to FDA to license a biological product as a biosimilar must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based on data derived from analytical, animal, and clinical studies showing that the biological product is highly similar; that the biological product and reference product have the same mechanism of action; the condition of use in the proposed biological product have been previously approved for the reference product; the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product; and the facility in which the biological product is manufactured meet applicable standards to assure that the product is safe, pure, and potent.[17]

An application submitted to FDA to meet the additional standard as "interchangeable" must contain information demonstrating biosimilarity, and also demonstrate that the biological product "can be expected to produce the same clinical result as the reference product in any given patient" and if the biological product is "administered more than once to an individual, the risks in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product in any given patient is not greater than the risk of using the reference product without such alternation or switch."[18] If FDA determines that a biosimilar is interchangeable with a reference product, then the biosimilar may be substituted for the reference product "without the intervention of the health care provider who prescribed the reference product."[19] No biosimilar has been approved yet by FDA as interchangeable. 18 states and Puerto Rico have passed legislation regarding biologics and biosimilar substitution.[20]

Other provisions of the BPCIA include:

- A 12-year exclusivity period from the date of first licensure of the reference product, during which approval of a 351(k) application referencing that product may not be made effective[21];
- A 4-year exclusivity period from the date of first licensure of the reference product, during which a 351(k) application referencing that product may not be submitted[22];

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[16] Section 351(i)(2) of the Public Health Service Act.

[17] Section 351(k)(2)(A) of the Public Health Service Act.

[18] Section 351(k)(4) of the Public Health Service Act.

[19] Section 351(k)(8) of the Public Health Service Act.

[20] National Conference of State Legislatures, *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars* (Jan. 4, 2016) (online at http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx).

[21] Section 351(k)(7) of the Public Health Service Act.

[22] Section 351(k)(7) of the Public Health Service Act.

- An exclusivity period for the first biological product determined to be interchangeable with the reference product for any condition of use, during which a second or subsequent biological product may not be determined interchangeable with that reference product[23];
- An exclusivity period for certain biological products for which pediatric studies are conducted in accordance with a written request from FDA[24];
- A transition provision for biological products that have been or will be approved under section 505 of the FD&C Act (21 U.S.C. 355) before March 23, 2020[25]; and,
- Establishes procedures for identifying and resolving patent disputes involving applications submitted under section 351(k) of the PHS Act.

B. FDA Regulatory Action

Since enactment, FDA has issued eight draft guidances and finalized four of them. FDA published draft guidances in 2012, and published final guidances in 2015 on the following topics:

- Scientific Considerations Demonstrating Biosimilarity to a Reference Product
- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation of 2009
- Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors of Applicants.

The remaining draft guidances include:

- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act
- Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009
- Nonproprietary Naming of Biological Products

[23] Section 351(k)(6) of the Public Health Service Act.
[24] Section 351(m) of the Public Health Service Act.
[25] Section 127 7002(e) of the Affordable Care Act.

FDA has also indicated that the agency is working on additional guidance related to interchangeability and labeling, among other topics. Additionally, the agency has also held two public hearings, one on November 2-3, 2010[26], and the other on May 11, 2012[27].

Although the U.S. has produced biologic drugs for several decades, the FDA only recently began the approval process for biosimilars. In March 2015, the FDA approved its first biosimilar, Zarxio, a drug that increases the levels of white blood cells in cancer patients and a biosimilar to Amgen's biologic Neupogen.[28] Zarxio launched in the U.S. on September 3, 2015.[29] Although it is currently the only approved biosimilar, FDA reports growing industry interest in this marketplace. Seven applications are publicly known to be filed for review, and 22 investigational new drug applications intended to support a biosimilar application had been filed with FDA as of September 30, 2015.[30] As of July 31, 2015, 57 proposed biosimilar products were enrolled in the FDA's Biosimilar Product Development Program (BDP).[31] In addition, between 2013 and 2015, FDA saw a 57 percent increase in industry development phase meetings, which are held for the benefit of companies that are in the early stages of biosimilar development or are considering joining the BDP.[32]

C. Overview of Biosimilars User Fee Act

BPCIA also directed FDA to develop recommendations for a biosimilar user fee program for fiscal years 2013 through 2017 in consultation with Congress, industry, scientific and academic experts, health care professionals, and patient and consumer advocates. The first Biosimilar User Fee Act (BsUFA) was enacted as a part of the FDA Safety and Innovation Act on July 9, 2012. The fees collected by the agency are used to support the review of marketing applications for biosimilar biological products and are meant to supplement funding appropriated by Congress. Fees collected under BsUFA include fees for marketing applications, manufacturing establishments, and products.

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[26] FDA, *Approval Pathway for Biosimilar and Interchangeable Biological Products Public Meeting* (Nov. 2-3, 2010) (online at http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm).

[27] FDA, *Draft Guidances Relating to the Development of Biosimilar Products; Public Hearing; Request for Comments* (May 11, 2012) (online at http://www.fda.gov/Drugs/NewsEvents/ucm265628.htm).

[28] FDA, *FDA approves first biosimilar product Zarxio* (Mar. 6, 2015) (online at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm).

[29] Novartis, *Sandoz launches ZarxioTM (filgrastim-sndz), the first biosimilar in the United States* (Sept. 3, 2015) (online at https://www.novartis.com/news/media-releases/sandoz-launches-zarxiotm-filgrastim-sndz-first-biosimilar-united-states).

[30] FDA, *Number of biosimilar investigational new drug applications (INDs) received in the month* (Sept. 30, 2015) (online at http://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=cder&id=CDER-RRDS-Number-of-biosimilar-INDs&fy=all).

[31] Woodcock J, *Biosimilars Implementation, Testimony of Janet Woodcock, M.D. Before the Committee on Health, Education, Labor and Pensions*, FDA, (Sept. 17, 2015) (online at http://www.help.senate.gov/imo/media/doc/Woodcock4.pdf).

[32] *Id.*

BsUFA performance goals[33] include targets for FDA to review 70 percent of applications for biosimilars within 10 months of receipt in fiscal years 2013 and 2014, 80 percent in fiscal year 2015, 85 percent in fiscal year 2016, and 90 percent in fiscal year 2017. Program development activities funded through biosimilar user fees include: biosimilar biological product development meetings; investigational new drug applications (INDs); development of the scientific, regulatory, and policy infrastructure necessary for review of biosimilar applications; and development of standards for biological products subject to review and evaluation. Other activities funded through the biosimilar user fees include review of advertising and labeling prior to approval of a biosimilar; review of required post-marketing studies; and inspection of biosimilar establishments.

III. BIOSIMILARS IN MEDICARE PART B

Currently, Medicare Part B drugs are reimbursed using the average sales price plus six percent methodology (ASP+6), which states that:

- a single-source drug (i.e. a drug without a generic substitute) or biologic is paid based on 106 percent of its own ASP; and
- a multiple-source drug (i.e. a drug with one or more generic substitutes) is paid based on the weighted average of the ASP for all equivalent brand and generic products (both the brand and generic versions receive the same ASP+6 percent rate).

However, the ACA provided that biosimilars would be reimbursed using a different approach. A biosimilar product is paid 100 percent of its own ASP, plus 6 percent of the ASP for the reference biologic. Thus, a lower priced biosimilar would receive an add-on payment greater than what 6 percent of its own ASP would yield because the add-on payment is calculated at 6 percent of the more expensive reference biologic.

In October, 2015, the Center for Medicare and Medicaid Services (CMS) released its final Physician Fee Schedule (PFS) rule, which included the Medicare Part B payment methodology for biosimilars. This policy took effect on January 1, 2016. In CMS's final PFS rule, each biosimilar that references the same brand biologic will be put into a single Healthcare Common Procedure Coding System (HCPCS) code. Therefore, regardless of the number of biosimilars approved to a certain reference biologic, only one code will be created and their payment will be based on the ASP all of the biosimilars in that HCPCS code.

[33] FDA, *Biosimilar Biological Product 2 Authorization Performance Goals and 3 Procedures Fiscal Years 2013 through 4 2017* (online at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf).

Proponents of the rule believe it will drive down biosimilar prices.[34] They argue that putting biosimilars into one code will drive down costs for Medicare and patients because manufacturers with lower-cost biosimilars will gain greater market share than manufacturers with higher-priced biosimilars. Thus, this will cause manufacturers to compete to have the lowest price. They argue that separate codes for biosimilars will remove the incentive to offer lower-cost biosimilars because each will be reimbursed using its own ASP. MedPAC also agreed that using one code would create more price competition than using a separate code for each biosimilar.[35]

Stakeholders who opposed the rule believe that arguments about price competition miss the mark for various reasons.[36] One argument maintains that there must first be a biosimilars market before there can be competition in the market. Stakeholders argue that this rule will disincentivize companies from entering the biosimilars marketplace. Or, alternatively, the rule will discourage manufacturers from getting biosimilars approved for multiple indications (and thus spending more on research and development) when a biosimilar approved for a single indication (thus spending less on research and development) is lumped into the same code.

Additionally, some stakeholders argue that the rule will lead to confusion and patient safety concerns. Tracking and following up on adverse events, they attest, would be easier if providers use separate HCPCS codes in claims data. With all biosimilars for a reference product in one code, it will not be possible to use claims data to help determine which biosimilar was administered to a patient, which could delay efforts to identify which biosimilar caused an adverse event. There may be alternative ways, however, to track this data.

Others argue that the rule inappropriately treats biosimilars like they are multiple-source or generic drugs. As mentioned, biosimilars by definition are not generic drugs because they are not exact copies of their reference products. Rather they create the same clinical outcome as their reference products. All biosimilars are unique, and not all biosimilars will be approved for all of the conditions of use for which their reference products were approved.

Finally, there is concern that the Administration's biosimilars policy is not consistently applied across FDA, Medicare Part B, Medicare Part D, and Medicaid. FDA, Medicare Part D, and Medicaid currently treat biosimilars more like single-source drugs (Secs. IV and V infra) and Medicare Part B now treats them like multiple-source drugs.

IV. BIOSIMILARS – MEDICAID

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[34] Community Catalyst, *Comments to CMS-1631-P* (Sept. 8, 2015) (online at http://www.regulations.gov/#!documentDetail;D=CMS-2015-0081-2232).

[35] Letter from Francis J. Crosson, M.D. to Acting Administrator Andrew Slavitt (Sept. 8, 2015) (online at http://www.medpac.gov/documents/comment-letters/medpac-comment-on-cms's-proposed-rule-on-the-physician-fee-schedule-and-other-revisions-to-part-b.pdf?sfvrsn=0).

[36] Bloomberg BNA, *Groups Concerned Over CMS Biosimilar Payment Rule* (Sept. 10, 2015) (online at http://www.bna.com/groups-concerned-cms-n17179935760/).

The amount Medicaid spends for a particular outpatient prescription drug reflects two components—the initial payment to the pharmacy and the rebates Medicaid receives from manufacturers. States set pharmacy payment policy within broad federal guidelines and requirements. For instance, to ensure that Medicaid is a prudent purchaser of drugs, federal and state policies have instituted upper limits on payment for multiple-source drugs. Additionally, there is a payment limit applied to all drugs to ensure that Medicaid does not pay more than the price generally available to the public. States set reimbursement rates, and then file claims for the federal portion of Medicaid reimbursement on a quarterly basis in the aggregate. In order for their products to be covered by Medicaid, drug manufacturers must also enter into a statutorily defined rebate agreement with the Secretary of the U.S. Department of Health and Human Services (HHS). These drug rebates are collected by the state on a quarterly basis, and are shared between the state and the federal government.

The Medicaid program largely views biosimilars as a third category of drugs for purposes of the Medicaid drug rebate program. Today, in the Medicaid Drug Rebate Program, CMS classifies biosimilars as "single-source drugs," which means that manufacturers must pay state Medicaid programs the branded drug product rebate for Medicaid utilization of biosimilar products.

CMS has also provided guidance to states on the classification of biosimilar products for Medicaid rebates and on strategies to reduce costs. The agency instructed state Medicaid programs to view the launch of biosimilar products as "a unique opportunity to achieve measurable cost savings and greater beneficiary access to expensive therapeutic treatments for chronic conditions."[37] State Medicaid programs were also encouraged to enter into additional supplemental rebate agreements with manufacturers, as they do with branded drugs. These additional agreements could result in additional savings, as a reduction in state Medicaid expenditures for biological products will also reduce the federal share dollars, for which CMS is responsible.

V. BIOSIMILARS – MEDICARE PART D

Medicare Part D generally covers self-administered drugs from every therapeutic category of prescription drugs, with formularies varying to a certain extent by plan. Medicare makes monthly prospective payments to plans for each Part D enrollee that are risk adjusted for a number of factors. Plans, in turn, manage Part D formularies and negotiate reimbursement with manufacturers.

[37] Center for Medicaid and CHIP Services, *Medicaid Drug Rebate Program Notice for Participating Drug Manufacturers, Release No. 92* (Mar. 30, 2015) (online at https://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Downloads/Rx-Releases/MFR-Releases/mfr-rel-092.pdf).

To date, CMS has provided guidance on coverage of biosimilars under Part D that clarifies the application of formulary review policies, low-income subsidy (LIS) and catastrophic cost sharing rules, and Coverage Gap Discount Program requirements for biosimilars. CMS noted that this guidance applies only to "biosimilar" products and that additional guidance may be issued for products designated as "interchangeable" at a later date.

Notably, CMS will not treat the reference biological product and biosimilar as different drugs for purposes of satisfying the "two distinct drugs" requirement for each of the categories and classes on Part D formularies. Therefore, even if both the reference biological product and its biosimilar are included in a particular category or class on a formulary, Part D sponsors are required to include at least one additional product in that category or class. CMS, however, treats biosimilars as single-source drugs under the LIS and the Catastrophic Cost Sharing programs in Medicare Part D because biosimilars do not meet the statutory and regulatory definitions of generic and multiple-source drugs. Accordingly, this means that biosimilars are subject to higher copayments for LIS eligible individuals and enrollees in catastrophic coverage.

While there are currently no Part D covered biosimilars, the agency has indicated that when applicable, it will evaluate plan sponsors' formulary change requests involving biosimilars on a case-by-case basis to determine whether they meet Part D formulary review and approval requirements based on information in the products' FDA-approved label. In addition, biosimilars are not applicable for the Medicare Part D Coverage Gap Discount Program and, therefore, are not discounted or otherwise subject to the program's requirements.

VI. WITNESSES

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