May 9, 2017

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Apotex Citizen Petition to Request FDA to require all Biosimilar applicants referencing NEULASTA to conduct their studies in at least one intended patient population.
Docket No. FDA-2017-P-2803

Dear Sir/Madam:

Coherus Biosciences, Inc. (Coherus) appreciates the opportunity to comment on the Apotex Citizen Petition (CP), identified above,[1] and to correct certain points of misunderstanding as to the role of clinical studies in a biosimilar application submitted under the regulatory pathway created by the Biologics Price Competition and Innovation Act (BPCIA) [42 U.S.C § 262 (k)][2]. As discussed in greater detail below, FDA must deny the CP. Apotex's misunderstanding has led the company to erroneously conclude that a specific type of clinical study is or is not required for regulatory approval of a biosimilar application. As such, Coherus requests that FDA correct Apotex's mistaken conclusion so that other biosimilars sponsors are not misled into believing that additional unnecessary, and therefore unethical, clinical studies[3] must be undertaken to obtain licensure of a biosimilar. Such studies will not change the nature of the final biosimilars approved. Instead, conducting such studies would take resources that may reduce access and affordability for the very patients waiting on the availability of these products for improved healthcare.

The biosimilars pathway was created to enable FDA to license multisource biologics. This can occur where the finding of safety, purity and potency[4] of a specific previously approved 351(a) "standalone" BLA[5] is shown to be relevant to the subsequent 351(k) biosimilar application by the demonstration of a close match between that originator reference product and the biosimilar candidate. The standard is highly similar to the reference product demonstrated using sensitive analytical methods, and biosimilarity is confirmed but not established by limited subsequent clinical studies. Each step in the development of a biosimilar requires a head-to-head comparison between the biosimilar and the chosen 351(a) reference product[6] – it is not between different indications for which the reference is used, nor between entirely different originator products containing different active ingredients, such as those discussed in the CP. And the better the analytical match, the fewer subsequent studies, including clinical, are expected because residual uncertainty has been minimized[7, 8].

Further, FDA guidance is clear that the most sensitive population to be used for Pharmacokinetic (PK) and Pharmacodynamic (PD) studies of biosimilars are healthy volunteers. The Agency provides the following reasons for this scientifically well-founded conclusion[9]:

> *Clinical PK and PD studies should be conducted in healthy subjects if the product can be safely administered to them. A study in healthy subjects is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK and/or PD variability compared with*

*a study in patients with potential confounding factors such as underlying and/or concomitant disease and concomitant medications.* [FDA Final Guidance **"Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"** December 2016]

And where biomarkers exist, their use is strongly encouraged[10]:

> *Use of a single scientifically appropriate PD biomarker ... can reduce residual uncertainty regarding the existence of any clinically meaningful differences between products and can significantly add to the overall demonstration of biosimilarity.* [FDA Final Guidance **"Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"** December 2016]

Finally, given the importance in assessing any therapeutic biologic for any potential for immunogenicity, healthy volunteers can provide particularly valuable information. For a biosimilar where comparative studies are possible, as opposed to standard of care for originator products, the most immune-responsive population has particular value in detecting any differences. For those products for conditions of use, such as oncology, where immunosuppression through concomitant drug therapy is likely, healthy volunteers are particularly important and strongly preferred to patients as they provide the greatest opportunity to detect any immunological response at all[11].

The goal overall is that any biosimilar sponsor compile, after an expedited development program, a data package that is scientifically well-founded and that provides evidence that the biosimilar will behave clinically in the same manner as its reference product. This can be achieved even though the data package is not expected to contain clinical trials in every indication or every population in which the reference product is in use. This point is aptly demonstrated by the five biosimilars FDA has licensed[12]. The concept of extrapolation is founded on the exquisite molecular match possible through the careful use of modern analytical methods[13]. Such a match is essential to the development of biosimilars, and ultimately to the development of interchangeable biologics. It is also data that are privileged to each sponsor and on the basis of which each clinical confirmatory program will have been individually negotiated with the Agency. As FDA has observed, the better the match the more focused the clinical confirmatory program can be:

> *Enhanced approaches in manufacturing science, as discussed in ICH Q8(R2), may facilitate production processes that can better match a reference product's fingerprint.[14] Such a strategy could further quantify the overall similarity between two molecules and may lead to additional bases for a more selective and targeted approach to subsequent animal and/or clinical studies.* [FDA Final Guidance **"Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product"** April 2015]

Apotex does not have access to any biosimilar application beyond their own. That clinical studies are listed publicly appears to have led Apotex to focus only on the clinical trials strategy, and the dataset arising from such, as the sole critical step in demonstrating biosimilarity. It is not. Indeed, Dr. John Jenkins, former Director of FDA's Office of New Drugs stated that he could see a time when no clinical studies may be required at all[15] – a possibility contemplated by Congress when it passed the BPCIA. This is not to negate the value of limited clinical studies, but to emphasize how clearly FDA has articulated that the basis of biosimilarity is an extremely clear analytical match, the best being referred to as

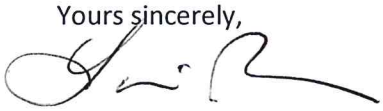
"fingerprint-like"[16, 17, 18]. A biosimilar candidate without a good match can never be approved as biosimilar to a reference product regardless of how many clinical studies are conducted[19]:

> *Insufficient analytical similarity: Certain differences in the results of the analytical characterization are sufficiently significant such that further development through the 351(k) regulatory pathway is not recommended unless, for example, modifications are made to the manufacturing process for the proposed biosimilar product that are likely to lead to the minimization or elimination of such differences.* [FDA Final **"Guidance Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"** December 2016]

That FDA has taken this approach is aptly demonstrated by the biosimilars that the Agency has approved to date. In none of those instances has FDA required studies to be conducted in every population in which the reference product was approved. Furthermore, in all cases, FDA's attention has been on the analytical match as the foundation of the agency's "totality of evidence" approach and to FDA's the determination of biosimilarity. Notwithstanding this, Coherus is aware that every biosimilar candidate is evaluated on a case-by-case basis, and that in many instances it may not be possible, because of the health risk to study volunteers, to conduct confirmatory clinical studies. Thus, despite the fact that health volunteers may be the most sensitive patients for immunological studies, they cannot be used for all biosimilars. Given that one of the most important reasons for conducting clinical studies with biosimilars is to assess immunogenicity, it is all the more critical that healthy patients are prioritized for the comparison of the biosimilar to its reference product.

Coherus appreciates the opportunity to comment on the issues raised in Apotex's CP and respectfully request that FDA deny the petition.

Yours sincerely,



Lisa Bell, Ph.D.
Executive Vice President, Global Regulatory Affairs

---

[1] Apotex and its subsidiary Apobiologix initially submitted a CP to FDA dated April 21, 2017, to which FDA assigned Docket No. FDA-2017-P-2528. That original CP appears to have been withdrawn and replaced by a CP dated May 3, 2017, and that is assigned Docket No. FDA-2017-P-2803.

[2] TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition And Innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA). Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed 28 April 2017)

[3] ICH E6 (R1) GUIDELINE FOR GOOD CLINICAL PRACTICE. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf ((accessed 28 April 2017)

[4] The FDA standard for licensure of a biological product as safe pure and potent under section 351(a) of the PHS Act has long been interpreted to include effectiveness (see 21 CFR 600.3(s) and the guidance for industry on

*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*). In this response, we use the terms *safety and effectiveness* and *safety, purity, and potency* interchangeably in the discussions pertaining to biosimilar products.

[5] To obtain licensure of a proposed product under section 351(k) of the PHS Act, a sponsor must demonstrate that the proposed product is biosimilar to a single reference product that previously has been licensed by FDA - see Sections 7002(a)(2) and (b)(3) of the Affordable Care Act, adding sections 351(k), 351(i)(2), and 351(i)(4) of the PHS Act. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed 28 April 2017)

[6] FDA Final Guidance: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry April 2015. The stepwise approach cumulatively creates the totality of evidence that FDA will evaluate discussed on page 7. Available at https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf (accessed 1May17)

[7] FDA Final Guidance: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry April 2015. Available at https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf (accessed 1May17). See Page 14

> *As a scientific matter, FDA expects a sponsor to conduct comparative human PK and PD studies (if there is a relevant PD measure(s)) and a clinical immunogenicity assessment. In certain cases, the results of these studies may provide adequate clinical data to support a conclusion that there are no clinically meaningful differences between the proposed biosimilar product and the reference product.*

[8] FDA Final Guidance: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry April 2015. Available at https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf (accessed 1May17). Page 7

> *A sufficient understanding of the mechanism of action (MOA) of the drug substance and clinical relevance of any observed structural differences, clinical knowledge of the reference product and its class that indicates low overall safety risks, and the availability of a relevant PD measure(s) may provide further scientific justification for a selective and targeted approach to animal and/or clinical studies.*

[9] FDA Final Guidance: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product December 2016. Available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf (accessed 1May17). Page 10

> *Clinical PK and PD studies should be conducted in healthy subjects if the product can be safely administered to them. A study in healthy subjects is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK and/or PD variability compared with a study in patients with potential confounding factors such as underlying and/or concomitant disease and concomitant medications.*

[10] FDA Final Guidance: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product December 2016. Available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf (accessed 1May17). Page 3

> *A. Exposure and Response Assessment to Support a Demonstration of Biosimilarity*
> *The objective of a well-designed clinical PK and PD study in a biosimilar development program is to evaluate the similarities and differences in the PK and PD profiles between the proposed biosimilar product*

*and the reference product. A well-designed clinical PK and PD study should include information about the exposure and, when possible, the exposure-response to the biological products, which are important for assessing whether there are any potential clinically meaningful differences between two products. Determining the exposure-response to a biological product can be particularly challenging because of the complex nature and heterogeneity of biological products. An evaluation of clinical pharmacology similarity should include assessments of PK similarity, and if applicable, PD similarity.*

*The PD biomarker(s) used to measure PD response should be a single biomarker or a composite of biomarkers that effectively demonstrate the characteristics of the product's target effects. Use of a single scientifically appropriate PD biomarker or a composite of more than one relevant PD biomarker can reduce residual uncertainty regarding the existence of any clinically meaningful differences between products and can significantly add to the overall demonstration of biosimilarity.*

[11] Final Guidance: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry April 2015. Available at https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf (accessed 1May17). Page 17:

> *The study population used to compare immunogenicity should be justified by the sponsor and agreed to by the Agency. If a sponsor is seeking to extrapolate immunogenicity findings for one condition of use to other conditions of use, the sponsor should consider using a study population and treatment regimen that are adequately sensitive for predicting a difference in immune responses between the proposed product and the reference product across the conditions of use. Usually, this will be the population and regimen for the reference product for which development of immune responses with adverse outcomes is most likely to occur (e.g., patients on background immunosuppressants would be less likely to develop immune responses than patients who are not immunosuppressed).*

[12] The biosimilars a;ready approved by FDA under PHS Act 351(k) are: Zarxio® (filgrastim-sndz) on 6Mar15 here; Inflectra®(infliximab-dyyb) on 5Apr16 here; Erelzi® (etanercept-szzs) on 30Aug16 here; Amjevita® (adalimumab-atto) on 23Sep16 here; Reflexis ® (infliximab-abda) on 21Apr17

[13] Final Guidance: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry April 2015. Available at https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf (accessed 1May17). Page 9-10: VII. DEMONSTRATING BIOSIMILARITY, A. Structural Analyses

[14] See the ICH guidances for industry *Q8(R2) Pharmaceutical Development* (ICH Q8(R2)), *Q9 Quality Risk Management* (ICH Q9), *Q10 Pharmaceutical Quality System* (ICH Q10), and *Q11 Development and Manufacture of Drug Substances* (ICH Q11) for guidance on enhanced approaches in manufacturing science.

[15] RPM FDA/CMS Summit December 2013, Public presentation and discussion by John Jenkins as part of a panel.

[16] For more information on fingerprint-like analysis, see Kozlowski S, Woodcock J, Midthun K, Sherman RB, 2011, Developing the Nation's Biosimilars Program, N Engl J Med; 365:385-388

[17] Final Guidance: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry April 2015. Available at https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf (accessed 1May17) Page 7

[18] FDA Draft Guidance "Considerations in Demonstrating Interchangeability With a Reference Product", page 6 *For example, a fingerprint-like characterization may reduce residual uncertainty regarding interchangeability and inform the data and information needed to support a demonstration of interchangeability, which may lead to a more selective and targeted approach to clinical studies necessary to demonstrate interchangeability.*

[19] FDA Final "Guidance Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product" December 2016. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf (accessed 1May17) Page 5

> Insufficient analytical similarity: Certain differences in the results of the analytical characterization are sufficiently significant such that further development through the 351(k) regulatory pathway is not recommended unless, for example, modifications are made to the manufacturing process for the proposed biosimilar product that are likely to lead to the minimization or elimination of such differences.

2017

# How Analytics and Confirmatory Studies in Healthy Volunteers Demonstrates Biosimilarity

COHERUS BIOSCIENCES | 333 Twin Dolphin Drive, Suite 600, Redwood City, CA 94065

# Table of Contents

## Executive Summary

Few biosimilars are yet approved in the US, but many more candidates are in development[1,2]. Multi-source biologics can be expected to impact the biologics market by fostering access and affordability through competition, just as occurred for generic drugs. Patients and their healthcare providers can be confident that all FDA-approved biosimilars meet FDA's strict standards for efficacy, safety and quality, and that they behave clinically just like their reference products. However, their development has key differences from originator medicines.

Demonstrating biosimilarity fundamentally relies on showing a tight analytical match between the reference product and the biosimilar candidate. The scientific axiom that *the same molecule can be expected to behave the same way clinically* applies to biologics and biosimilars, as well as small molecule drugs and generics. Hence, demonstration of a highly similar analytical match for a biosimilar makes relevant all the safety and efficacy information about the reference product, as well as all the experience with its clinical use. Clinical trials simply confirm this match established analytically (unlike phase 3 trials for a brand new biologic which are to show safety and efficacy *a priori* for the new active ingredient). And the better the analytical match, the fewer the required clinical studies expected by FDA because the uncertainty as to how the biosimilar will behave clinically is low too.

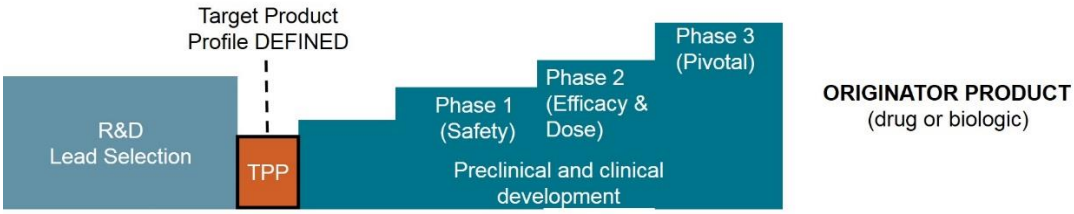
FDA currently requires a trial in the most sensitive population to (1) identify any differences in pharmacokinetics (and pharmacodynamics, when an appropriate marker is available) and immunogenicity, and (2) assess a single transition from the reference product to the biosimilar for products administered more than once. Hence, except where the target is related to the disease itself, conducting that confirmatory clinical study with healthy subjects is preferable. By way of example, we use the filgrastim family of proteins where a clinical trial program in healthy volunteers is the best, most sensitive, and most ethical way to confirm biosimilarity, and combined with the analytic data, complete a regulatory filing to meet biosimilarity approval requirements. Patient data would add no new information.

## Introduction – New Medicines, Generics and Biosimilars

**Traditional development of a new medicine** has to show that the new product is safe and efficacious in each indication (see Figure 1, below). To achieve this, a promising compound or molecule undergoes preclinical testing in animals and then the sponsor files an Investigational New Drug Application (IND) with FDA to allow clinical trials. Sponsors typically conduct three phases of clinical studies (Phase 1, 2, and 3)[3]. In Phase 1, a small number of healthy volunteers are given the product to identify any toxicity and determine how the drug is metabolized and excreted. In Phase 2, a larger number of patients are given the product to obtain preliminary data on efficacy as well as gain additional information on safety. Phase 3 studies utilize large patient populations, and are designed to demonstrate safety and efficacy of the product to FDA for each indication sought. During review of the submitted marketing application, FDA evaluates all the data on the product and determines whether the sponsor has demonstrated that the drug or biologic is safe and

effective in each indication tested. All FDA-approved drugs and biologics are made to the same high quality (known as current Good Manufacturing Practices, cGMP[4]).

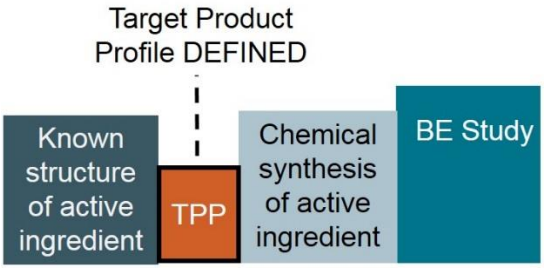
**Figure 1:** Traditional Drug Development




**Generic drug development** follows a very different path because a generic drug is a chemical match of an already FDA-approved drug (see Figure 2, below). As such, a generic drug sponsor does not have to "re-prove" the safety and efficacy of the drug in all indications, but rather must demonstrate that the generic is therapeutically equivalent to that specific FDA-approved drug (known as the "reference product")[5]. This means that it is pharmaceutically equivalent (i.e., contains the same active ingredient) and bioequivalent (i.e., the same rate and extent of absorption of the drug) to that specific reference product.

Generic sponsors demonstrate bioequivalence (BE) with BE studies (also known as pharmacokinetic/ pharmacodynamic (PK/PD) studies) comparing the systemic exposure profile of the generic to the reference product in healthy subjects. A showing of bioequivalency allows the generic sponsor to rely on (or "reference") the approval of the FDA-approved drug to establish that the generic drug is safe and effective. The scientific basis underlying an abbreviated development process is that *the same molecule can be expected to behave the same way clinically (in all indications)*. Because a generic drug is bioequivalent and a chemical match, no clinical trials are necessary for approval of a generic drug. In fact, often FDA waives the BE study for injected drugs entirely. As for all FDA-approved products, generic drugs are manufactured to the same high quality as innovator drugs.

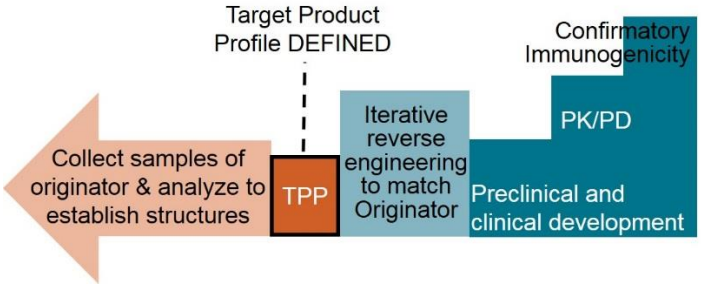
**Figure 2**: Generic Drug Development



**Biosimilarity** builds on the regulatory concepts and scientific basis underlying the abbreviated development model for generics, the fundamentals of originator products, as well as on the decades-old regulatory model used to support manufacturing changes known as comparability[6]. FDA uses comparability to decide that a post- manufacturing change innovator biologic, even with analytical differences, can be expected to perform clinically the same as the pre- change product[7]. As such, the application of high similarity standards to biologics is well established and the experience at FDA is considerable[8]. It is well understood that most drugs are chemically synthesized[9] and show little to no variability between batches, whereas most biologics are made in living systems and can show natural variability between batches. Nonetheless, the scientific axiom that *the same molecule can be expected to behave the same way clinically (in all indications)* still applies to biologics and biosimilars. However, because biologics can show intrinsic, as well as batch-to-batch variation, the biosimilar, unlike a generic, does not rely on solely showing bioequivalence.

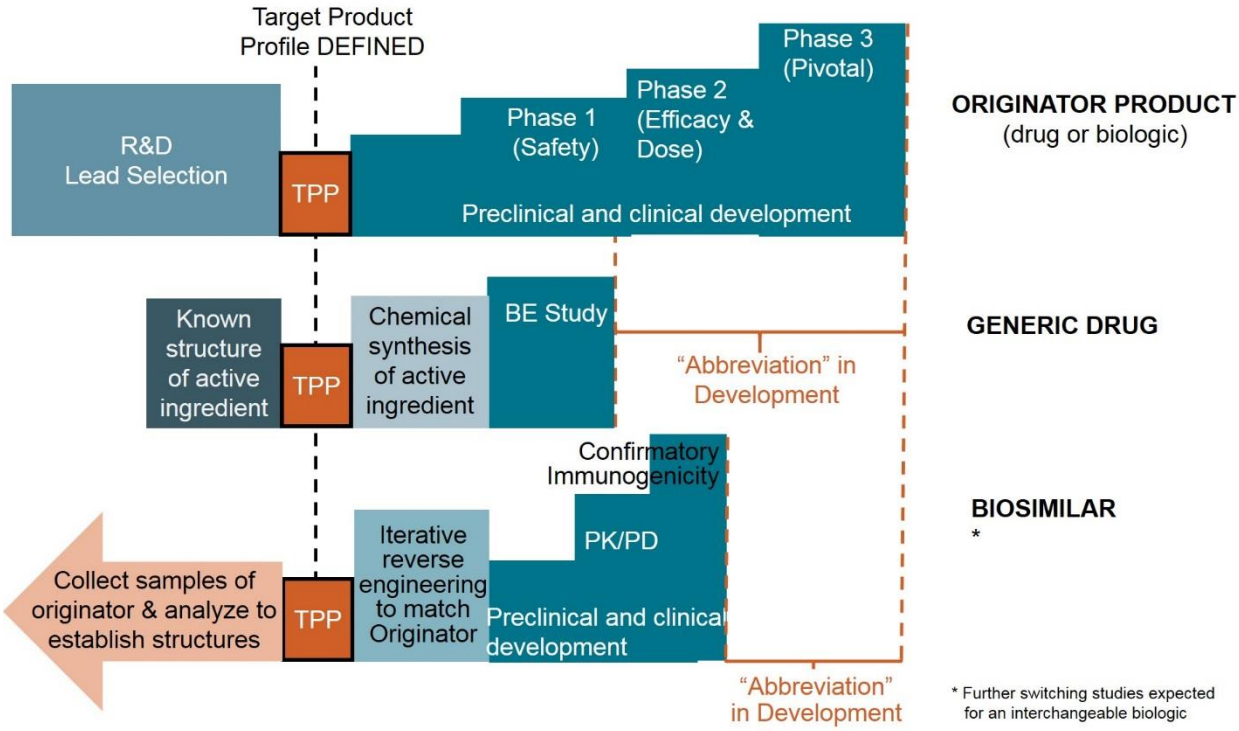
As described in more detail below, biosimilar sponsors instead show that their biosimilar candidate is "highly similar" to its reference product in multiple analytical assays, and on this basis the same clinical outcomes can be expected. Following such a showing, FDA may require a confirmatory clinical study(s). Just like an originator biologic, a biosimilar development program follows a stepwise approach, but one that is based on this "sameness" premise and so differs fundamentally from creation of a new medicine and demonstration of safety and efficacy *a priori*. Instead, more like a generic, a biosimilar sponsor must demonstrate a head-to-head match between the biosimilar candidate and its reference product at every stage in the development process (see Figure 3, below).

**Figure 3**: Biosimilar Development




By combining the three figures above in Figure 4, below, it is possible to see how the development of biosimilars offers abbreviation in the development phase, and yet that the resulting product can be equivalent to its reference product in terms of the clinical outcomes expected.

**Figure 4**: *Comparing Traditional, Biosimilar, and Generic Development*




## Analytics are the Fundamental Basis of the Biosimilarity Determination – The Science of Matching

The comprehensive, head-to-head comparisons of the biosimilar candidate with the reference product using state-of-the-art analytics is the foundation of biosimilarity. A high degree of analytic similarity impacts the need for clinical data. The lack of analytic high similarity cannot be remedied by a clinical trial showing indistinguishable results between the biosimilar candidate and its reference.

Most biologics are made by natural processes in living systems so some level of inherent variability among multiple batches likely exists. Nonetheless, healthcare providers and patients can be confident that different batches of any biologic can be expected to behave the same way clinically. FDA-required good quality control ensures this for all products[10], even after manufacturing changes, such as scale ups or site changes[11]. However, this inherent variability for most biologics, means that a biosimilar will not match its reference product in the same manner as a generic small molecule drug. This is why the first step for a biosimilar sponsor is to collect multiple samples of the originator biologic they plan to use as their reference product (e.g., different batches over time; batches from different times relative to their expiration date, possibly batches approved in multiple countries, but always including US-sourced product). Then they comprehensively analyze those samples with multiple state-of-the-art analytical and functional tests to identify the variability

across these originator product samples and use these to create a profile[12] that the biosimilar will match (i.e., be "highly similar" to).

The biosimilar sponsor then engineers, and re-engineers as many times as needed, a process that creates their biosimilar to match this profile. This means the biosimilar falls within the variability seen with the reference product samples as a whole – often called the "goal posts"[13]. Manufacturing changes over the lifetime of the reference product may have created part of the variation, but patients and their providers know that these have not resulted in clinically meaningful differences as those changes were also overseen by the same regulators using the "highly similar" analytical standard[14].

Once a biosimilar candidate is created, the sponsor conducts extensive analytical head-to-head tests to identify any differences between the biosimilar candidate and the reference product, but not all differences matter equally. Nonetheless, all differences must be explained. Quality attributes that are known or thought to impact clinical performance of the molecule are considered "critical quality attributes" (e.g., presence and pattern of certain glycans), and biosimilar sponsors assess these particularly carefully.

Biosimilar sponsors use their experience and what is known in the scientific literature or from their own studies about the molecule to determine what attributes are or might be clinically relevant. In addition, FDA is familiar with determining which attributes may impact clinical performance of biologics given, by definition, the reference product is well-established[15]. The Agency has years of experience comparing pre- and post- manufacturing change innovator biologics to determine if, even with analytical differences, the post-change product can be expected to perform clinically the same as the pre-manufacturing change product. If yes, the post-change product is released, if not, the post-change product is considered a "new" product and must obtain separate approval to enter the market[16]. In fact, FDA will always have had at least 12 years of experience with the reference product before approving a biosimilar to that reference product[17].

*BUT HOW DOES A SPONSOR KNOW IF A QUALITY ATTRIBUTE IS CLINICALLY RELEVANT?*

After the biosimilar sponsor has conducted their analytic and functional comparisons, has identified any differences and determined which, if any, may be clinically relevant, the sponsor will meet with FDA to specifically discuss the analytic match results and get Agency concurrence on further development[18]. Unless the analytic match is good enough to meet the "highly similar" standard, the product cannot continue development as a biosimilar[19]. Clinical trials are generally recognized to be less sensitive than analytics for detecting a difference so they cannot make up for a lack of an analytical match, but they do confirm expected safety and efficacy, and show that the immunogenicity responses are also the same for the biosimilar and its reference product.

*THE BETTER THE MATCH, THE BETTER THE CANDIDATE, AND THE FEWER CLINICAL STUDIES REQUIRED TO CONFIRM BIOSIMILARITY*

Somewhat counterintuitively, the quality of the match is inversely proportional to the required clinical studies. That is, FDA will expect fewer, smaller or more tailored clinical studies for a biosimilar with a better match (often called "fingerprint-like"). Conversely, a biosimilar that is a poorer match (but still "highly similar") to its reference will likely require more clinical data for approval. FDA determines what additional studies a biosimilar sponsor must conduct by considering any residual uncertainty that exists between the biosimilar and its reference after reviewing the analytic match data, because this matching determines whether the products can be expected to behave the same way clinically. Indeed, FDA has said that there may be a point when no clinical studies are needed at all. But for now, it is important to keep in mind that more clinical data does not mean a "better" biosimilar[20].

## Healthy Volunteers are Best for Confirmatory Clinical Studies

The final step in the step-wise approach to biosimilar development, based on the analytic and functional data presented to FDA and with the Agency's concurrence[21], is the limited confirmatory clinical study(s). Sponsors conducting any study in human populations must consider the minimum number of participants needed to achieve the desired result. Unnecessary clinical studies that will not yield new information on which useful clinical decisions can be made are always unethical[22]. Consequently, the study design for a biosimilar differs significantly from conventional Phase 3 studies for an originator biologic as a biosimilar study does not "re-prove" the safety and efficacy of the reference product, but rather confirms that a highly similar match exists between the biosimilar candidate and the reference product.

While trial design is product-specific, every confirmatory clinical study is a head-to-head comparison between the reference product and the biosimilar conducted at the approved dose of the reference product[23]. The point is to show clinically meaningful differences if they exist[24]. FDA currently requires a trial that assesses pharmacokinetics (and pharmacodynamics, when an appropriate marker is available) and immunogenicity[25]. Additionally, FDA asks sponsors to include a single transition from the reference product to the biosimilar for products administered more than once.

For all confirmatory clinical trials, FDA requires that the biosimilar sponsor conduct the study in the most sensitive population – i.e., the population most able to show any clinically-meaningful differences between the biosimilar candidate and the reference product[26]. Especially important in choosing the most sensitive population is a population's immunological status. Healthy patients can be invaluable for showing immune responses as their responses are not compromised by disease or use of other medicines.

Also important is choosing appropriate clinical endpoint(s). An optimal marker is sensitive and well-established, inherent in the mechanism of action of the biologic, and readily monitored in a clinical setting because it is clinically relevant (e.g., absolute neutrophil count (ANC) for filgrastim-containing products).

For all originator biologics, and many biosimilars, phase 3 or confirmatory clinical studies, respectively, can only be conducted in patients because the target of the therapeutic product is related to the disease itself[27]. But for other biosimilars, conducting a confirmatory clinical study with healthy subjects is appropriate and indeed preferred wherever possible[28] (e.g., because these individuals are not immunosuppressed and so will have complete immune responses).

Certain types of biologics lend themselves more to the use of healthy subjects. An instructive example is the filgrastim family of proteins[29], including filgrastim (Neupogen® (filgrastim)[30] and the biosimilar Zarxio® (filgrastim-sndz)[31]) and pegfilgrastim (Neulasta®[32]) and Granix®[33].

*"A STUDY IN HEALTHY SUBJECTS IS CONSIDERED TO BE MORE SENSITIVE IN EVALUATING THE PRODUCT SIMILARITY BECAUSE IT IS LIKELY TO PRODUCE LESS PK AND/OR PD VARIABILITY COMPARED WITH A STUDY IN PATIENTS WITH POTENTIAL CONFOUNDING FACTORS SUCH AS UNDERLYING AND/OR CONCOMITANT DISEASE AND CONCOMITANT MEDICATIONS." FDA BIOSIM CLINPHARM GUIDANCE [26]*

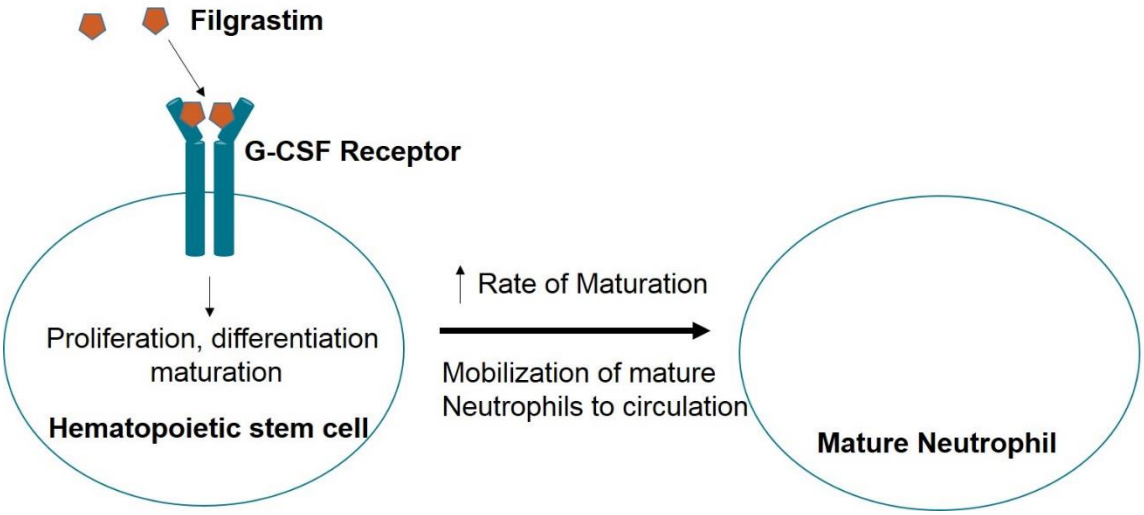
Filgrastim is a simple protein (175 amino acids and without post-translational modifications) found in all humans, and one that rarely induces a significant immune response. Pegfilgrastim[34] is a long-acting form of filgrastim that requires fewer injections for patients during a course of treatment, but which works in the same way.

*"IF SAFETY OR ETHICAL CONSIDERATIONS PRECLUDE THE PARTICIPATION OF HEALTHY SUBJECTS IN HUMAN PK AND PD STUDIES FOR CERTAIN PRODUCTS (E.G., IMMUNOGENICITY OR KNOWN TOXICITY FROM THE REFERENCE PRODUCT), OR IF PD BIOMARKERS CAN ONLY BE RELEVANT IN PATIENTS WITH THE RELEVANT CONDITION OR DISEASE, THE CLINICAL PHARMACOLOGY STUDIES SHOULD BE CONDUCTED IN SUCH PATIENTS." FDA CLINPHARM GUIDANCE [26]*

The mechanism of action of filgrastim and pegfilgrastim is well-known[35] (see Figure 5) and shared across all FDA-approved indications of both. Consequently, the clinical effects of filgrastim and pegfilgrastim are the same, namely to increase absolute neutrophil count (ANC). Importantly, this outcome, i.e., a temporary increase in white blood cell count, is not in any way harmful to the healthy population participating in the study, and it gives a very clear and measurable response to the exogenously administered growth factor (e.g., any member of the filgrastim family of proteins) making ANC an optimal marker. Conducting confirmatory clinical trials in healthy patients minimizes the greatest confounders of PD, i.e., baseline patient immune status and chemotherapy[36]. Furthermore, the greatest impact on

pegfilgrastim PK is the PD (ANC) due to neutrophil-mediated clearance. Hence, for this family of molecules, studies in healthy subjects are the most appropriate and, therefore, the population required by FDA for approval of any filgrastim family biosimilar.

**Figure 5**: *Filgrastim Mechanism of Action*




However, some biosimilar candidates in the US may also have additional clinical studies included in their FDA filings even if FDA did not request those studies. Because FDA will ask for all evidence on the product, this may reflect the fact that the biosimilar candidate has also been approved in other highly-regulated markets. The same applies for any biologic or drug under review at FDA. In addition, post market experience with any prior use of the biosimilar candidates elsewhere will be provided to FDA. A sponsor may also choose to conduct additional clinical studies for reasons other than to obtain approval. However care must be taken in such situation(s), as doing more studies than is necessary to get approval, and after the product is being made using the final process at scale, does not create a better product and as such could be unethical. FDA recently admonished one biosimilar sponsor for conducting additional clinical studies in other indications for purely commercial reasons, stating that the Agency had not required the additional studies[37]. This extra data can be confused by some health care providers and their patients to mean that the biosimilars with additional clinical data are better. This is not the case.

## Conclusion

The foundation of biosimilarity is demonstrating a highly similar analytical match between the reference product and the biosimilar candidate[38]. Showing this match leads to an expectation of no clinically meaningful differences when the biosimilar is used in the same manner in the same settings of care as the reference product. Indeed, all the information about the reference product throughout its lifetime, and all the experience with its use, is made relevant to the biosimilar by the demonstration of the analytical match and its approval by FDA as a biosimilar[39].

For some molecules, as shown by the examples discussed above, a confirmatory clinical study conducted solely with healthy subjects is the best and most sensitive way to confirm biosimilarity, and combined with the analytic data completes a regulatory filing containing all the information necessary to demonstrate biosimilarity. For such biosimilars, clinical data in patients is not needed and such studies would be unethical. Instead, an appropriately tailored clinical trial program in healthy volunteers that minimizes the time, patient burden and resources needed to get safe, effective, quality biosimilars to patients expeditiously is optimal, encouraged by FDA, and meets all approval requirements.

Ultimately biosimilars, by containing active ingredients that match those of their reference products, yet also providing an additional source of medicines, aid competition and support greater access and affordability for all stakeholders in the US. Healthcare providers and their patients can be secure in knowing that all FDA-approved biosimilars meet FDA's strict standards for efficacy, safety and quality and will behave in the same manner clinically as their reference products.

## References

[1] The FDA home page for information on biosimilars can be found at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm (accessed Apr. 20, 2017).

[2] Witness Statement of Janet Woodcock House Energy & Commerce Committee Hearing "Examining FDA's Generic Drug and Biosimilar User Fee Program," March 2, 2017, available at: http://docs.house.gov/meetings/IF/IF14/20170302/105631/HHRG-115-IF14-Wstate-WoodcockJ-20170302.PDF (accessed Apr. 20, 2017) ("As of February 2017, 64 programs were enrolled in the BPD Program and CDER has received meeting requests to discuss the development of biosimilars for 23 different reference products").

[3] See FDA Website, "The FDA's Drug Review Process: Ensuring Drugs and Safe and Effective", available at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm (accessed Apr. 20, 2017).

[4] See FDA Website, "Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations", available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm (accessed Apr. 20, 2017).

[5] Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the Hatch-Waxman Act), available at: http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf (accessed Apr. 20, 2017).

[6] ICH Q5E "Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process", 2005 available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed Apr. 20, 2017); EMA Guideline on the Principles of Regulatory Acceptance of 3Rs (Replacement, Reduction, Refinement) Testing Approaches, 2016, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500174977.pdf (accessed Apr. 20, 2017).

[7] Schiestl *et al* (April 2011) "Acceptable Changes in Quality Attributes of Gylcosylated Biopharmaceuticals", *Nature Biotechnology*, 29(4):310-312.

[8] Vezér, B. *et al* (2016): Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents, Current Medical Research and Opinion, DOI: 10.1185/03007995.2016.1145579, available at: http://dx.doi.org/10.1185/03007995.2016.1145579 (accessed Apr. 20, 2017). In the US use of comparability is not public as it is in the EU, but the product variations in EU and US are often seen to match.

[9] For historical reasons, a few biologics are currently regulated in the US as drugs and follow-on products have been FDA approved through the generic approval pathway (e.g., Glatopa® (glatiramer acetate) is a generic to Copaxone® (glatiramer acetate)).

[10] See FDA Website, "Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations", available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm (accessed Apr. 20, 2017).

[11] ICH Q5E "Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process", 2005 available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed Apr. 20, 2017).

[12] Many sponsors use a Target Product Profile (TPP) to guide and focus product development. A TPP can include things such as a product's formulation and characteristics, the goals of the development program, the optimal product label, studies intended to support approval with that label, and a summary of the development program. See FDA Draft Guidance, March 2007, "Target Product Profile – A Strategic Development Process Tool, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf (accessed Apr. 20, 2017).

[13] Mark McCamish & Gillian Woollett (2011) "Worldwide Experience with Biosimilar Development", *mAbs* 3(2):209-217, available at: http://www.tandfonline.com/doi/full/10.4161/mabs.3.2.15005

[14] In the US use of comparability is not public as it is in the EU, but the product variations in EU and US are often seen to match. See Schiestl *et al* (April 2011) "Acceptable Changes in Quality Attributes of

Gylcosylated Biopharmaceuticals", *Nature Biotechnology*, 29(4):310-312; Vezér, B. *et al* (2016): Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents, Current Medical Research and Opinion, DOI: 10.1185/03007995.2016.1145579, available at: http://dx.doi.org/10.1185/03007995.2016.1145579 (accessed Apr. 20, 2017).

[15] A biosimilar cannot be approved in the US before the originator used as reference has held its license for 12 years. See § 351(k)(7) in TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed Apr. 20, 2017).

[16] We know of one instance where a manufacturing change led to a clinically different version of the original product discovered during a metadata analysis. This is Eprex® (epoetin alfa) in Europe where a major manufacturing change to remove Human Serum Albumen during the New Variant CJD scare led to aggregation and an increase in immunogenicity. See Casadevall *et al* (2005) "Epoetin-Induced Autoimmune Pure Red Cell Aplasia" *J Am Soc Nephrol* 16:S67-S69.

[17] A biosimilar cannot be approved in the US before the originator used as reference has held its license for 12 years. See § 351(k)(7) in TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed Apr. 20, 2017).

[18] For what is called a "Type 3" meeting. See FDA Guidance, November 2015, "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants", available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf (accessed Apr. 20, 2017).

[19] FDA Guidance "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product", December 2016, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf (accessed Apr. 20, 2017) ("However, certain differences in the results of the analytical characterization can preclude a determination by FDA that the proposed biosimilar product is highly similar to the reference product and, therefore, the further development of the proposed biosimilar product through the 351(k) regulatory pathway is not recommended.") FDA has said that clinical studies that show no clinically meaningful difference cannot compensate for the lack of analytical similarity.

[20] John Jenkins, FDA CMS Summit, Washington DC, December 2013

[21] For what is called a "Type 3" meeting. See FDA Guidance, November 2015, "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants", available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf (accessed Apr. 21, 2017).

[22] World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, available at http://jamanetwork.com/journals/jama/fullarticle/1760318 (accessed Apr. 20, 2017).

[23] We do not discuss obtaining an FDA designation of interchangeability in this paper. See definition of interchangeable biologic in TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed Apr. 20, 2017). The agency issued a draft guidance on the topic and we expect additional information on the required data burden as manufacturers obtain this designation from FDA for their biosimilar products. See FDA Draft Guidance, "Considerations in Demonstrating Interchangeability With a Reference Product", January 2017, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf (accessed Apr. 20, 2017).

[24] See definition of biosimilar and interchangeable biologic in TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed Apr. 20, 2017).

[25] FDA Guidance "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product", December 2016, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf (accessed Apr. 20, 2017) ("These clinical pharmacology studies may address residual uncertainties that remain after the analytical evaluation, can add to the totality of the evidence supporting a demonstration of biosimilarity, and can guide both the need for and design of subsequent clinical testing to support a demonstration of no clinically meaningful differences in the overall demonstration of biosimilarity.").

[26] FDA Guidance "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product", December 2016, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf (accessed Apr. 20, 2017).

[27] For example, cancer markers, such as for Rituxan®.

[28] FDA Guidance "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product", December 2016, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf (accessed Apr. 20, 2017)

[29] Filgrastim is also known as GCSF and stimulates the proliferation of white blood cells. It is used to prevent infections in patients going through chemotherapy and to stimulate blood cell production for bone marrow transplantation.

[30] Neupogen® U.S. label available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103353s5188.pdf (accessed Apr. 20, 2017).

[31] The first biosimilar approved in the US was Zarxio®, and the label available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125553s007lbl.pdf (accessed Apr. 20, 2017).

[32] Neulasta® U.S. label available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125031s184lbl.pdf (accessed Apr. 20, 2017).

[33] Granix® U.S. label available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125294s040lbl.pdf (accessed Apr. 20, 2017).

[34] Neupogen® U.S. label available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103353s5188.pdf (accessed Apr. 20, 2017).

[35] FDA Guidance "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", April 2015, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (accessed Apr. 20, 2017) ("Such [functional] assays also may be used to provide additional evidence that the MOA of the two products is the same to the extent the MOA of the reference product is known.").

[36] Saab YB et al (2003) "Filgrastim use: evaluation in cancer and critically ill non- cancer patients", *Cancer Therapy* 1:191–196.

[37] Statement of FDA Nikolay Nikolov, FDA Clinical Team Leader at FDA's July 12, 2016 Arthritis Advisory Committee meeting to discuss Amgen's biosimilar adalimumab, see pages 371-372 of Meeting Transcript, available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM520028.pdf (accessed Apr. 20, 2017) ("I just want to clarify for the committee that there is no expectation, from the FDA at least, that there will be studies in multiple indications. . . .Unfortunately, we are seeing biosimilar sponsors proposing to do multiple studies in multiple indications, which to us is not the right way to approach biosimilars.").

[38] Leah Christl, Presentation at RAPS Meeting, September 30, 2014, "FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US", available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandAppr

oved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM428732.pdf (accessed Apr. 20, 2017).

[39] As such, we know more about the safety and efficacy of an FDA-approved biosimilar upon approval then we do about any new biologic.