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VIA ELECTRONIC DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Apotex Inc. and Apobiologix (collectively "Apotex") submits this petition under 21 U.S.C. § 355(q) and 21 C.F.R. § 10.30 and associated provisions to request that the Commissioner of Food and Drugs (the "Commissioner") and the Director for the Center for Drug Evaluation and Research ("CDER") (collectively "FDA") take certain actions to ensure a robust approval process for biosimilar approvals.

This petition specifically asks that FDA require all biosimilar applicants referencing NEULASTA[®] (pegfilgrastim¹) (Biologics License Application (BLA) No. 125031) held by Amgen, Inc. and Amgen USA Inc. (collectively "Amgen") to conduct their comparative clinical efficacy studies (including pharmacokinetics (PK) and pharmacodynamics (PD) studies and immunogenicity studies) in at least one intended patient population.

Underlying this petition is Apotex's position that, for healthy subjects with normal absolute neutrophil counts (ANC) counts, comparative clinical studies administering pegfilgrastim alone would not demonstrate "no clinically meaningful differences" between a proposed biosimilar and NEULASTA[®] for one of the indications for NEULASTA[®]. In particular, demonstrating a comparable boosted ANC in a healthy patient would not necessarily predict a comparable decreased incidence of infection (as manifested by febrile neutropenia) for cancer chemotherapy patients receiving pegfilgrastim after one or multiple chemotherapy cycles. First, a healthy subject by definition does not have neutropenia and would likely not have a fever or demonstrate other signs of an infection with an intact immune system.² Perhaps more importantly, while additional cycles of chemotherapy with pegfilgrastim in a cancer patient could demonstrate faster ANC recovery rates and increased pegfilgrastim clearance caused by an

¹ FDA has proposed and finalized guidance entitled "Nonproprietary Naming of Biological Products" (Jan. 2017) that described FDA's current thinking that all biological products should include a nonproprietary name that includes an FDA-designated suffix. At this point, however, FDA's Drugs@FDA website and Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations continue to use the core nonproprietary names without the FDA-designated suffix for NEUPOGEN[®] (filgrastim) and NEULASTA[®]. As a result, this petition will continue to use the core nonproprietary names without the FDA-designated suffix for these products.

² Scadden ¶ 28.

expanded neutrophil and neutrophil precursor mass in the later cycles, a healthy subject would not show either effect, because his or her ANC count would be normal to begin with.

With this background in mind, for biological products such as pegfilgrastim, the nature of this molecule and its mechanism of action suggests that clinically meaningful differences, when assessed in diseased patients, will not necessarily be discernable in healthy patients. To the extent that FDA accepts a clinical study design only in healthy subjects, FDA should require such biosimilar applicants to demonstrate that there is a correlation in ANC activity and a reduced incidence of infection over the duration of exposure to pegfilgrastim in the indicated patient population. This is because the literature demonstrates that cancer chemotherapy patients process pegfilgrastim more slowly and are exposed to pegfilgrastim for much longer than healthy subjects, thus undermining the conclusion that the comparison does not reveal clinically meaningful differences in the intended patient population.

Apotex also requests that FDA require biosimilar applicants referencing NEULASTA[®] to conduct immunogenicity studies over at least four and preferably six cycles, which reflects a median or typical initial course of most chemotherapies, when comparing NEULASTA[®] and the proposed biosimilar product.

Apotex has a vested interest in ensuring that the emerging biosimilars industry is held to standards that assure not only that approved biosimilars have been shown to be highly similar in terms of analytic comparisons but also that robust data establishes that there are no clinically meaningful differences in terms of safety and effectiveness. Apotex has submitted biosimilar BLAs (also known as 351(k) applications) for both NEUPOGEN[®] (filgrastim), BLA No. 103353 and NEULASTA[®], and is developing a suite of other biosimilar and biological products under its Apobiologix subsidiary.³ Apotex filed its BLAs based on meetings with FDA as well as its understanding of FDA's requirements for demonstrating comparative clinical similarity in terms of safety, purity, and potency, in particular the requirements for developing a biosimilar for NEULASTA[®].

ACTIONS REQUESTED

Apotex respectfully requests the Commissioner take the following actions:

- (1) Require all biosimilar applicants referencing NEULASTA[®] in an application for approval of pegfilgrastim, demonstrate no clinical meaningful differences by conducting a comparative clinical efficacy study (including PK, PD, and immunogenicity studies) in at least one of NEULASTA[®]'s indicated patient population.

³ For example, Apobiologix has indicated in its R&D website page that it has not only launched its filgrastim referencing NEUPOGEN[®] in the European Union in 2013 and Canada in 2015, it has submitted this application to FDA and is also in clinical phases for epoetin alfa referencing PROCREDIT[®] and bevacizumab referencing AVASTIN[®] as well as pre-clinical/clinical for rituximab referencing RITUXAN[®] and pre-clinical for trastuzumab referencing HERCEPTIN[®]. See Apobiologix, R&D Overview, <http://www.apobiologix.com/rd/default.asp> (last accessed May 3, 2017).

(2) Require all biosimilar applicants referencing NEULASTA[®] that intend to rely on comparative clinical PK, PD, and immunogenicity in all or some healthy subjects to conduct sufficient clinical PK, PD, and immunogenicity studies in at least one of NEULASTA[®]'s indicated patient population to demonstrate: (1) a correlation in activity between diseased patients and healthy subjects and (2) evidence where applicable that the healthy subject data is significantly more sensitive than the representative intended patient population.

(3) Require all biosimilar applicants referencing NEULASTA[®] conduct immunogenicity studies: (1) in at least one of NEULASTA[®]'s indicated patient population and (2) over at least four and preferably six cycles of cancer treatment (chemotherapy), reflecting the median or typical course of most chemotherapies for which the use of NEULASTA[®] is indicated.

(4) Require all biosimilar applicants that have not done (1) or (2), and (3) to withdraw their applications from consideration until the further studies have been conducted to meet these criteria.

STATEMENT OF GROUNDS

I. Factual Background

A. Referenced Pegfilgrastim (NEULASTA[®])

FDA first approved NEULASTA[®] on January 31, 2002, “to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.”⁴ On November 13, 2015, NEULASTA[®]'s labeling was modified to include an additional indication: “to increase survival in patients acutely exposed to myelosuppressive suppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).” This latter indication was approved under the provisions of 21 C.F.R. Part 601, Subpart H (Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible), with certain restrictions for safe use, information to be provided to patient recipients, and postmarketing studies.⁵ This second use is very infrequent and cannot be tested clinically, so this petition focuses primarily on the cancer chemotherapy uses.⁶

Reducing the incidence of infection is important, because not only does febrile neutropenia require hospitalization and intravenous anti-infectives, but the consequences of febrile neutropenia are often serious and may include death.⁷ Infections are invasions or

⁴ NEULASTA[®] (pegfilgrastim) Prescribing Information (Dec. 2016) at 2.

⁵ NEULASTA[®], FDA Supplemental Biological License Application (sBLA) Approval Letter (Nov. 13, 2015 for sBLA received Feb. 13, 2015).

⁶ See Scadden ¶ 17.

⁷ Lyman, G. et al., *Risk Models for Predicting Chemotherapy-Induced Neutropenia*, 10 *The Oncologist* 427-37, 431 (2005) (“Lyman I”).

multiplications of microorganisms such as bacteria, viruses, and fungi and may cause symptoms, or cause no symptoms and be subclinical, and may be localized or spread through the body.⁸ The body's ability to fight such infections depends on the presence of a type of white blood cells (WBC) called neutrophils, which are produced in the bone marrow and are a type of granulocyte.⁹

Neutropenia is the absence or scarcity of neutrophils and is dangerous because, without sufficient neutrophils, the body is helpless against infection. Because neutrophils can be destroyed by chemotherapy or radiation therapy for cancer, neutropenia is common in cancer patients, with resulting immune system depression. This effect is magnified by the fact that chemo- or radiation-therapy also damages the rapidly-dividing mucosal cells that line the airway and intestine.¹⁰

Neutropenia is measured in terms of absolute neutrophil count (ANC),¹¹ which is derived by multiplying the WBC count by the percentage of neutrophils in the patient's differential WBC count. The percentage of neutrophils consists of the segmented (fully mature neutrophils) plus the bands (almost mature neutrophils). The normal range for the ANC equals 1.5 to 8.0 (1,500 to 8,000/mm³). In practical clinical terms, a normal ANC is 1.5 or higher and a low ANC is less than 0.5.¹² Neutropenia is defined as ANC less than 0.5 or less than 1.0 with an anticipated decline to less than 0.5 in the next 48 hours.¹³

Febrile neutropenia is neutropenia accompanied by fever, which is also a sign of infection. Specifically, neutropenic fever is a single oral temperature of greater than 38.3°C (101°F) or a temperature of greater than 38.0° C (100.4° F) for more than one hour in a patient with neutropenia.¹⁴

In patients undergoing chemotherapy and radiation therapy, ANC drops after therapy and recovers slowly, reflecting the fact that the bone marrow is recovering and new white blood cells are beginning to grow and mature. However, full immune system recovery is slow, and chemotherapy and radiation therapy patients are at risk of infection due to neutropenia for extended periods of time.¹⁵

⁸ Medical Definition of "infection", <http://www.medicinenet.com/script/main/art.asp?articlekey=12923> (last accessed May 3, 2017).

⁹ Scadden ¶ 15.

¹⁰ *Id.*

¹¹ Medical Definition of "absolute neutrophil count", <http://www.medicinenet.com/script/main/art.asp?articlekey=20030> (last accessed May 3, 2017) ("ANC Definition").

¹² *Id.* ANC Definition. An ANC between 0.5 and 1.5 is considered abnormal but "safe."

¹³ Denshaw-Burke, M., *Neutropenic Fever Empiric Therapy*, Medscape.com (Feb. 11, 2016) <http://emedicine.medscape.com/article/2012185-overview> (last accessed May 3, 2017).

¹⁴ *Id.*

¹⁵ ANC Definition; Scadden ¶ 15.

B. Filgrastim v. Pegfilgrastim

One way to reduce the incidence of infection and potential manifested febrile neutropenia is to enhance the recovery of neutrophils after chemotherapy or radiation. Filgrastim is a recombinant methionyl form of human granulocyte colony-stimulating factor (G-CSF) that enhances the recovery of neutrophils following chemotherapy.¹⁶ Because filgrastim has a short half-life in humans (~3.5 hours) due to its high renal clearance, chemotherapy patients must receive daily injections to achieve its therapeutic effects.¹⁷

To minimize the need for daily injections, pegfilgrastim, a sustained-duration form of filgrastim was developed by covalently bonding a polyethylene glycol molecule (PEG) to the N-terminal methionine residue of filgrastim.¹⁸ One form of PEG may differ from another considerably in terms of size/weight (200 – 40,000 Daltons) and impurity profile.¹⁹ PEGylation of therapeutic proteins involves a variety of general and site-specific reactions and purification steps that can result in a variety of products. NEULASTA[®] contains a pegfilgrastim with a single 20 kDa PEG attached to the N-terminus and has a sustained duration of action when compared to filgrastim, due to the reduced renal clearance of the PEGylated molecule.²⁰ The resultant molecule exhibits the same mechanism of action as filgrastim but is eliminated primarily by neutrophil G-CSF-receptor-mediated clearance rather than by renal clearance.²¹ In addition, pegfilgrastim is more slowly absorbed than filgrastim (1-2 days for time from administration to maximum concentration (T_{max}) versus 4 hours for filgrastim), because it is principally absorbed via the lymphatic system rather than blood capillaries.²² However, once pegfilgrastim is absorbed, the self-regulating neutrophil-mediated clearance of pegfilgrastim contributes to its sustained action and efficacy over one treatment per chemotherapy cycle, as described below.

C. Pegfilgrastim in Chemotherapy Cancer Patients v. Healthy Subjects

Pegfilgrastim exhibits differential clearance in cancer patients undergoing chemotherapy over multiple cycles compared to healthy subjects, due to the effect of chemotherapy on ANC. In cancer patients, pegfilgrastim is administered 24 hours after chemotherapy, resulting in an initial decrease in ANC followed by a one-day initial increase in ANC, probably due to the release of relatively mature neutrophils. ANC thereafter declines continually for about seven days, while pegfilgrastim exposure remains high, because there are too few neutrophils to remove pegfilgrastim. Approximately seven days from chemotherapy, the bone marrow begins to

¹⁶ Yang, B. et al., *Pharmacokinetics and Pharmacodynamics of Pegfilgrastim*, 50(5) *Clinical Pharmacokinetics* 295-306, 296 (2011) (“Yang”); see also Roskos, L. et al., *Pharmacokinetic/Pharmacodynamic Modeling of Pegfilgrastim in Healthy Subjects*, 46 *Journal of Clinical Pharmacology* 747-57, 747 (“Roskos”).

¹⁷ *Id.*

¹⁸ Roskos at 747.

¹⁹ International Pharmaceutical Excipients Council of the Americas, *Inactive ingredient Database Issues with ANDAs: Background Document*, 1-31 (Dec. 9, 2011), <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandgenerics/ucm291010.pdf> (last accessed May 3, 2017)

²⁰ Jevsevar, S. et al, *PEGylation of therapeutic proteins*, 5 *Biotechnology Journal* 113-28, 118 (2010) (“Jevsevar”).

²¹ Yang at 297-98.

²² *Id.* at 299-300.

recover and increases neutrophil production with the help of pegfilgrastim, which then begins to be removed through the neutrophil-mediated clearance pathway. In a dose-ranging study conducted by Amgen for approval of NEULASTA® in women with high-risk breast cancer administered pegfilgrastim after chemotherapy, pegfilgrastim treatment was repeated 21 days for up to four cycles. Here, pegfilgrastim clearance was faster in cycle 3 than cycle 1, and the time to ANC recovery was shortened in cycle 2 and subsequent cycles, suggesting that pegfilgrastim expanded the neutrophil and neutrophil precursor mass in the later cycles, resulting in the increased drug clearance.²³

For healthy patients, during the first hour after pegfilgrastim administration, ANC counts decrease followed by a significant increase in ANC, which continues to rise because of increased neutrophil proliferation. At this point, the magnitude and duration of ANC elevation is dose dependent but less than dose proportionally. While the neutrophil-mediated clearance pathway is rapid, it can be overloaded at higher doses, which extends Tmax from 8 to 24 hours.²⁴

D. Decreasing the Incidence of Infection in Chemotherapy Cancer Patients v. Healthy Subjects Administered Pegfilgrastim

Determining whether the incidence of infection would be reduced for a chemotherapy patient administered pegfilgrastim is a multi-factorial analysis beyond ANC. Various studies have suggested some factors include advanced age, poor performance status, comorbidities, low baseline blood counts, and high chemotherapy intensity, including need for repeated cycles of therapy.²⁵ When cytotoxic chemotherapy is indicated for a cancer, typical treatment includes multiple cycles of chemotherapy followed by a washout period for the body to recover. For example, to treat breast cancer, multiple treatment cycles are usually required, depending on the chemotherapy regime used, often ranging between four-eight cycles with six being a median or typical number of chemotherapy cycles for multiple drug therapies such as TAC (docetaxel/doxorubicin/cyclophosphamide).²⁶ Because of the high incidence of severe neutropenia with TAC, the only way to ensure dose delivery and dose intensity of this regimen (which is essential for therapeutic effect) is by the use of G-CSF to prevent the severe neutropenia that otherwise occurs if not administered, and which is dose-limiting.²⁷

As noted above, reducing the incidence of infection is important, because the consequences of febrile neutropenia are often serious and may include death.²⁸ Particularly for myelosuppressive chemotherapies associated with a high incidence of febrile neutropenia, such

²³ Yang at 298-99.

²⁴ Yang at 298.

²⁵ Lyman, G. et al., *Risk Models for Predicting Chemotherapy-Induced Neutropenia*, 10 *The Oncologist* 427-37, 435 (2005) (“Lyman I”); Lyman, G. et al., *Predicting Individual Risk of Neutropenic Complications in Patients Receiving Cancer Chemotherapy*, 117(9) *Cancer* 1917-27 (2011) (“Lyman II”); Mayor, S., *Neutropenia in cancer patients: risk factors and management*, 35 *Cancer World* 15-22, 19-21 (2010) (“Mayor”)

²⁶ Hassan, M. et al, *Chemotherapy for breast cancer (Review)*, 24 *Oncology Reports* 1121-31, 1124 (“Hassan”) (citing a BCIRG 001 study of 1,491 patients taking TAC or another drug therapy every three weeks (21 days) for 6 cycles; other studies cited in the Review ranged from 4-12 cycles depending on the chemotherapy regimens studied); Scadden ¶ 24.

²⁷ Scadden ¶ 30.

²⁸ Lyman I at 435.

as TAC, pegfilgrastim is indicated not only for the first cycle of therapy but for each cycle, to reduce the likelihood for hospitalization and the need for intravenous anti-infectives or serious adverse events.²⁹ But the response to any G-CSF, including pegfilgrastim, is highly variable for each individual and each cycle, as is the incidence of infection.³⁰ While currently there is only one pegfilgrastim in the U.S., different grades of PEG attached in a different manner to pegfilgrastim theoretically could result in a different response and elimination rate based on the chemical structure, further changing the dynamic for a reduced incidence of infection.³¹

For healthy subjects with normal ANC counts, administering pegfilgrastim administration alone would not demonstrate a decreased incidence of infection based on ANC counts alone. Given the inherent risks with chemotherapy, it would not be ethical to administer chemotherapy to healthy subjects and then randomize them to NEULASTA[®] versus a proposed biosimilar version of NEULASTA[®] to compare the decreased incidence of infection.³² Because a healthy subject already has normal ANC counts, boosting that ANC count would not likely demonstrate a reduced incidence of infection.³³ And while there is some possibility for fever caused by an infection that a healthy subject could contract, by definition there would be no neutropenia. Perhaps more importantly, while additional cycles of chemotherapy with pegfilgrastim in a cancer patient could demonstrate faster ANC recovery rates and increased pegfilgrastim clearance caused by an expanded neutrophil and neutrophil precursor mass in the later cycles, a healthy subject would not show either effect, because his or her ANC count was normal to begin with.³⁴

E. Approved Biosimilars

To date, FDA has approved five biosimilar applications, all of which included comparative clinical PK, PD, and immunological data conducted in at least one indicated patient population, in addition to detailed comparative analytical characterizations and other requirements for approval. Some of these products already had biosimilar approvals for similar or identical products in Europe and other countries including post-market data. Neither FDA nor the European Medicines Association (EMA) has approved a biosimilar version of NEULASTA[®] yet.³⁵ On March 6, 2015, FDA approved Sandoz's biosimilar ZARXIO[®] (filgrastim-sndz)

²⁹ Vogel, C., et al., *First and Subsequent Cycle Use of Pegfilgrastim Prevents Febrile Neutropenia in Patients with Breast Cancer: A Multicenter, Double-Blind, Placebo-Controlled Phase III Study*, 23(6) *Journal of Clinical Oncology* 1178-84, 1181, 1183 (2005) ("Vogel"); see also Perez, E., et al., *Optimizing Adjuvant Chemotherapy in Early-Stage Breast Cancer*, 19(14) *Oncology* 1759-67 (2005) ("Perez") (noting dose-dense TAC is drug of choice for node-positive breast cancer and febrile neutropenia is common with TAC and can be minimized with a G-CSF).

³⁰ Zhuge, C., et al., *Neutrophil dynamics in response to chemotherapy and G-CSF*, 293 *Journal of Theoretical Biology* 111-20 (2012) ("Zhuge"); Scadden ¶ 40.

³¹ Scadden ¶¶ 27-28.

³² Scadden ¶ 28.

³³ Scadden ¶ 39.

³⁴ Scadden ¶ 14.

³⁵ Several versions of pegfilgrastim are reportedly available in India. Genetic and Bioimilars Initiative, *Biosimilars of pegfilgrastim*, (Apr. 7, 2017), <http://www.gabionline.net/Biosimilars/General/Biosimilars-of-pegfilgrastim> (last accessed May 3, 2017).

referencing Amgen's NEUPOGEN[®].³⁶ Sandoz's ZARXIO[®] 351(k) application included clinical data testing PD, PK, and immunogenicity that involved 174 healthy volunteers, 388 breast cancer patients receiving myelosuppressive chemotherapy, and 121 healthy stem cell donors, as well as post-marketing experience from Europe since 2009 and in over 60 countries worldwide that included more than 3,800 patients treated and observed.³⁷ On April 5, 2016, FDA approved Celltrion's biosimilar INFLECTRA[®] (infliximab-dyyb) referencing Janssen's REMICADE[®] (infliximab).³⁸ Celltrion's INFLECTRA[®] 351(k) application included clinical data testing PD, PK, and immunogenicity studies that involved 213 healthy subjects, 606 patients with active Rheumatoid Arthritis (RA), and 250 patients with Ankylosing Spondylitis (AS) in addition to uncontrolled data on safety and effectiveness with 1,234 adult patients with active Crohn's Disease (CD) and Ulcerative Colitis (UC) in the United Kingdom and Korea, and a cross-immunogenicity study using sera from Inflammatory Bowel Disease (IBD).³⁹ On August 30, 2016, FDA approved Sandoz's ERELZI (etanercept-szszs) referencing Amgen's ENBREL (etanercept).⁴⁰ Sandoz's ERELZI 351(k) application included clinical data testing that involved 216 healthy volunteers and 531 patients with plaque-type psoriasis (PsO).⁴¹ On September 23, 2016, FDA approved Amgen's AMJEVITA (adalimumab-atto) referencing Abbvie's HUMIRA[®] (adalimumab).⁴² Amgen's AMJEVITA 351(k) application included PD, PK, and immunogenicity that involved 203 healthy subjects, 526 shorter-term RA patients and 467 longer-term RA patients, and 350 PsO patients.⁴³ On April 21, 2017, FDA approved Samsung Bioepis's ("Samsung's") RENFLEXIS[®] (infliximab-abda) referencing Janssen's REMICADE[®] (infliximab).⁴⁴ Samsung's RENFLEXIS[®] 351(k) application included clinical data described as comparative safety and equivalent efficacy data that involved 584 patients with moderate to

³⁶ ZARXIO[®] approval letter, Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2015/125553Orig1s000ltr.pdf (last accessed May 3, 2017).

³⁷ Sandoz ZARXIO[®] Advisory Committee Briefing Materials (Jan. 7, 2015) at 25, <https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm428782.pdf> (last accessed May 3, 2017).

³⁸ INFLECTRA[®] approval letter, Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/125544Orig1s000ltr.pdf (last accessed May 3, 2017).

³⁹ Celltrion INFLECTRA[®] Advisory Committee Briefing Materials (Feb. 9, 2016) at 28, <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484860.pdf> (last accessed May 3, 2017).

⁴⁰ ERELZI[®] approval letter, Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/761042Orig1s000ltr.pdf (last accessed May 3, 2017).

⁴¹ Sandoz GP2015 (Proposed Inn: ETANERCEPT) Advisory Committee Briefing Materials (June 6, 2016) at 33, <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM510494.pdf> (last accessed May 3, 2017).

⁴² AMJEVITA[®] approval letter, Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/761024Orig1s000ltr.pdf (last accessed May 3, 2017).

⁴³ Amgen AMJEVITA[®] Background Information for the Advisory Committee (June 12, 2016) at 12, <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM510295.pdf> (last accessed May 3, 2017).

⁴⁴ RENFLEXIS[®] approval letter, Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2017/761054Orig1s000ltr.pdf (last accessed May 3, 2017).

severe rheumatoid arthritis across 73 sites in 11 countries.⁴⁵ Some of these applicants only used healthy subjects to generate PK data.

F. Biosimilar Pegfilgrastim Application Filed with Only Healthy Patient Data

Apotex is aware of at least one biosimilar applicant that has publicly stated that its application was filed with comparative clinical PK, PD, and immunological data in only healthy volunteers, which is a departure from the previous biosimilar applications. On October 6, 2016, Coherus Biosciences, Inc. (“Coherus”) issued a press release stating that its 351(k) application for pegfilgrastim had been filed with a Biosimilar User Fee Act (BSUFA) date of June 9, 2017 (i.e., indicating it had been filed in August 9, 2016).^{46,47} Coherus had previously reported in July 2016 that its 351(k) would be supported by PK/PD data looking at PK, maximum concentration (Cmax), area under the curve (AUC), and PD, which was ANC and ANCmax and ANC AUC looking at a 90% confidence interval within margins of 80-125%.⁴⁸ Coherus described this as a randomized, single-blind, three-sequence, three-period crossover study in healthy subjects looking at PK, PD and safety (including immunogenicity) of 6 mg subcutaneous dose of Coherus’s pegfilgrastim compared to NEULASTA®.⁴⁹ The study reportedly contained a total of 122 healthy volunteers randomized to one of three treatment sequences, each with three treatments. “Subject inclusion criteria, procedures, and study design, as well as other measures, reflected modifications addressing findings in the previous study CHS-1701-03, successfully decreasing subject variability and eliminating the extreme subject outliers previously observed.”⁵⁰ Although acknowledging that pegfilgrastim is a “relatively biologically complex molecule,” Coherus’s Chief Medical Officer of Coherus, Barbara Finck, M.D., nevertheless indicated “confidence” that Coherus’s pegfilgrastim “will produce the expected clinical effect in patients,” confirming that Coherus has not actually evaluated the clinical effect of its biosimilar product in patients (i.e., only healthy subjects).⁵¹

Based upon the information in Coherus’s press releases, the company’s two comparative studies appear to be the studies identified in the ClinicalTrials.gov database as NCT02418104

⁴⁵ *Samsung Bioepis’ Biologics License Application for SB2 Infliximab Biosimilar Accepted by FDA* (May 24, 2016), <http://www.samsungbioepis.com/en/newsroom/detail/Samsung-Bioepis-Biologics-License-Application-for-SB2-Infliximab-Biosimilar-Accepted-by-FDA.html> (last accessed May 3, 2017).

⁴⁶ *Coherus BioSciences Submits 351(k) Biologics License Application to U.S. Food and Drug Administration for CHS-1701 (Pegfilgrastim Biosimilar Candidate)*, Globe Newswire (Aug. 9, 2016) <http://investors.coherus.com/phoenix.zhtml?c=253655&p=irol-newsArticle&ID=2194263> (last accessed May 3, 2017).

⁴⁷ *Coherus BioSciences Announces FDA Acceptance of 351(k) Biologics License Application to U.S. Food and Drug Administration for CHS-1701 (Pegfilgrastim Biosimilar Candidate)*, Globe Newswire (Oct. 6, 2016) <http://investors.coherus.com/phoenix.zhtml?c=253655&p=irol-newsArticle&ID=2210016> (last accessed May 3, 2017)

⁴⁸ *Coherus Announces Positive Topline Results for CHS-1701 (Pegfilgrastim Biosimilar Candidate) Pharmacokinetic and Pharmacodynamic Biosimilarity Study*, Globe Newswire (July 11, 2016) <http://investors.coherus.com/phoenix.zhtml?c=253655&p=irol-newsArticle&ID=2184363> (last accessed May 3, 2017)

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ *Id.*

and NCT02650973.⁵² Information available on that website indicates that the latter trial, NCT02650973, was a randomized, single-blind, 3-period crossover study *in healthy subjects*. The study design involved three treatment sequences in which subjects received Coherus's product and NEULASTA[®], in separate treatments administered in a random order. Coherus's earlier trial, described by the company as a double-blind, randomized, two-period, parallel arm study in 303 *healthy subjects* "with an intact immune system"⁵³ appears to be NCT02418104, a two-arm trial in which subjects received either Coherus's product or NEULASTA[®] dosed twice. Based on this information, it is apparent that the studies submitted for its biosimilars pegfilgrastim candidate did not involve any diseased patients for the indicated uses, and the immunological studies provided only two doses in the initial study of 303 healthy patients and three doses in the second study of 122 healthy patients.

Amgen has alleged that Coherus misappropriated trade secrets and other information from Amgen, including information related to the manufacturing process for NEULASTA[®].⁵⁴ Amgen stated that the manufacturing process for NEULASTA[®] is complex and contains many trade secrets related to the pegfilgrastim and m-PEG-aldehyde starting materials, as well as key operating parameters for the PEGylation reaction, other key operating parameters, reagents, and materials used for purification and final concentration and formulation.⁵⁵ If some or all of the allegations are substantiated, these actions may have saved Coherus considerable time and expense not only in developing a drug that is safe, pure, and potent but also in ensuring a high degree of similarity to the reference drug, thus potentially reducing the regulatory hurdles to address the residual uncertainty it would have faced in establishing the comparability of Coherus's proposed biosimilar filgrastim and NEULASTA[®].⁵⁶

G. Apotex's Biosimilar Pegfilgrastim

As part of its biosimilar pegfilgrastim application, Apotex conducted comparative efficacy Phase III studies comparing its drug to both the U.S. and European form of NEULASTA[®] in patients with breast cancer to demonstrate a similar reduction in infection, which is not easily predicted, among other endpoints.⁵⁷ Apotex's study patients were actively

⁵² See <https://clinicaltrials.gov/ct2/show/NCT02650973?lead=Coherus&rank=1>

⁵³ *Coherus Announces CHS-1701 (Neulasta[®] Biosimilar) Met Both Primary Endpoints in Regirstation-Enabling Immunogenicity Study*, Globe Newswire (Feb. 1, 2016) <http://investors.coherus.com/phoenix.zhtml?c=253655&p=irol-newsArticle&ID=2134384> (last accessed May 3, 2017)

⁵⁴ *Amgen Inc. v. Coherus Biosciences*, No. 56-2017-00493553-CU-BT-VTA (Cal. Super. Ct. Mar. 3, 2017) ("Coherus litigation").

⁵⁵ *Id.* at 10-11 (Complaint, Mar 3, 2017).

⁵⁶ *Id.* at 11 (Complaint, Mar. 3, 2017) and see FDA, *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (Apr. 2015) ("Scientific Guidance") at 7 ("For example, rigorous structural and functional comparisons that show minimal or no difference between the proposed product and reference product with strengthen the scientific justification for a selective and targeted approach to animal and/or clinical testing to support a demonstration of biosimilarity.") and at 13 ("The nature and scope of the clinical studies will depend on the nature and extent of residual uncertainty about biosimilarity after conducting structural and functional characterization and, where relevant, animal studies.").

⁵⁷ EU Clinical Trials Register, EudraCT Number 2011-002678-21, <https://www.clinicaltrialsregister.eu/ctr-search/search?query=apotex+and+pegfilgrastim> (last accessed May 3, 2017).

undergoing multiple cycles of chemotherapy, permitting the study sites to measure PK, PD, and immunogenicity variables in one of the key indications for NEULASTA[®]. Apotex's Phase III trials were conducted through six cycles of chemotherapy, mimicking typical chemotherapy exposure to pegfilgrastim for breast cancer patients, measuring not only duration of severe neutropenia but also a set of secondary endpoints which included time-to-ANC-recovery, rates of neutropenia with fever by cycle and across the cycles, the frequency of culture-confirmed infections and incidence of intravenous antibiotic use and hospitalization. The study also assessed certain safety endpoints including incidence of adverse events and presence of antibodies and other tests indicating an immunological reaction. Apotex conducted these studies recognizing the importance for a first-time biosimilar pegfilgrastim to demonstrate no clinically meaningful differences with respect to its referenced product, NEULASTA[®]. Concurrently with this Phase III study, Apotex conducted Phase I studies in healthy subjects, comparing Apotex's pegfilgrastim to NEULASTA[®] focusing on pegfilgrastim AUC, C_{max}, ANC and E_{max} (maximum effect observed over the sampling interval), which also measured various safety and immunogenicity factors.⁵⁸

II. Discussion

Consistent with FDA's guidance and its previous biosimilar approvals, FDA should continue to require biosimilar applicants to conduct and submit comparative clinical PK, PD, and immunological data conducted in at least one indicated patient population, in addition to detailed comparative analytical characterizations and other requirements for approval. In some instances, it may be appropriate to require, in addition, comparative PK, PD, and immunological studies in healthy subjects, e.g., confirmatory data to support extrapolation of other indications.

A. The BPCIA Requires Clinical Studies in at Least One Referenced Indication

FDA may approve a biosimilar product under the new 351(k) pathway under the Public Health Service Act as amended by the Biosimilars Price Competition and Innovation Act of 2009 (BPCIA). A critical component to such approval is a demonstration of biosimilarity, which means that, in addition to being analytically highly similar to a single reference product, "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product."⁵⁹ According to a key FDA biosimilar official:

Clinically meaningful differences could include differences in the expected range of safety, purity, and potency of the proposed and reference product. By contrast, slight differences in rates of occurrence of adverse events between the two products ordinarily would not be considered clinically meaningful.⁶⁰

⁵⁸ Desai, K. et al., *Confirmation of Biosimilarity in a Pharmacokinetic/Pharmacodynamic Study in Healthy Volunteers for an Analytically Highly Similar Pegfilgrastim*, 5(5) *Clinical Pharmacology in Drug Development* 354-63 (2016).

⁵⁹ 42 U.S.C. § 262(i)(2)(A).

⁶⁰ Kozlowski, S., *FDA perspectives: Biosimilar Development with a Lens on Quality Presentation* (Sept. 17, 2014), <http://pqri.org/wp-content/uploads/2015/11/Kozlowski.pdf> (last accessed May 3, 2017).

The BPCIA further provides the method by which “no clinically meaningful differences” may be demonstrated:

[A] clinical study or studies (including the assessment of immunogenicity and pharmacokinetics and pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.⁶¹

FDA generally expects that the clinical studies will establish statistical significance in a comparative efficacy study for at least one intended use that the proposed product is neither inferior to the reference product by more than a specified margin nor superior to the reference product by a specified margin (possibly different).⁶² For immunogenicity studies, FDA recommends a comparative parallel design (head-to-head) in treatment-naïve patients, taking into consideration the conditions and duration of use and the conditions of the patients, e.g., whether immunosuppressed.⁶³

While FDA has the discretion to determine that this or any required element for a biosimilar application is not needed,⁶⁴ FDA’s guidances have embraced the concept that comparative clinical PK/PD and immunogenicity studies must be conducted “[a]s a scientific matter.”⁶⁵ And if there is a meaningful correlation between PK and PD results and clinical effectiveness, convincing PK and PD results may make a comparative efficacy study unnecessary.⁶⁶

For a first-time biosimilar referencing NEULASTA[®], therefore, a biosimilar applicant would be expected to need to conduct a comparative efficacy study, which could perhaps be replaced by a convincing PK and PD study for subsequent biosimilar applicants referencing NEULASTA[®], once the necessary correlations between comparative efficacy and PK and PD could be made, along with an appropriate immunogenicity study.

B. Comparative Analytics for Biological Products Have Improved but Cannot Substitute for Clinical PK and PD, and Immunogenicity Studies in Patient Populations for Intended Indications

Assuming that a convincing argument involving clinical PK and PD studies could be made to waive the need for a comparative efficacy study, comparative analytics alone would be insufficient at this time to support a biosimilar application. Instead, analytical data provides the foundation for a biosimilar product development program and helps guide the type and amount of animal and clinical studies to reduce the residual uncertainty in order to support a

⁶¹ 42 U.S.C. § 262(k)(2)(A)(i)(1)(cc).

⁶² “Scientific Guidance” at 20.

⁶³ *Id.* at 16-17.

⁶⁴ 42 U.S.C. § 262(k)(2)(A)(ii).

⁶⁵ Scientific Guidance at 14.

⁶⁶ *Id.* at 15.

demonstration of biosimilarity. To this end, FDA encourages sponsors to use state-of-the-art technology to detect and characterize differences between the proposed product and reference product.⁶⁷ At the same time, “there may be an incomplete understanding of the relationship between a product’s structural attributes and clinical performance” despite the ability to measure those analytic attributes.⁶⁸

For a new biosimilar product, such as pegfilgrastim, there are no analytical standards that currently can predict the effect of observed analytical differences on clinical performance (for purposes of establishing that there are “no clinically meaningful differences”) or the expected range of safety, purity, and potency.⁶⁹ In particular, there could be differences in the PEG used to PEGylate filgrastim, as well as different sites of filgrastim to bind PEG, either of which could result in a differential activity, clearance, or immunogenicity.⁷⁰ As a result, FDA should expect a biosimilar applicant referencing NEULASTA[®] to conduct the necessary animal and clinical studies comparing safety and efficacy, supported by comparative PK, PD, and immunogenicity studies between the proposed biosimilar and referenced NEULASTA[®] product.

C. Comparative PK, PD, and Immunogenicity Studies Cannot Be Conducted Only in Healthy Subjects for a Biosimilar Such as Pegfilgrastim

FDA will generally require comparative PK and PD studies, and sponsors need to provide a scientific justification for selecting healthy subjects instead of the indicated patients by considering current knowledge of the intra- and inter-subject variability of the human PK and PD for the reference product and the ability of a proposed patient population to detect differences in PK and PD profiles.⁷¹ The proposed PD measures, moreover, should be relevant to clinical outcomes, be measurable to ascertain the full PD response, and have the sensitivity to detect clinically meaningful differences between the proposed product and the reference product.⁷² In most cases, the study population is the same population that supported the referenced indication(s) but may also be a subset of such patient population, e.g., patients with genetic markers to predict response.⁷³

FDA has prescribed limited circumstances when comparative PK, PD, and immunogenicity studies may be conducted in healthy subjects. In general, the study population should be the “most informative” for detecting and evaluating differences in PK and PD profiles between the proposed biosimilar and referenced product.⁷⁴ In theory, healthy patient population could be more sensitive and provide fewer “potential confounding factors such as underlying

⁶⁷ FDA, *Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* (Apr. 2015) at 6.

⁶⁸ *Id.*

⁶⁹ Scadden ¶ 32.

⁷⁰ Scadden ¶ 20.

⁷¹ Scadden ¶ 36.

⁷² *Id.*

⁷³ Scientific Guidance at 19.

⁷⁴ FDA, *Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (Dec. 2016) (“PK/PD Guidance”) at 10.

and/or concomitant disease and concomitant mediations.⁷⁵ In practice, however, safety or ethical reasons could preclude the use of healthy subjects (e.g., immunogenicity or known toxicity from the reference product) and the PD biomarkers are often only relevant in patients with the relevant condition or disease.⁷⁶ In most cases, therefore,

[a] population that is representative of the patient population to which the drug would be targeted will be appropriate unless a study in a different population would be more sensitive to detect potential differences between the proposed biosimilar product and the reference product.⁷⁷

In the context of the requirements for interchangeable biosimilars, FDA further explained that a benefit-risk analysis is important to include when considering comparative clinical studies using healthy subjects:

FDA strongly recommends that sponsors use patients in switching studies because these studies are designed to mimic how the proposed interchangeable product will be used in clinical practice. In a circumstance where a sponsor considers using healthy subjects, the sponsor should weigh the benefit of exposing healthy subjects to a proposed interchangeable product during the course of a clinical study against the risk of having them develop antibodies to the product, which in turn may preclude them from being able to receive the treatment in the future, if needed. However, there may be some limited situations where it is clinically and ethically appropriate to use healthy subjects in switching studies.⁷⁸

In essence, demonstrating “no clinically meaningful differences” for biosimilarity means that when a proposed biosimilar is used instead of the reference product, even when not submitted as an interchangeable, the study population in the proposed study should reflect the full intended PD response for the proposed indication(s), i.e., studies with patients. At the same time, a benefit-risk analysis should be considered when healthy subjects are considered as the study population to prevent the subjects from developing antibodies that could preclude the therapy in the future or otherwise make such treatment unethical or not feasible.⁷⁹

NEULASTA[®] has two indications, both to reduce the incidence of infection by boosting an individual’s ANC count. When a G-CSF product such as pegfilgrastim is administered to healthy patients, similar side effects would be expected as with cancer chemotherapy patients, including short-term toxicities resulting in bone pain, which is common, as well as more rare

⁷⁵ *Id.*

⁷⁶ *Id.*

⁷⁷ *Id.*

⁷⁸ FDA, *Guidance for Industry: Considerations in Demonstrating Interchangeability with a Reference Product* (Draft Jan. 2017) (“Interchangeability Guidance”) at 13.

⁷⁹ *Id.*

instances of splenic rupture, cardiovascular events, acute lung injury and possibly death.⁸⁰ Some studies have suggested that the PK/PD-relationship in healthy subjects administered pegfilgrastim may be useful to model optimum serum concentrations of pegfilgrastim in cancer chemotherapy patients.⁸¹

Yet as described above, pegfilgrastim differs from filgrastim in that its half-life and absorption are longer, and its duration of action is dependent on an individual's ANC at the start of administration, which by definition is different between cancer chemotherapy patients and healthy subjects.⁸² And because cancer chemotherapy patients are necessarily exposed to pegfilgrastim for a longer duration due to the neutrophil G-CSF-mediated clearance rather than renal clearance,⁸³ neutrophil recovery time is a clinically meaningful parameter to compare between a proposed biosimilar and its reference product. Even if Coherus did benefit from obtaining some or all of Amgen's confidential manufacturing information for NEULASTA[®], for example, it would still be necessary to test its product in chemotherapy cancer patients to demonstrate biosimilarity for exposure and clearance, because these could differ even if ANC increases appeared similar in healthy subjects.⁸⁴

Reduction of the incidence of infection, moreover, cannot be demonstrated in healthy subjects, when by definition they already have immune systems in a normal ANC range, and it clearly would not be ethical to provide chemotherapy prior to pegfilgrastim administration to healthy subjects to demonstrate a similar recovery rate. For these reasons, FDA should require Coherus and any other applicant for a biosimilar version of pegfilgrastim referencing NEULASTA[®] to conduct comparative clinical studies in at least one indicated patient population in addition to any confirmatory comparative clinical data in healthy subjects.

D. Comparative Clinical Efficacy or PK, PD, and Immunogenicity Data in Healthy Subjects Must Be Correlated with Similar Studies in Patients from One Indication

To the that extent Coherus or another applicant wants to conduct additional comparative clinical studies in healthy subjects, these studies must be correlated to similar studies from patients in at least one indication for the referenced product. As noted previously, if there is a meaningful correlation between PK and PD results and clinical effectiveness, convincing PK and PD results may make a comparative efficacy study unnecessary.⁸⁵ In addition confirmatory PK, PD, and immunogenicity data from both one patient indication and health subjects may help support extrapolation to additional indicated uses for the referenced product.

⁸⁰ Tigue, C. et al., *Granulocyte-colony stimulating factor administration to healthy individuals and persons with chronic neutropenia or cancer; an overview of safety considerations from the Research on Adverse Drug Events and Reports project*, 40 Bone Marrow Transplantation 185-92, 188 (2007) ("Tigue").

⁸¹ Roskos at 756.

⁸² Scadden ¶ 14.

⁸³ *Id.*

⁸⁴ *See* Scadden ¶ 40.

⁸⁵ Scientific Guidance at 15.

Assuming there is a correlation and utility to conducting such studies, care must still be taken to protect and monitor healthy subjects from unnecessary risks, e.g., for pegfilgrastim, short-term toxicities such as bone pain and more rare instances of splenic rupture, cardiovascular events, acute lung injury and possibly death.⁸⁶ In addition, FDA recommends that the sponsor weigh the benefit of exposing healthy subjects to a biosimilar product against the risk of having them develop antibodies to the product, which could preclude future use of the product.⁸⁷

E. Comparative Immunogenicity Studies Should be Conducted Over the Projected Treatment for the One Indication Studied

As part of a biosimilar application, FDA requires sponsors to conduct parallel studies comparing the proposed biosimilar product to its reference product for the potential for the development of antibodies that may prevent the use of pegfilgrastim in the future. For these studies, a sponsor should take into consideration the conditions and duration of use and the conditions of the patients, e.g., whether immunosuppressed.⁸⁸ Pegfilgrastim may be used for any number of cycles of chemotherapy as indicated. As a result, FDA should require a sponsor to conduct a typical course of chemotherapy for a representative cancer where filgrastim is typically used.

Specifically, FDA should require sponsors to conduct comparative clinical immunogenicity through a minimum of four and preferably six cycles of chemotherapy to match the typical duration for use of pegfilgrastim. Amgen tested NEULASTA[®] in metastatic breast cancer patients using chemotherapy only through four cycles.⁸⁹ Since then, the standard of treatment of metastatic breast cancer has evolved to typically employ TAC over four-eight cycles with six being a typical course.⁹⁰ The half-life and duration of exposure would be expected to differ over multiple chemotherapy cycles, where the cumulative toxic effects of chemotherapy would exert progressive suppression of neutrophil numbers and production. With repeated use of pegfilgrastim over multiple cycles of chemotherapy, the potential for developing antibodies or other immunological responses to the pegfilgrastim increases.⁹¹ FDA, therefore, should require sponsors to continue testing for the potential for antibody development for filgrastim of pegfilgrastim to develop over the full cycles of chemotherapy through a minimum of six cycles.

Coherus only reported testing immunogenicity through two-three cycles of pegfilgrastim in healthy subjects. Yet a cancer chemotherapy patient likely would be exposed to pegfilgrastim for a far longer duration through at least four and typically six cycles of pegfilgrastim chemotherapy. FDA should require, therefore, that the principal immunological studies be conducted in at least six cycles of chemotherapy.

⁸⁶ Tigue at 188.

⁸⁷ See Interchangeability Guidance at 13.

⁸⁸ Scientific Guidance at 16-17.

⁸⁹ Medical Officer Clinical Review for NEULASTA[®] (Jan. 31, 2002) at 31.

⁹⁰ Hassan at 1124; Scadden ¶ 29.

⁹¹ Scadden ¶ 39.

F. Clinician Uptake of Biosimilar Pegfilgrastim

Finally, if FDA required sponsors to conduct more rigorous comparative clinical efficacy in cancer chemotherapy patients through at least four and preferably six cycles of chemotherapy, oncologists would more likely consider using biosimilar versions instead of their referenced counterparts. When considering the arguments raised in this petition, Apotex consulted with Dr. David T. Scadden, M.D., an internationally-recognized leader in hematology, stem cells, and clinical oncology. Dr. Scadden's background is explained more fully in the attached declaration, but in brief, he is a Professor of Medicine at Harvard Medical School, Harvard University, Professor and Co-chair (or Chair) of the Department of Stem Cell and Regenerative Biology, in the Faculty of Arts and Science and the Harvard Medical School, co-founder and co-director of the Harvard Stem Cell Institute, and directs the Massachusetts General Hospital Center (MGH) for Regenerative Medicine, where he served as the Chief of Hematologic Malignancies for the MGH in the Cancer Center. As noted by Dr. Scadden in his attached declaration, he would be skeptical about whether comparative PK and PD testing in healthy subjects would address concerns for the extended exposure a cancer chemotherapy patient would have to pegfilgrastim.⁹² In particular, Dr. Scadden was concerned that different forms of pegfilgrastim could be processed differently by cancer chemotherapy patients with reduced or damaged neutrophils over multiple chemotherapy cycles in contrast to healthy patients with normal levels of neutrophils.⁹³ As a result, he believes clinicians would prefer using a biosimilar product that had been tested in cancer chemotherapy patients over multiple chemotherapy cycles to confirm that there were no clinically meaningful differences.⁹⁴

III. Conclusion

For the reasons cited above, FDA should require that biosimilar applicants, particularly first-time biosimilar applicants, referencing NEULASTA[®] clinically test their products in at least one indicated patient population in terms of clinical efficacy and PK, PD, and immunogenicity over a median or typical course of chemo- or radiation therapy. To the extent applicants rely on some clinical data from healthy subjects, applicants must demonstrate a correlation between such data and one indicated patient population, along with evidence that use of healthy subject data has some relevance in terms of being significantly more sensitive than the use of the indicated patient population in one or more parameter, e.g., immunogenicity sensitivity. And all biosimilar applicants referencing NEULASTA[®] should conduct their immunogenicity studies in a medial or typical course of chemo- or radiation therapy before any such studies first and before any such studies are conducted in healthy subjects, to demonstrate anticipated actual use and reduce the risks for healthy subjects in those studies.

IV. Economic Impact

Economic Impact information will be submitted at the request of the Commissioner.

⁹² Scadden ¶¶ 37, 40.

⁹³ Scadden ¶ 37.

⁹⁴ Scadden ¶¶ 39, 41.

V. Environmental Impact

Petitioner claims categorical exclusion under 21 CFR §§ 25.30, 25.31, 25.32, 25.33, or § 25.34 or an environmental assessment under § 25.4.

VI. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 14, 2017. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am making these representations on behalf of Apotex as part of my responsibilities as an employee of Apotex; I am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,



Steven G. Lydeamore

President, Apobiologix