DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Designation of Official Names and Proper Names for Certain Biological Products

Docket No. FDA- 2015-N-0648

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

Economics Staff
Office of Planning
Office of Policy, Planning, Legislation, and Analysis
Office of the Commissioner

Table of Contents

I. Introduction and Summary

The labeling of biological products features a nonproprietary name. This name generally reflects certain scientific characteristics of the products, such as chemical structure and pharmacological properties.

Chemically synthesized small-molecule drugs that contain the same active ingredient (e.g., a generic drug approved under section 505(j) of the Federal Food, Drug & Cosmetic Act and its reference listed drug) generally share the same nonproprietary name. Biological products, however, are typically more structurally complex than such small-molecule drugs, and the processes by which they are manufactured are more complex as well. Accordingly, a biosimilar product licensed under section 351(k) of the Public Health Service Act (the PHS Act) is required to be "highly similar" to, but not the "same" as, its reference product.

In this proposed rule, we use the following terms to describe the relationships between biological products: originator biological products, related biological products, biosimilar products, and reference products. For a given category of biological products, we refer to the first product licensed under section 351(a) of the PHS Act as an "originator biological product." A biological product subsequently licensed under section 351(a) of the PHS Act may contain a drug substance for which certain nomenclature conventions would be expected to provide for use of the same drug substance name as the originator product licensed under section 351(a) of the PHS Act. We refer to the subsequently licensed 351(a) product as a "related biological product." A "biosimilar product" is licensed under section 351(k) of the PHS Act. Among other requirements, a biosimilar product must be "highly similar" to a "reference product" that is a biological product licensed under section 351(a) of the PHS Act.

FDA may designate the official name and the proper name (henceforth referred to as the

nonproprietary name) for biological products. When FDA licenses a biological product under section 351 of the Public Health Service Act (PHS Act), FDA designates a "proper name" in the license for use upon each package of the biological product. FDA also has authority to designate a proper name for a licensed biological product by regulation. Similarly, under section 508 of the FD&C Act, FDA may designate an "official name" for a biological product if it determines that such action is necessary or desirable in the interest of usefulness and simplicity. Once FDA designates an official name, this is the only official name that can be used in any future publication of an official drug compendium.

FDA is proposing to provide a standardized format for the nonproprietary names of originator biological products, related biological products, and biosimilar products that would allow these products to be distinguished from each other. In a draft guidance entitled "Nonproprietary Naming of Biological Products," FDA has described a naming convention under which the nonproprietary names of these products would have a suffix, and have the same format regardless of licensure pathway. The nonproprietary names would consist of a core name that is the name adopted by the United States Adopted Names (USAN) Council for the drug substance, when available, and an FDA-designated suffix composed of four lowercase letters attached with a hyphen. Shared core names would indicate a relationship among products and result in products with a shared core name being located together in electronic databases to help health care providers identify these products.

FDA is proposing a regulation to designate the official name and the proper name of certain biological products consistent with this proposed naming convention. This proposed rule would change the nonproprietary names of (1) four reference products for which a biosimilar has been approved or for which it has been publicly disclosed that an application for a proposed

biosimilar product has been submitted, (2) a related biological product to one of these reference products, and (3) a biosimilar product (see Table 1 for a listing of these products). In the absence of this regulation, one biosimilar would have a designated suffix (filgrastim-sndz) while its reference biological product would not (filgrastim). This pattern could be repeated for the other three biological products for which there is a publicly disclosed 351(k) application if such applications are approved with nonproprietary names that include designated suffixes.

Table 1: Summary of proposed names of biological products

Biologics License Application (BLA) Number	Current name	Proposed name
BLA 103234	epoetin alfa	epoetin alfa-cgkn
BLA 103353	filgrastim	filgrastim-jcwp
BLA 125553	filgrastim-sndz	filgrastim-bflm
BLA 125294	tbo-filgrastim	filgrastim-vkzt
BLA 103772	infliximab	infliximab-hjmt
BLA 125031	pegfilgrastim	pegfilgrastim-ljfd

The proposed rule, if finalized, would designate the official names and the proper names of certain biological products. We estimate the one-time costs of learning about the rule, submitting labeling supplements and forms to the FDA, changing labeling on affected products, FDA review of labeling supplements and forms, and educational efforts of firms. One-time costs, in 2013 dollars, range from $0.78 million to $3.04 million. Over 10 years, the annualized costs from $0.10 million to $0.40 million with a 7 percent discount rate and from $0.09 million to $0.35 million with a 3 percent discount rate. We lack sufficient data to include other potential costs of the proposed rule or to quantify the benefits of the proposed rule, if finalized.

II. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866,

Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Office of Management and Budget (OMB) has determined that this proposed rule is a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule would only affect one small entity, the Agency proposes to certify that the proposed rule would not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

A. Need for the Rule

Current nonproprietary names for biological products do not have a standardized format, even when products are highly similar or otherwise related. For example, there is a reference biological product that has a core name only, and a biosimilar product that has the same core

name plus a suffix. Consumers (healthcare providers and patients) may be less likely to view the biosimilar as an alternative to the reference product if only the biosimilar product has a suffix. It is possible that consumers would perceive that products with suffixes are inferior to those without suffixes. If they choose a product based on this perception of inferiority or because the format of names leads them to believe the biosimilar is not a viable alternative, they may not choose the product that they would have chosen if they had better information. Because these product names have different formats, consumers may incorrectly infer that there are clinically meaningful differences between these products that the FDA has not found.

An information asymmetry exists between firms marketing biological products, who are highly knowledgeable about the characteristics of their products, and consumers, for whom there are opportunity costs to learn about biological products. A format that adds a suffix to the core name of a reference product, the core name of potential reference products, and the core name of a biosimilar product could send a more neutral signal to the market about biosimilar products that may avoid misperceptions of inferiority based on the nonproprietary name. Avoiding such misperceptions could result in consumers choosing a more optimal product than they would if they did incorrectly infer superiority or inferiority. Moreover, any perception of inferiority stemming from the current names may reduce future competition between biosimilar products and their reference biological products, leading to higher prices for patients and payers than would exist if both biosimilar products and reference products had suffixes.

If in the future FDA continues to name biosimilar products with a suffix it could lead to biosimilars having a suffix while their reference products do not. If consumers perceive the presence or absence of a suffix as a signal of the inferiority or superiority of a product, overcoming such an incorrect perception will add to the consumer's burden in learning about a

biological product and increase the information asymmetry between the consumer and the firm. Consumers may be less likely to view the biosimilar as a viable alternative to the reference product if only the biosimilar product has a suffix. If consumers incorrectly conclude that the presence or absence of a suffix indicates clinically meaningful differences between such products that FDA has not found, those perceived differences will be a barrier to competition. Less differentiation between the formats of the names of these products may lead to more competition between products than would exist if only one of the products had a suffix. Alternatively, consumers may incur some opportunity costs in overcoming any misperceptions caused by differences in naming format as they learn about biological products. The proposed rule, if finalized, removes the possibility of misperceptions based on the format of the names for certain products, reducing potential information asymmetry.

In the past, the Agency has assigned prefixes to the nonproprietary names of certain related biological products. We now have two biological products that share a core name, where one product name has a prefix and the other product name has a suffix. To reduce potential confusion, the rule also proposes to remove the prefix and add a suffix to the nonproprietary name of the related biological product that shares a core name with a reference biological product and a biosimilar product.

B. Affected Firms and Products

The proposed rule would affect firms that hold 6 approved biologics license applications (BLAs). Two additional firms may incur costs in repackaging and labeling two of the six products. The Agency's national drug code (NDC) listing database identifies 64 NDCs for the affected BLAs. Each NDC represents a package which may contain one or more individually labeled vials, syringes, or blister packs. In total, we estimate that the proposed rule would require

firms to change labeling for 64 distinct packages.

In addition to package labels, the proposed rule would require that BLA holders change the prescribing information that accompanies the product and is sometimes referred to as the package insert. BLA holders for the six biological products that are the subject of this proposed rule would revise the prescribing information to incorporate the new nonproprietary name where appropriate. Consequently, BLA holders would need to revise the prescribing information and submit a prior approval labeling supplement to the Agency for the six affected products.

C. Costs of the Proposed Rule

1. Administrative Costs

We expect that each distinct BLA holder (four entities) would have marketing managers, regulatory affairs staff, and lawyers review the rule. With a reading speed of 200-250 words per minute (Ref. [1]), it would take each person more than one hour to read the rule, if finalized. We round up to two hours per person to allow time to review and interpret the rule. If each affected BLA holder has two marketing managers, two regulatory affairs staff, and two legal staff review the rule, and each spends two hours reading and interpreting the rule, the total costs for the affected entities would be about $7,000. This estimate uses median wages from the Bureau of Labor Statistics (BLS) for marketing managers in the pharmaceutical industry of $67.95 per hour (adjusted for overhead to $135.90 per hour) and median wages for lawyers of $75.44 per hour ($150.88 per hour adjusted for overhead). Since the BLS does not specifically list wages for regulatory affairs staff, we approximate regulatory affairs wages with the wages for lawyers. We exclude relabelers from the cost of learning about the rule as they may be informed of the name change by the BLA holder. We request comment on any costs to relabelers that we do not capture. We also request comment on all estimates of learning about the rule for purposes of

estimating administrative costs associated with the rule, if finalized.

2. Costs to modify labeling – prescribing information

The Agency has recently estimated that large drug manufacturers would incur about $7,770 in one-time costs to revise prescribing information and to upload the revised labeling to our listing database. A repackager/relabeler would incur about $1,340 in one-time costs to revise its labeling to match the labeling of the reference listed drug and upload the revised labeling (see table 10 on page 26 in the report available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/UCM427798.pdf). Updated to 2013 dollars, these one-time costs would equal about $8,000 and $1,400. Because the proposed rule would require that BLA holders obtain prior approval of the required labeling changes, we estimate that affected BLA holders might spend 40 hours to prepare a supplement, including any time they spend during the comment period to discuss alternative suffixes with the agency. With a wage (for pharmacists) of $120 including 100 percent overhead, BLA holders might spend about $4,800 to prepare each prior approval supplement. In total, each BLA holder would incur one-time costs of about $12,800 adjusted to 2013 dollars. In total, the one-time costs to modify the prescribing information for the six affected BLA holders would equal about $77,000.

Two additional firms may incur costs to revise labeling to match changes made by the BLA holders. However, these 2 firms would not incur any additional cost to prepare a prior approval supplement. At about $1,400 for each affected product, these firms would spend about $4,200 to revise prescribing information.

The one-time total cost for affected firms to revise prescribing information would equal about $81,000. We request detailed comment from affected firms about our cost estimates.

3. Costs of changing package labels

We estimate the cost of changing the package labels for each affected NDC, using a Labeling Cost Model developed by RTI International. The affected products are typically packaged as vials in a carton or as pre-filled syringes in a carton. For each product there is, at minimum, an inner label on the vial or syringe and an outer label that would need to be changed. As the Labeling Cost Model does not specifically include data on prescription drugs, we use labeling cost data for over-the-counter (OTC) insulin syringes as a proxy. Over-the-counter insulin syringes are medical devices, and like other OTC products, are not directly comparable to the biological products affected by the proposed rule. Packaging for insulin syringes and for biological products may share certain features, such as a label on the inner packaging as well as a label on the carton.

The cost of package label changes is driven primarily by the amount of time the firm has to make the change. If firms have sufficient time to coordinate the package label changes that would be required by the rule with their own scheduled package label changes, costs would be lower. If firms have a short time frame in which to make changes, they would incur higher labor costs and greater label inventory losses. We assume that firms will not coordinate the required label changes with other label changes, and therefore will not save on the costs of the label change by combining it with other planned label changes. We assume the change to the label will be minor, requiring no redesign or change in color.

We estimate that firms will incur a one-time, per package cost of $8,060 to $31,967 to change the package labels (2013 dollars). Agency listing data shows that there are 64 NDCs associated with the affected BLAs. Multiplying the per package cost by the number of NDCs yields package relabeling costs ranging from $515,000 (64*$8,060) to $2,045,000 (64*$31,967).

In some cases, the labels of the 64 products subject to the rule may be similar to one another. If some labels are similar, this approach may overestimate cost. We request detailed comment on the expected cost of changing package labels.

4. Costs of submitting forms to update marketing materials

BLA holders would also be required to update their marketing materials to reflect the new nonproprietary name of the biological product. BLA holders must submit Form 2253 for each piece to be updated. Normally BLA holders submit a general correspondence letter for each BLA notifying FDA of the intent to change the materials. Based on the nature of the change, FDA may permit submission of representative materials in a general correspondence letter rather than submission each individual material, and costs of submission may be somewhat lower than estimated.

We assume it takes a marketing manager one hour to prepare a general correspondence letter to the FDA. According to the Bureau of Labor Statistics, marketing managers have a median hourly wage of $67.95 (in 2013), which we multiply by two to account for benefits and overhead. We estimate that the cost to prepare correspondence letters for six BLAs would be $815 ($67.95*2*6*1).

The estimated paperwork burden for each Form 2253 is two hours (see Table 2). Between July 2013 and February 2014, holders of the five BLAs that are the subject of this proposed rule (excluding the BLA holder for filgrastim-sndz) together submitted an average of 46.5 Form 2253s per month. For a low estimate, we assume that each BLA holder would only have to update two months of marketing materials, based on the assumption that the life-cycle of the material is two months (at least some marketing materials for these BLA holders, sales aids, have a life-cycle of less than two months). We assume that the BLA holder for filgrastim-sndz may

submit a similar number of Form 2253s as the other BLA holders affected by the rule. Because the form submissions for filgrastim-sndz are not included in our data, we adjust the total number of forms up by the average number of forms for the remaining five BLAs over two months to 112 (46.5*2/5*6). For two months of forms, we estimate costs of about $30,000 ($67.95*2*112*2).

For a high estimate, we use the total number of Form 2253s submitted in the 18 month window between July 2013 and February 2015. If BLA holders must update all materials for which they have submitted 2253s over the past 18 months, and they used the same number of forms to submit, they would have to submit 837 forms. We adjust this number up to 1004 (837/5*6) to account for the Form 2253s that may need to be submitted for materials related to filgrastim-sndz. The total number of Form 2253s could be lower if BLA holders submit multiple pieces of marketing material per form. We request comment and data on the average lifecycle of marketing materials affected by the proposed rule. We estimate the cost for a marketing manager to prepare these forms to be $273,000 (($67.95*2*1004*2).

We estimate the total costs of submitting paperwork to change marketing materials to be about $31,000 to $274,000. We welcome comments on this approach.

Table 2: Cost to industry of submitting forms to update marketing materials

	Lower Bound	Upper Bound
Number of Form 2253s	112	1004
Preparation time per Form 2253 (hours)	2	2
Cost per hour ($)	136	136
Preparation cost ($)	30,333	272,996
Correspondence letter cost ($)	815	815
Total ($)	31,148	273,811

Note: Number of forms is rounded. Total costs are based on unrounded number of forms and unrounded wages.

BLA holders would also incur costs to update the affected marketing materials themselves. We anticipate that these costs would vary by type of material. Updating marketing materials could be more costly if firms replace material that is still in use. How much marketing material each BLA holder replaces may depend on the BLA holder's schedule for introducing additional product bearing the new name into the market following approval of the supplement. Generally, the name used in marketing materials should match the name on product labeling, though in this case there will be a transition period for many or all of the affected products as supplies of product already in the market bearing the old name are exhausted. We lack information to estimate the costs to update marketing material to reflect the new nonproprietary name. We request detailed comment on our assumptions and the potential costs of replacing marketing materials.

5. Costs of education about the nonproprietary name changes

Though not specifically required by the proposed rule, firms may decide to engage in some outreach and education to inform practitioners, payers, and consumers of the nonproprietary name change. FDA anticipates that these activities may include letters to hospitals and healthcare practitioners, and advertisements in medical journals.

To estimate the costs of direct mail, we looked at price lists for various printing and mailing services for first class mail. Prices (including postage) ranged from $0.541 per piece for a folded brochure with no envelope to $1.67 per piece for a 8.5" x 11" letter in an envelope with color. We assume that firms would send mailings for each product to hospitals and to specialists most likely to prescribe that product. Hematologists, oncologists, and nephrologists would most likely prescribe epoetin alfa, filgrastim, tbo-filgrastim, filgrastim-sndz, and pegfilgrastim.

According to the Association of American Medical Colleges (Ref. [2]), there were 13,774 hematologists and oncologists and 9,394 nephrologists in the United States in 2014. Gastroenterologists, rheumatologists, and dermatologists would be most likely to prescribe infliximab. According to the Association of American Medical Colleges, there were 13,626 gastroenterologists, 5,357 rheumatologists, and 11,363 dermatologists in the United States in 2014. We multiply the number of specialists and hospitals likely to prescribe the brand with the cost per piece of direct mail and the number of affected brands. We assume that these costs would be incurred for seven affected branded products produced under the six affected BLAs (Epogen (BLA 103234), Procrit (BLA 103234), Neupogen (BLA 103353), Granix (BLA 125294), Remicade (BLA 103772), Neulasta (BLA 125031), and Zarxio (BLA 125553). We welcome comments on this approach. We estimate $116,000 to $359,000 in mailing costs (see Table 3) assuming seven affected brands. Actual costs to the affected firms may be lower than these estimates, as firms may target their mailings to physicians most likely to prescribe their products, consolidate mailings, or distribute letters as part of their normal detailing activities rather than by mail. Costs could exceed our estimate if firms choose to send mailings to a broader range of practitioners than indicated here and costs may be lower since such mailings are at the discretion of the manufacturer. We welcome comment on the expected size of such educational mailings.

BLA holders may also choose to inform practitioners of a nonproprietary name change through an advertisement in a medical journal. We found prices for one page, black and white advertisements for leading specialty journals to range from $1,585 to $3,680. If one advertisement were placed for each of the seven branded products, the cost would range from about $11,000 to about $26,000. These costs could be higher if BLA holders elected to run

multiple advertisements.

For each new piece of educational material, firms may need to submit Form 2253. We assume that firms would not need to submit an additional correspondence letter for these educational materials. We assume that the seven branded products would submit two pieces of educational material: a journal advertisement and a letter to practitioners. We estimate the cost of submitting forms for educational materials to be $4,000 (14*2*$136). We estimate total cost for educational activities to be approximately $131,000 to $389,000. We request comment on the projected costs of mailing, advertising, and submitting forms.

We do not include the costs associated with drafting letters for practitioners and preparing journal advertisements; we request comment on the costs of these activities. In addition, firms may also create press releases, or make changes to web content to help inform the public about the nonproprietary name changes. We request comment on the potential costs of these activities as well.

Table 3: Costs of educational activities

	low estimate ($)	high estimate ($)
Direct mail costs	116,410	359,344
Journal advertising cost	11,095	25,760
Submission of 2253s	3,805	3,805
Total	131,310	388,909

Some education may be included in ongoing programs or detailing activities already in place. We request comments on the educational activities affected BLA holders would be likely to undertake specifically discussing the nonproprietary name change, if the proposed rule were finalized, as well as associated costs.

6. Costs of changing prescribing and reimbursement systems

If the proposed rule is finalized, once labeling supplements containing the proposed names are approved, companies with prescribing and reimbursement systems would update their systems to include the new names. It may be appropriate for such systems to maintain both the old and new names to the extent that product bearing the old names remains on the market following approval of the supplements. These systems draw on databases that are updated frequently as formularies change or as new products enter the market. FDA would take steps to ensure that its drug listings that interface with other databases and systems reflect the newly designated nonproprietary name. We request detailed comment on potential costs of changes that would need to be addressed through other mechanisms, and any other costs associated with systems or references that use the nonproprietary name. We specifically request comments on the potential need for modifications to systems that populate electronic prescribing information on the basis of a specific diagnosis and associated costs for such changes.

7. Costs to official compendia

If finalized, official compendia may be affected by the proposed rule. We request comment on the adjustments that official compendia may make in response to the proposed rule, if finalized.

8. Potential loss of revenue to affected firms due to competition

In the event that one of the reference products affected by the proposed rule faces competition from a biosimilar product, the proposed nonproprietary name change may affect the level of competition between those two products. If the names of both the reference biological product and the biosimilar product have suffixes, the presence or absence of a suffix could not be used as an indication of the approval pathway. If the use of suffixes for reference and biosimilar products help reduce misperceptions that biosimilar product are inferior or have clinically

meaningful differences from their reference products, this may result in an incremental increase in adoption of a biosimilar and an incremental decrease in use of the reference product. If this occurs, reference products affected by the name change may experience a loss of revenue beyond the loss in revenue that would occur if the reference product's name remained unchanged. This loss of revenue may be the result of both (1) a reduction of the future number of units sold of the reference product, as some patients begin to use the biosimilar product that in the absence of the name change would have used the originator product, and (2) a reduction in price, due to greater competition stemming from any increase in perceived sameness of the products. This loss of revenue is not a cost of the rule, but rather represents a transfer to biosimilar companies, patients, and to payers. As biosimilar companies gain market share, some revenue that previously went to originator companies will go to biosimilar companies. With an increase in competition, any reduction in price will be a transfer to the entities paying for the drug, be it private or public payers or patients.

9. Potential impact on consumers

When consumers (health care practitioners and patients) look up biological products, a difference in naming format may make it easier to identify and remember products. Under the proposed rule, if finalized, consumers may need to expend more effort in identifying the intended product. Consumers would not be able to rely on identifying products based on the absence of a suffix or the presence of a prefix. We request comment on the potential impact on consumers of the proposed nonproprietary name changes.

D. Cost to Government

The proposed rule, if finalized, would codify the official name and proper name for the six affected BLAs. The Agency would spend additional time reviewing six prior approval

supplements. The Agency estimates that it will take 10 hours to review each supplement. For six supplements, at a cost of $116 per hour, the cost of reviewing supplements would be $6,960.

In addition, FDA would need to review revised marketing materials for the affected products. Some examples of marketing materials include television advertisements, direct mail, exhibit displays, and electronic communications. For each affected BLA, the manufacturer may send a general correspondence letter announcing intent to change their marketing materials. FDA estimates that it will take about 30 minutes to review each letter. We anticipate that there will be marketing materials where the name would have to be changed for each of the six affected BLAs. For a cost of review of $116 per hour, reviewing the correspondence letters would cost FDA $347 (6*0.5*$116).

The affected manufacturers would also have to submit Form 2253 to the FDA to change marketing materials. Over the past 18 months, there have been 837 Form 2253s submitted for 5 of the affected biological products. If all of these materials were distinct from one another and at least one material on the Form 2253 required a name change, those manufacturers would have to submit up to 837 Form 2253s as a result of the proposed rule, if finalized. The data does not include Form 2253s filed for filgrastim-sndz. We adjust the total number of forms up by the average number of forms per the remaining five BLAs to 1004 (837/5*6). The total number of Form 2253s could be lower if BLA holders submit multiple pieces of marketing material per form. FDA estimates that it will take 0.25 to two hours to review each Form 2253 (see Table 4).

At least some marketing materials have a life-cycle far shorter than 18 months. For example, sales aids for the five of the products affected by the proposed rule for which FDA has historical data may be replaced within two months. If most marketing materials are used for a similar amount of time as sales aids, manufacturers would only have to change two months'

worth of marketing materials. On average, there are 93 Form 2253s submitted for the affected products per two-month period. We adjust this number of Form 2253s up to account for filgrastim-sndz to 112 (46.5/5*6). If the lifecycle of marketing materials were such that manufacturers only had to submit two months of Form 2253s, the review cost to FDA could be as low as $3,000.

FDA may also need to review 2253s for the educational materials that firms may create as a result of the rule. As these 2253s may be in addition to the number of 2253s usually submitted by firms, we account for them separately. We assume that these materials could be included in the general correspondence letter sent for other marketing materials, and that no separate letter would be necessary. We assume that each of the seven affected brands would create a letter to practitioners and a journal advertisement. Firms would submit 14 Form 2253s, for a cost of $400 (14*0.25*$116) to $3000 (14*2*$116). Total cost of FDA review ranges from $4,000 to $236,000. We request comment on this approach.

Table 4: Cost of FDA review of marketing material

	Lower Bound	Upper Bound
Number of Form 2253 reviews	112	1004
Review time per 2253 (hours)	0.25	2
Cost per hour ($)	116	116
FDA Form 2253 review cost ($)	3,225	232,180
Correspondence letter review cost ($)	347	347
Review of 2253s for educational materials ($)	405	3,236
Total ($)	3,976	235,763

Note: Number of forms is rounded. Total costs are based on unrounded number of forms and unrounded wages.

Although FDA does not consider cost impacts on other Federal health care payers, we recognize that any changes to drug prices as a result of naming conventions and any competition effects will have a direct impact on Federal health care spending.

E. Summary of the Annualized Costs of the Rule

The total costs of the proposed rule include the costs to learn about the rule, modify prescribing information, modify labels of the affected biological products, and educational activities to inform the public about name changes (see Table 5). Table 6 summarizes these costs which range from $0.78 million to $3.04 million. As shown in 6, the annualized costs of the proposed rule, if finalized, range from about $0.09 million to $0.35 million with a 3 percent discount rate and range from about $0.10 million to $0.40 million with a 7 percent discount rate.

Table 5: Summary of Costs

Cost element	Total One-Time Costs Lower Bound ($)	Total One-Time Costs Upper Bound ($)
Cost of learning the rule	7,003	7,003
Modify prescribing information	81,104	81,104
New labels	515,853	2,045,900
Industry marketing submissions	31,148	273,811
FDA review of supplements	6,960	6,960
FDA review of marketing submissions	3,976	235,763
Costs of educational activities	131,310	388,909
Total	777,354	3,039,450

Table 6: Summary of one-time and annualized costs

One-Time Costs Lower Bound ($ mil)	One-Time Costs Upper Bound ($ mil)	Total Annualized Costs with 3 Percent Discount Rate Lower Bound ($ mil)	Total Annualized Costs with 3 Percent Discount Rate Upper Bound ($ mil)	Total Annualized Costs with 7 Percent Discount Rate Lower Bound ($ mil)	Total Annualized Costs with 7 Percent Discount Rate Upper Bound ($ mil)
0.78	3.04	0.09	0.35	0.10	0.40

Note: Total costs are annualized over 10 years.

F. Potential Benefits of the Proposed Rule

1. Consumer and Producer Surplus

One possible outcome of these proposed name changes is that they may enhance competition between current and future biosimilar products and the reference products that are the subject of this proposed rule, if finalized. In the absence of this regulation, one biosimilar would have a suffix (filgrastim-sndz) while its reference biological product would not (filgrastim), and this pattern could be repeated for the other three biological products for which there is a publicly disclosed 351(k) application if such applications would be approved with nonproprietary names that include a distinguishing suffix. To the extent that consumers have inaccurate perceptions due to differences in the use of suffixes, those differences would exacerbate the information asymmetry that exists between firms and consumers of biological products. A difference in the format of the name between the reference biological product and the biosimilar product could result in inaccurate perceptions of inferiority of an approved biosimilar product and potentially reduce competition. Requiring the affected reference products to bear a suffix, however, may help avoid any such perceptions about current and future biosimilar products. Accordingly, these name changes could support the uptake of biosimilars and more robust competition in the markets for certain biological products.

More competition between biological products could result in lower prices and cost savings for payers and patients. If prices for these biological products fall, more patients could have access to these drugs. Taken together, the biological products that are the subject of this proposed rule have annual revenues in the billions of dollars, and competition has been limited. While the entry of biosimilars to the market is likely to result in increased total (consumer and

producer) surplus, we lack data on the extent to which the nonproprietary name or any name changes for these six products would enhance competition and increase surplus, and request comment on these potential effects.

There are several reasons to believe that any incremental increase in cost savings generated as a result of the proposed rule, if finalized, would be modest. However, as discussed below, incorporation of distinguishing suffixes in the nonproprietary names of these six biological products would facilitate safe use and may improve pharmacovigilance for these products. The biological products affected by the rule are expensive and carefully managed by payers. Payers will decide how to structure their formularies with the introduction of biosimilar products, and are likely to favor products based on performance and price rather than on the product names. In many instances, these types of drugs may be prescribed by specialists familiar with biological products and biosimilars. It is unknown if the nonproprietary name or any changes to that name would have any impact on the decisions of these specialists. Furthermore, savings that may result would be limited to the markets for the six products affected by this rule.

As consumers find names of products informative, names may have the greatest potential to affect consumer perceptions and behavior if they are in place at the time of product entry. The presence or absence of a suffix is most likely to affect perceptions of patients and practitioners when they first learn about a biosimilar product and first compare it to the reference product. It is uncertain how long this initial learning period may last, and how much of the effect of a name change may diminish if a biosimilar enters some time before a name change for the reference product. After some initial period of learning about a competing biosimilar product, patients and practitioners may pay less attention to the name of the reference product as they may have already formed perceptions of the reference product and the biosimilar product. The proposed

rule, if finalized, would have maximum effect on cost savings if the name changes for the affected reference products were to happen before or close to the launch of a biosimilar product.

2. Avoidance of medication errors and improved pharmacovigilance

The incorporation of distinguishing suffixes in the nonproprietary names of these six biological products may increase the likelihood that the biological product selected by the health care provider is the same biological product that the patient receives. If a suffix were somehow dropped in the course of prescribing, ordering, or dispensing, and another product with the same core name had no suffix, it is possible that a patient would receive a different product than the physician had intended. If each product has a suffix, and the suffix was dropped, the error would be more likely to be detected.

Inadvertent switching between biological products that have not been shown to be interchangeable may pose an increased risk of immune response. As noted in the preamble, effects could include adverse reactions to the product or reduced efficacy for the affected patient. We lack data on the extent to which inadvertent switching could increase the risk of these adverse effects. We also lack data on the potential effect suffixes for the products identified in this proposed rule might have on inadvertent switching. We request comments and data.

FDA issues this proposed rule in an effort to help the healthcare industry improve pharmacovigilance for the six affected products. The ability to track adverse events to a specific manufacturer's biological product enables the Agency and the manufacturer to identify and address a problem. If the Agency cannot identify a biological product's manufacturer, remedial action (including recall) may need to include a broader set of products, which may restrict patient access to safe and effective products for which no such problem exists. If one product has a suffix and another is known by the core name without a suffix, and if the nonproprietary name

was reported in an adverse event report and the suffix was omitted, and if the report did not have other information to clearly identify the product, the adverse event could be misattributed. Misattribution could delay remedial action in the event of a problem with a product.

G. Uncertainty

Although we have information about the products and application holders affected by the proposed rule, we lack information about many other potential costs and benefits. Designating distinguishable suffixes in the nonproprietary names of these six biological products may affect systems not directly regulated by us. We lack evidence about how the health care industry, industries providing services to the health care industry, the insurance industry, and consumers would respond to these changes. Consequently we may have excluded some of the costs and benefits from our analysis, and request detailed comment from affected parties about these missing elements. Moreover, we estimated the costs to change the labeling of the affected biological products with models designed for other products than prescription drugs. This introduces some uncertainty in these estimates. Thus, our estimate may under or overstate the actual costs to revise labeling.

H. Alternatives

1. One alternative would be to require name changes for 40 products regulated by the Center for Drug Evaluation and Research that have “N/A” as their reference product exclusivity expiry date in the Purple Book. The designation “N/A” as the reference product exclusivity expiry date means that more than 12 years (or 12 years and 6 months in the case of a product that has earned pediatric exclusivity) have passed since the date of licensure of the product, and thus any reference product exclusivity that the product may have had would have expired. Accordingly, this alternative would require name changes for 40 products for which there is no

exclusivity bar to submission and approval of an application for a proposed biosimilar product, rather than the four reference products for which a biosimilar has been approved or for which it has been publicly disclosed that an application for a proposed biosimilar product has been submitted. This would be more expensive than the proposed rule, as many more products would be affected. The average quantified cost to change the name of a biological product specified in the proposed rule is $129,000 to $506,000. We multiply the average cost by 40 affected products to estimate the cost of $5.18 million to $20.24 million under this alternative. This alternative may cost exceed these estimates, however, because it does not capture any differences in costs that were unquantified in the analysis.

If a large number of biological products have suffixes, and biosimilars are developed to those products, it may increase accuracy of prescribing and adverse event reporting. It is difficult to predict how many of biological products would face biosimilar competition, however.

2. An alternative naming scheme could use suffixes derived from the name of the license holder rather than suffixes with no meaning. For a list of alternative names, see Table 8. In this alternative, the name for filgrastim-sndz would not have to change, reducing one-time costs to about $0.72 million to $2.77 million. It is possible that some BLA holders would prefer nonproprietary names that include a suffix derived from the name of the license holder, as it may make remembering the name of the product easier for healthcare providers. Depending on the recognition of the firm's name and the associations that consumers may have with the suffix derived from the firm's name, this convention may confer some advantage to particular firms. Any advantage based on the suffix seems less likely with suffixes devoid of meaning.

Adding suffixes to the six affected biological products derived from the name of the license holder may have implications for future naming of interchangeable products.

Interchangeable products are biosimilar products that meet additional standards specified in the BPCIA. The BPCIA further defines interchangeability to mean "that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." Using suffixes based on firm names may restrict the type of suffix that can be designated for interchangeable products in a way that the proposed suffixes would not. Assigning suffixes derived from the name of the license holder might prevent an interchangeable product from having the same suffix as its reference product. Assigning suffixes devoid of meaning could allow an interchangeable product to have the same suffix as its reference product. If suffixes based on firm name prevented an interchangeable from having the same suffix as its reference product, it is possible that the interchangeable could have a competitive disadvantage that would not exist if suffixes were devoid of meaning. We request comment on the potential implications of this alternative.

Table 7: Alternative names based on firm names

BLA Number and Holder	Current name	Proposed name
103234, Amgen, Inc.	epoetin alfa	epoetin alfa-amgn
103353, Amgen, Inc.	filgrastim	filgrastim-amgn
125553, Sandoz, Inc.	filgrastim-sndz	filgrastim-sndz
125294, Sicor Biotech UAB	tbo-filgrastim	filgrastim-srbt
103772, Janssen Biotech, Inc.	infliximab	infliximab-jnsn
125031, Amgen, Inc.	pegfilgrastim	pegfilgrastim-amgn

I. International Effects

Labeling changes that would be required by the proposed rule would apply only to products marketed in the United States. We welcome comment on any potential international effects of this proposed rule.

J. Impact on Small Entities

The Regulatory Flexibility Act requires a Regulatory Flexibility Analysis (RFA) unless the Agency can certify that the proposed rule would have no significant impact on a substantial number of small entities. The Small Business Administration establishes thresholds for small entities by industries based on the North American Industry Classification System (NAICS). The Small Business Administration considers as small Pharmaceutical Preparation Manufacturing firms (NAICS 325412) with fewer than 750 employees and Biological Product Manufacturing firms (NAICS 325414) with fewer than 500 employees. The U.S. Census Bureau classifies relabelers as Drugs and Druggists' Sundries Merchant Wholesalers (NAICS 424210) and considers firms with 100 or fewer employees as small. All BLA holders and one additional firm affected by the proposed rule exceed the SBA size standard. However, the other affected firm has fewer than 100 employees. With annual sales estimated at $3.6 million, the one-time costs of the proposed rule for this firm would total about 0.1 percent of annual sales, well below our threshold for a significant economic impact. Thus, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

References

[1] L. A. Robinson, J. K. Hammitt, J. Baxter, L. Ludwig and M. Black, "Guidelines for Regulatory Impact Analysis," Department of Health and Human Services, Washington, DC, 2015.

[2] "2014 Physician Specialty Data Book," Association of American Medical Colleges, 2014.