

May 7, 2015

Jennifer Carver  
HCPCS Public Meeting Coordinator  
Centers for Medicare & Medicaid Services  
7500 Security Boulevard, Mail Stop C5-08-27  
Baltimore, MD 21244-1850

**BY ELECTRONIC DELIVERY**

**RE: Centers for Medicare and Medicaid Services Healthcare Common Procedure Coding System Public Meeting, May 7, 2015**

Dear Ms. Carver:

The Biotechnology Industry Organization (BIO) is pleased to provide comments in response to the May 7 Centers for Medicare and Medicaid Services (CMS) Healthcare Common Procedure Coding System (HCPCS) Public Meeting Agenda for Drugs, Biologicals and Radiopharmaceuticals ("Public Meeting Agenda").<sup>1</sup>

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place. In that way, our members' novel therapeutics, vaccines, and diagnostics not only have improved health outcomes, but also have reduced healthcare expenditures due to fewer physician office visits, hospitalizations, and surgical interventions.

BIO represents an industry that is devoted to discovering, and ensuring patient access to, innovative treatments. Accordingly, we closely monitor coding policies for their potential impact on patient access to the drugs and biologicals most appropriate for them. With respect to the Public Meeting Agenda, BIO urges CMS to consider the following recommendations:

- CMS should create unique HCPCS codes for each and every biosimilar product, including those that share a reference product; and
- CMS should issue unique HCPCS codes for each new beta amyloid radiopharmaceutical, consistent with the Agency's stated policy.

Each of these recommendations is discussed in further detail, below.

**I. CMS Should Create Unique HCPCS Codes for Each and Every Biosimilar Product, Including Those That Share a Reference Product.**

As CMS is aware, BIO has strongly supported the provision of a separate HCPCS code for a reference biological and for any biosimilar product later approved, consistent with the statute that provides for separate payment rates for reference biologicals and biosimilar

---

<sup>1</sup> Centers for Medicare and Medicaid Services (CMS). 2015. Centers for Medicare and Medicaid Services (CMS) Healthcare Common Procedure Coding System (HCPCS) Public Meeting Public Meeting Agenda for Drugs, Biologicals and Radiopharmaceuticals, available at: <https://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/Downloads/May-7-2015-DrugAgenda.pdf>.

products. We reiterate this support and acknowledge CMS's recent statement that the Agency will create separate code to distinguish the biosimilar from the reference biological.<sup>2</sup> However, the Agency also indicated in that it is considering policy options for coding of additional biosimilars, and will release further guidance in the future. BIO strongly urges CMS to create unique Level II HCPCS "J" codes for each and every biosimilar product, including those that share a reference product, as soon as feasible for CMS.

Specifically, with respect to Agenda Item 1 on the Public Meeting Agenda—the request to establish a new Level II HCPCS "J" code to identify Zarxio™ (filgrastim-sndz), a biosimilar to the reference drug Filgrastim—we urge CMS to provide a distinct Level II HCPCS "J" code for Zarxio, as requested by the applicant, such that Zarxio can be distinguished from any additional biosimilar products subsequently approved with respect to the same reference product (filgrastim). We are concerned that the HCPCS Panel's preliminary decision to create a code that is not specific to Zarxio may effectively circumvent a robust, iterative guidance process with respect to coding for biosimilars that is inclusive of deliberations on the part of a broad range of stakeholders. We also are concerned that the Agency's preliminary decision with respect to Zarxio inappropriately reflects a nomenclature standard that is akin to what it has established for generic small-molecule drugs. Furthermore, given the scientific complexities of developing and manufacturing biologicals, and the scientific and regulatory differences between generics and biosimilars, we are concerned that the absence of distinct HCPCS codes of each and every biosimilar product will create confusion for providers and dispensers, hinder effective pharmacovigilance, and potentially jeopardize patient safety. Further detail on each of these issues is included in the sections below.

**A. There is no regulatory assessment of the similarity among multiple biosimilars that share a reference product, thus it cannot be assumed that these products are similar to, let alone interchangeable with, each other.**

Congress, in enacting the Biologics Price Competition and Innovation Act (BPCIA), recognized that the generic drug legal and regulatory construct is inappropriate for biosimilar products due to scientific differences between the two classes of products.<sup>3</sup> By way of background, in order to receive regulatory marketing approval, a generic drug application (Abbreviated New Drug Application (ANDA)) must, by statute and regulation, contain certain information to show that the proposed drug product is the same as a previously-approved brand drug.<sup>4,5</sup> Based on this information, it can be assumed that two

---

<sup>2</sup> CMS. 2015. *Food and Drugs Administration Approval of First Biosimilar Product*. MLN Matters® Number: SE1509, available at: <http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE1509.pdf>.

<sup>3</sup> Pub. L. No. 111-148 (March 23, 2010) (Patient Protection and Affordable Care Act, Title VII – Improving Access to Innovative Medical Therapies, Subtitle A—Biologics Price Competition and Innovation) (codified as Public Health Service Act § 351(k)). *Also see* Woodcock, J., et al. 2007 (April). The FDA's Assessment of Follow-on Protein Products: A Historical Perspective. *Nature Reviews Drug Discovery* 6: 437-442.

<sup>4</sup> FDCA § 505(j), 21 U.S.C. § 355(j).

<sup>5</sup> In this context, it is important to note that the FDA Orange Book and the FDA Purple Book are distinct. The Orange Book identifies drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act and contains therapeutic equivalence evaluations for approved multisource prescription drug products. Biosimilar products are not listed in the Orange Book. The FDA Purple Book lists biological products approved under section 351 of the Public Health Service Act, including any biosimilar and interchangeable biological products licensed by FDA (in the Purple Book, these products are listed under the reference product to which biosimilarity or interchangeability was demonstrated). For more information, *see* FDA. 2014. *Orange Book, 34<sup>th</sup> Edition, Preface and Introduction*, available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm>; *Also see*: FDA. 2015. *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm>.

generics of the same brand drug are identical not only to the brand drug, but also to each other.

By contrast, biosimilars are not, by definition, direct copies of the reference product. Due to the complex structure of biologics and the associated manufacturing processes, the regulatory assessment of biosimilars is predicated on demonstrating—through analytical non-clinical and clinical data—that the biosimilar is “highly similar” to an innovator/reference biologic in terms of structural characteristics with an absence of clinically meaningful differences.<sup>6,7,8</sup> Moreover, since biosimilars are approved on the grounds that they are highly similar, but not identical to, a given reference product, interchangeability with the reference product cannot be assumed. Indeed, the Food and Drug Administration (FDA) may affirmatively designate a biosimilar as interchangeable with a reference product only after an additional determination that: (1) it can be expected to produce the *same* clinical results as the reference product *in any given patient*; and (2) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.<sup>9</sup>

Therefore, unlike generics, it cannot be assumed that a biosimilar is identical to its reference product, let alone that multiple biosimilars of the same reference product are identical to each other.<sup>10</sup>

Indeed, the regulatory approval process for a biosimilar in no way focuses on the relationship among biosimilars of the same reference product. For example, the regulatory approval pathway does not require that multiple biosimilars of the same reference product demonstrate similarity to each other in any respect. Nor does this pathway include an assessment of similarity between or among these products. Instead, each of these products is approved based only on whether it is “highly similar” to the reference product. Determinations of interchangeability also are made solely based on the comparison of an individual biosimilar with the reference product. In the absence of data that directly compare the quality, safety, and efficacy attributes of multiple biosimilars sharing the same reference product, there can be no expectation or conclusion of biosimilarity—let alone interchangeability—between or among these products.

---

<sup>6</sup> In testimony before Congress, FDA Deputy Commissioner Janet Woodcock described the scientific challenges of demonstrating biosimilarity as (but not limited to): “It is the combination of the protein’s amino acid sequence and its structural modifications that give a protein its unique functional characteristics. Therefore, the ability to predict the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product. Although this currently may be possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products.” See Janet Woodcock, Deputy Commissioner, Chief Medical Officer, FDA, testimony before the Subcommittee on Health, Committee on Energy and Commerce, May 2, 2007, at [http://energycommerce.house.gov/cmte\\_mtgs/110-hehrg.050207.Woodcock-testimony.pdf](http://energycommerce.house.gov/cmte_mtgs/110-hehrg.050207.Woodcock-testimony.pdf).

<sup>7</sup> For additional details on the scientific challenges of demonstrating biosimilarity, see Congressional Research Service. 2010. *FDA Regulation of Follow-On Biologics*. CRS 7-5700, RL34045, pp. 7-12, available at: [https://primaryimmune.org/advocacy\\_center/pdfs/health\\_care\\_reform/Biosimilars\\_Congressional\\_Research\\_Service\\_Report.pdf](https://primaryimmune.org/advocacy_center/pdfs/health_care_reform/Biosimilars_Congressional_Research_Service_Report.pdf).

<sup>8</sup> See Shepherd, J. M. 2014. *Biologic Drugs, Biosimilars, and Barriers to Entry*. Emory University School of Law, Emory Legal Studies Research Paper No. 14-284.

<sup>9</sup> Public Health Service Act § 351(k)(4).

<sup>10</sup> Under the BPCIA, a reference product is defined as a product approved under section 351(a) of the Public Health Service Act. A biosimilar, on the other hand, is approved under section 351(k) of that Act. Therefore, a product approved as a biosimilar cannot be used as a reference product in a subsequent biosimilar application. See Public Health Service Act § 351(i)(4).

**B. The absence of a distinct HCPCS code for each and every biosimilar, including those that share a reference product, will create confusion for providers and dispensers and could potentially harm patients.**

Based on the scientific and regulatory differences between biosimilars and generics described in the previous section, including the fact that the regulatory approval process for biosimilars does not establish any degree of similarity among multiple biosimilars of the same reference product, we strongly urge CMS to provide a distinct HCPCS code for each and every biosimilar to prevent confusion among providers and dispensers for the following two reasons.

First, because biologicals are generally physician-administered, rather than dispensed at pharmacies, HCPCS codes, and not National Drug Codes (NDCs), are generally the mechanism used to report the utilization of these therapies on claims forms.<sup>11</sup> Thus, without distinct HCPCS codes, it will be difficult to specify exactly which therapy is being prescribed for an individual patient and to ensure that the patient continues to receive the specific therapy intended for his/her treatment. Switching a biologic medication, even with products in the same therapeutic class, can destabilize the patient, as the switched product may not adequately respond to the needs of that patient.

Second, the implication of multiple biosimilar products sharing the same HCPCS code—namely, that these therapies are somehow equivalent and/or interchangeable—would be confusing for prescribers and dispensers, as no such relationship would have been established during the regulatory approval process. Such confusion may, in turn, negatively impact patients because the differences between biosimilars can impact how an individual patient responds to a therapy—biologics, as large protein molecules synthesized in living cells, have increased structural complexity that can affect a product's function and clinical safety, efficacy, and immunogenicity, as compared to small-molecule drugs, which are chemically synthesized.

**C. The absence of a distinct HCPCS code for each and every biosimilar, including those that share a reference product, will hinder effective pharmacovigilance and can therefore jeopardize patient safety.**

The complexity of biologics described in previous sections also can have important pharmacovigilance implications. Where minor differences are found between two biologic products, there are limits to the certainty that such differences will not have clinical consequences. Additionally, clinical trials may not be sufficiently powered to detect the rare

---

<sup>11</sup> The Medicaid program requires that NDCs are reported on claims forms (see Deficit Reduction Act of 2005, Pub. L. No. 109-171, Sec. 6002(a)), but there is evidence to suggest that NDC reporting is inconsistent despite this requirement, for example, see CMS. 2012. *Important Information Concerning the Medicare Crossover Process and State Medicaid Agency Requirements for National Drug Codes (NDCs) Associated with Physician-Administered Part B Drugs*. MLN Matters®, Number: SE1234, available at: <http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/se1234.pdf>. Accurate reporting of exactly which biopharmaceutical was used is crucial to tracking Medicaid utilization of these products, including for purposes of program integrity and compliance within the Medicaid Drug Rebate Program. While there is a mechanism in place to crosswalk HCPCS codes to NDCs, to function accurately, this crosswalk would rely on the availability of distinct HCPCS "J" codes for each and every biosimilar. For more information on the Medicaid Drug Rebate Program, see CMS. 2015. *Medicaid Drug Rebate Program Data*, available at: <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Medicaid-Drug-Rebate-Program-Data.html>.

adverse events associated with new products.<sup>12</sup> These two realities, taken together, mean that, as more patients use products in less controlled settings post-approval, critical safety and efficacy information is learned through post-market safety surveillance and outcomes research.<sup>13</sup> In these settings, the ability to distinguish between products—including two or more biosimilars of the same reference product—is necessary to promote efficient data aggregation and disaggregation, and to ensure that events observed through post-market safety surveillance and outcomes research are accurately attributed to the specific product that was used. As noted previously, given that biologics are often physician-administered, HCPCS codes are generally relied on to bill for these products. Thus, a distinct HCPCS code for each and every biosimilar, including for biosimilars of the same reference product, is critical to a robust pharmacovigilance infrastructure.

Furthermore, adverse events associated with biologics, including immunogenicity risks, can have significant clinical consequences. FDA staff has noted that “[t]racking adverse events associated with the use of reference and biosimilar products will be difficult if the specific product or manufacturer cannot be readily identified, and appropriate strategies must be developed to ensure the implementation of robust, modern pharmacovigilance programs for biologics.”<sup>14</sup> Distinct HCPCS codes for biosimilars of the same reference product are integral to ensuring that adverse events are traced to the correct product and facilitate the collection of more timely and accurate adverse event data in order to inform critical clinical decisions about the use of biologics.

Finally, a cornerstone of patient safety, the combined ability to prevent prescribing errors (including inappropriate substitution) and accurately attribute adverse events, depends upon the ability of patients, prescribers, and dispensers to accurately identify specific products. BIO believes that distinct HCPCS codes for biosimilars of the same reference product are necessary to further such efforts to promote and enhance patient safety.

## **II. CMS Should Issue Unique HCPCS Codes for Each New Beta Amyloid Radiopharmaceutical, Consistent with the Agency’s Stated Policy.**

Agenda Items 5 and 6, respectively, identify two distinct requests to establish a unique Level II HCPCS code to identify Flutemetamol F18 Injection (trade name: VizamyI™) and florbetaben F 18, (trade name: Neuraceq™), both FDA-approved for Positron Emission Tomography (PET) imaging of the brain to estimate Beta amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s Disease (AD) and other causes of cognitive decline.<sup>15</sup> The preliminary decision in both cases was that “[e]xisting code A9599 ‘Radiopharmaceutical, diagnostic, for beta-amyloid positron emission tomography (PET) imaging, per study dose’ adequately describes the product that

---

<sup>12</sup> Jesse Berlin, et al., Adverse Event Detection in Drug Development: Recommendations and Obligations Beyond Phase 3, *Am. J. Public Health*, Vol. 98, No. 8, 1366–1371 (August 2008). Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2446471/pdf/0981366.pdf>.

<sup>13</sup> Examples of biological products that have exhibited immunogenicity issues include Factor VIII, interferon-alpha, interferon-beta, interleukin-2, erythropoietin, granulocyte macrophage colony stimulating factor, calcitonin, growth hormone, denileukin-diftitox, and megakaryocyte derived growth factor. See Schellekens, H. 2002 (June) Bioequivalence and the Immunogenicity of Biopharmaceuticals. *Nature Reviews Drug Discovery* 1(6): 457-62, Table 1.

<sup>14</sup> Kozlowski, S., et al., 2011. Developing the Nation’s Biosimilar Program. *New England Journal of Medicine* 365: 385-38.

<sup>15</sup> See VizamyI Label Information (12/04/2014), available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/203137s002lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203137s002lbl.pdf); also see Neuraceq Label Information (04/03/2014), available at: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#labelinfo](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo).

is the subject of this request.”<sup>16</sup> However, these preliminary decisions appear in contrast to CMS’s existing policy, specifically that:

**Each new beta amyloid radiopharmaceutical will require a separate code.** Therefore, for the interim period, HCPCS code (A9599) - Radiopharmaceutical for beta-amyloid positron emission tomography (PET) imaging, diagnostic, per study dose shall be used with an effective date of January 1, 2014. After a new beta amyloid radiopharmaceutical is approved for a separate, individual HCPCS code, a subsequent CR [change request] will be issued to update this NCD policy.<sup>17</sup>

Thus, to be consistent with its own stated policy, BIO urges CMS to issue a unique HCPCS code for each new beta amyloid radiopharmaceutical, including the two such requests included on the Public Meeting Agenda.

### III. Conclusion

BIO appreciates the opportunity to provide input for the Agency’s consideration on the issue of HCPCS codes for biosimilar products. We reiterate our recommendation that CMS issue a distinct HCPCS code for each and every biosimilar product. At minimum, the HCPCS Panel should establish the unique HCPCS code for Zarxio as requested by the applicant and work collaboratively with all stakeholders to establish guidance on the future treatment of HCPCS codes for biosimilars. We also reiterate our recommendation that a unique code be granted to each new beta amyloid radiopharmaceutical, consistent with existing CMS policy. Please do not hesitate to contact me with any questions or if I can provide any further information.

Sincerely,

/s/

Kristin Viswanathan  
Director, Health Policy & Research

---

<sup>16</sup> Public Meeting Agenda at p. 12, 13, available here:

<http://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/Downloads/May-7-2015-DrugAgenda.pdf>.

<sup>17</sup> CMS first issued this policy in a March 2014 MLN Matters notice, see CMS. 2014 (March 27, 2014). Medicare National Coverage Determination (NCD) for Beta Amyloid Positron Emission Tomography (PET) in Dementia and Neurodegenerative Disease. *MLN Matters® Number: MM8526*, available at: <http://www.cms.gov/outreach-and-education/medicare-learning-network-mln/mlnmattersarticles/downloads/MM8526.pdf> (emphasis added). For the change request identified in the policy statement, see CMS. 2014 (March 27). Medicare National Coverage Determination (NCD) for Beta Amyloid Positron Emission Tomography (PET) in Dementia and Neurodegenerative Disease. *CMS Manual System Transmittal 2915, Change Request 8526*, available here: <http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R2915CP.pdf>.