Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004
T +1 202 637 5600
F +1 202 637 5910
www.hoganlovells.com

December 21, 2022

By Electronic Submission

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

CITIZEN PETITION

The undersigned, on behalf of Octapharma USA, Inc.[1] and Octapharma Pharmazeutika Produktionsge mbH[2] (collectively, Octapharma) submits this petition under Section 351 of the Public Health Service Act (PHSA), Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA), and 21 CFR 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs set aside the approval of three Biologics License Applications (BLAs) for plasma-derived fibrinogen products submitted by three blood centers—Central California Blood Center, Community Blood Center, Inc. in Appleton, Wisconsin, and Gulf Coast Regional Blood Center (collectively, the Blood Centers). Octapharma further requests that the Commissioner refrain from approving any additional similarly manufactured fibrinogen products without requiring clinical studies.[3]

[1] Octapharma USA, Inc. markets and distributes Fibryga® in the United States.

[2] Octapharma Pharmazeutika Produktionsge mbH, an Austrian company, holds the BLA for Fibryga.

[3] In September 2022, Octapharma filed a complaint in the U.S. District Court for the District of Columbia alleging that FDA violated the Administrative Procedure Act by failing to require clinical studies before approving three recent fibrinogen complex products. The parties agreed to seek a stay from the court to permit Octapharma to engage in further administrative review of the matter with FDA, in the form of this petition. Joint Mot. To Stay Proceedings, *Octapharma USA, Inc. v. Becerra*, No. 1:22-cv-02782-CKK, Nov. 10, 2022 (D.D.C. 2022). The judge granted the stay, and FDA promised to respond to Octapharma's petition within 6 months of receipt. Min. Order to Stay, *Octapharma USA, Inc. v. Becerra*, No. 1:22-cv-02782-CKK, Nov. 15, 2022 (D.D.C. 2022).

Hogan Lovells US LLP is a limited liability partnership registered in the District of Columbia. "Hogan Lovells" is an international legal practice that includes Hogan Lovells US LLP and Hogan Lovells International LLP, with offices in: Alicante Amsterdam Baltimore Beijing Birmingham Boston Brussels Colorado Springs Denver Dubai Dusseldorf Frankfurt Hamburg Hanoi Ho Chi Minh City Hong Kong Houston Johannesburg London Los Angeles Luxembourg Madrid Mexico City Miami Milan Minneapolis Monterrey Munich New York Northern Virginia Paris Perth Philadelphia Rome San Francisco São Paulo Shanghai Silicon Valley Singapore Sydney Tokyo Warsaw Washington, D.C. Associated Offices: Budapest Jakarta Riyadh Shanghai FTZ Ulaanbaatar. Business Service Centers: Johannesburg Louisville. Legal Services Center: Berlin. For more information see www.hoganlovells.com

Octapharma is the sponsor of BLA 125612/67 for Fibryga, which was initially approved for the treatment of acute bleeding episodes in adults and children with congenital fibrinogen deficiency.[4] When FDA approved Octapharma's BLA in June 2017, it treated Fibryga as a "blood derivative." Under 21 CFR 606.3(c) and the agency's historic practice, a blood product is regulated as a "blood derivative" rather than a "blood component" if the product is subjected to manipulations that exceed separation of human blood by mere "physical or mechanical means."

Because FDA elected to classify Fibryga as a blood derivative, Octapharma was required to conduct two clinical studies to demonstrate that the product is safe, pure, and potent (effective) for use in treatment of congenital fibrinogen deficiency. And following the approval of the BLA, Octapharma has been subject to additional post-marketing requirement studies to ensure the continuous safety of the product in the indicated population. In addition, FDA has required that Octapharma conduct additional studies in order to secure licensure for Fibryga to be used in treating other forms of fibrinogen deficiency, such as acquired fibrinogen deficiency.

Between December 2021 and April 2022, FDA licensed three fibrinogen products sponsored by the Blood Centers[5] under the name "Pathogen Reduced Cryoprecipitated Fibrinogen Complex" (Blood Center products) for broad use in the treatment of all fibrinogen deficiency disorders, including congenital and acquired forms of the disease.[6] The Blood Centers manufacture those fibrinogen products using a device called the INTERCEPT Blood System for Pathogen Reduced Cryoprecipitated Fibrinogen Complex (INTERCEPT Blood System). Like Fibryga, the Blood Center products manufactured using the INTERCEPT Blood System are subjected to complex chemical manipulations, including a pathogen reduction process through treatment with photochemical (amotosalen) and ultraviolet radiation—processes clearly beyond the "physical or

[4] *See* Section 1, Fibryga Prescribing Information, *available at* https://www.fda.gov/media/105864/download.

[5] *See* FDA Alphabetical List of Licensed Establishments Including Product Approval Dates *at* 16, 19, and 30, *available at* https://www.fda.gov/media/76356/download.

[6] *See* Circular of Information for the Use of Human Blood and Blood Components, (Dec. 2021) at 38, *available at* https://www.aabb.org/docs/default-source/default-document-library/resources/circular-of-information-watermark.pdf?sfvrsn=7f5d28ab_5 (*Circular*) (stating that Pathogen Reduced Cryoprecipitated Fibrinogen Complex is indicated for "[t]reatment and control of bleeding, including massive hemorrhage, associated with fibrinogen deficiency."); *see also* FDA Guidance, An Acceptable Circular of Information for Use of Human Blood and Blood Components (Mar. 2022) *at* 1-2, *available at* https://fda.gov/media/86898/download (FDA Blood Circular Guidance) (recognizing that the specific labeling instructions for products described in the *Circular* are adequate for the administration and use of the products).

mechanical means" for products regulated as blood components. So, to the extent FDA believes that Fibryga is a blood derivative, the Blood Centers' fibrinogen products also should have been considered blood derivatives, and subject to the same requirements pre-and post-approval.

But the Blood Centers' fibrinogen products instead were licensed to be regulated as blood *components*. As a result of this erroneous classification, the Blood Centers were not required to conduct any pre-approval clinical studies to demonstrate the safety, purity, and potency of their products. Nor are they subject to the other post-marketing requirements that may be necessary to assure their continuous safe use.

FDA's decision to license the Blood Center products as blood components rather than blood derivatives is a direct violation of the agency's established interpretations of its regulations, policies, and procedures. Because FDA acted contrary to its own regulations by classifying the Blood Center products as blood components, and because FDA treated Fibryga differently—and without reasoned justification—from these Blood Center products notwithstanding the material similarities in the manufacturing processes of the products, FDA has fallen short of the foundational requirements of the Administrative Procedure Act (APA). And because these Blood Center products have not been demonstrated to be safe, pure, and potent, their use in the treatment and control of bleeding resulting from fibrinogen deficiency creates risks to patients not adequately assessed by FDA.

For all of these reasons, Octapharma therefore requests that FDA set aside its licensure of the Blood Center products and refrain from licensing any additional similarly manufactured products as blood components.

ACTION REQUESTED

Octapharma respectfully requests that FDA undertake the following actions:

1. Set aside the BLAs for blood products licensed to the Blood Centers and manufactured using the INTERCEPT Blood System because:

    a. These fibrinogen products are manufactured by chemical means beyond the physical and mechanical manipulations required for products regulated as blood components;

    b. Their regulation as blood components rather than blood derivatives is in contravention of FDA's regulations and historic practice; and

c. These products have not been established to be safe, pure, and potent through rigorous clinical studies as required by the Public Health Service Act (PHSA).

2. Refrain from licensing any additional fibrinogen products manufactured with the INTERCEPT Blood System as blood components for the same reasons.

STATEMENT OF GROUNDS

I. LEGAL BACKGROUND

A. Regulation of Blood Components

Although all biological products must meet the statutory requirement of safety, purity, and potency, FDA has historically treated blood components and blood derivatives differently. For many years, fundamental components of human blood, such as red blood cells, platelets, and plasma, have been safely extracted and used to treat patients with deficiencies of those blood components. Based on this long history of effective use, FDA applies a more lenient standard in approving blood products that qualify as a blood *component*.

The PHSA does not define "blood component." However, FDA, by regulation, defines a blood component as a "product containing a part of human blood separated by physical or mechanical means."[7] FDA has exempted blood components from many stringent pre-and post-approval requirements:

First, FDA does not require clinical studies for blood component products.[8] This exemption is based on the long, widespread, and historically recognized effectiveness of blood components in treating certain conditions or diseases.[9]

[7] 21 CFR 606.3(c).

[8] *See* FDA Guidance, Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h (May 1999) *at* 13-14, *available at* https://www.fda.gov/media/124371/download (FDA Guidance for Human Blood and Blood Components) (clinical data not required for BLA submissions for blood components unless the product is novel).

[9] *See* FDA, Proposed Rule, Biological Products; Blood and Blood Derivatives; Implementation of Efficacy Review, 50 Fed. Reg. 52,602, 52,604-05 (Dec. 24, 1985), *available at* https://archives.federalregister.gov/issue_slice/1985/12/24/52583-52707.pdf#page=20.

Second, blood components are not subject to extensive labeling review.[10] FDA does not require specific, individual labeling for blood components intended for transfusion. Instead, FDA recognizes an external document, the *Circular*, as an acceptable extension of container labels for blood components.[11] The *Circular* is prepared jointly by the Association for the Advancement of Blood & Biotherapies, American Red Cross, America's Blood Centers, and the Armed Services Blood Program.[12] When FDA accepts a version of the *Circular* through guidance, a manufacturer or blood center may label its blood components by including a copy of the *Circular* in the packaging of the blood component without seeking prior approval for the labeling from FDA, so long as the manufacturer implements the information relating to that particular blood component in the *Circular* without any major modifications.[13]

In addition to the foregoing, blood components are not subject to safety reports, prescription drug user fees, and pediatric assessments required by the Pediatric Research Equity Act (PREA) imposed on blood derivatives.[14]

B. Regulation of Blood Derivatives

The PHSA does not define "blood derivative" either. But in light of the definition of "blood component" cited above, FDA's regulations (along with its guidance and licensure practices) identify what a "blood derivative" is not: If the method used is solely "physical or mechanical," the product is a blood component; if not, it is a blood derivative.[15] Some examples of blood

[10] *See* FDA Guidance for Human Blood and Blood Components *at* 12-13.

[11] 21 CFR 606.122; *see also* FDA Blood Circular Guidance *at* 1-2.

[12] *See Circular at* PDF 1.

[13] *See* FDA Blood Circular Guidance *at* 2.

[14] *See* FDA Guidance for Human Blood and Blood Components *at* 13-14; *see also* 21 USC 379g(1) (exempting blood components from definition of drug applications subject to drug user fees); FDA Postmarket Requirements and Commitments Database for Required PREA Studies (filtered product search "fibrinogen complex" versus "immune globulin"), *available at* https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm (containing no listing for blood component such as fibrinogen complex, but listing outstanding PREA study requirements for blood derivatives such as immune globulin).

[15] *See, e.g.*, 21 CFR 606.3(c); FDA Guidance for Human Blood and Blood Components *at* 6, 12-14 (explaining that clinical data, safety reports, and labeling review are not required for BLA submissions for blood components unless the product is novel); Package Insert for Octaplas, *available at* https://www.fda.gov/media/123132/download (describing clinical trials required for plasma that is pathogen-reduced using solvent/detergent chemical treatments); Package Insert for Ceprotin, *available at* https://www.fda.gov/media/75033/download (describing clinical trials required for protein C concentrate manufactured by purifying human plasma with filtration and chromatographic procedures, and by reducing

products currently regulated as blood derivatives include albumin products, fibrinogen products such as RiaStap (fibrinogen concentrate) and Fibryga (fibrinogen (human)), immune globulin products, and fibrin sealant products.[16]

The regulatory process for approving a blood *derivative* involves additional—and exhaustive—procedures. Companies that wish to distribute blood derivatives must submit a BLA accompanied by clinical studies demonstrating that the product is "safe, pure, and potent."[17] Potency is defined in part by effectiveness.[18] And proof of effectiveness in biologics (*e.g.*, blood products) must with limited exceptions consist of "adequate and well-controlled studies."[19]

Additionally, FDA requires that each blood derivative product be distributed with product-specific FDA-approved labeling that provides adequate directions for use, including "statements of all conditions, purposes, or uses for which such drug is intended," unless FDA informs the applicant otherwise.[20] A biological product is considered misbranded if it does not contain adequate instructions for use.[21] If a misbranded product is sold or distributed in interstate commerce, the distributor faces civil and criminal consequences.[22]

II. FACTUAL BACKGROUND

A. Fibrinogen Deficiency

When human blood vessels are damaged by physical or vascular injuries that result in bleeding, hemostasis is restored through a number of proteins and enzymatic reactions that lead to the

---

viral transmission risk through detergent treatment, heat inactivation, and immunoaffinity chromatography).

[16] *See* FDA, List of Fractionated Plasma Products, *available at* https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/fractionated-plasma-products.

[17] 42 USC 262(a)(2)(C)(i).

[18] 21 CFR 600.3(s).

[19] *See* 21 USC 355(d); *see also* FDA Draft Guidance, Demonstrating Substantial Effectiveness for Human Drug and Biological Products (Dec. 2019) *at* 4 n.6, *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products.

[20] 21 CFR 201.5; 21 CFR 610.61.

[21] 42 USC 262(b); 21 USC 352(f)(1).

[22] *See* 21 USC 331(a); 21 USC 332; 21 USC 333(a).

deposition and maturation of fibrin—a primary component of blood clots.[23] Fibrinogen is a precursor protein to the fibrin in blood clots, and as such, is a critical part of the blood clotting process.[24] In the absence of adequate quantities of fibrinogen, or in the absence of properly structured fibrinogen protein, patients can experience a range of adverse effects, ranging from mild blood disorders to acute hemorrhagic events and death.[25] Fibrinogen-related disease states can be either congenital or acquired.

Congenital fibrinogen deficiency is an inherited autosomal recessive disorder that includes a group of rare fibrinogen disorders: these diseases range from a complete lack of fibrinogen (afibrinogenemia), to reduced levels of fibrinogen (hypofibrinogenemia), to formation of dysfunctional fibrinogen (dysfibrinogenemia), to a reduction of both quality and quantity of fibrinogen (hypodysfibrinogenemia).[26] Afibrinogenemia, the most extreme form of congenital fibrinogen deficiency, occurs in approximately 1:1,000,000 people.[27]

Acquired fibrinogen deficiency results from below-threshold levels or malformation of the fibrinogen protein. It is not inherited. Acquired fibrinogen deficiency may be caused by a number of scenarios, including blood loss from major trauma or surgery, acute leukemia, and injury to the liver.[28] As a result, it is more prevalent than congenital fibrinogen deficiency.[29]

Both congenital and acquired fibrinogen deficiencies can be treated via fibrinogen replacement therapy, which involves achieving a target plasma concentration fibrinogen level.[30] Available

---

[23] Chaudry, *et al.*, Physiology, Coagulation Pathways, STATPEARLS, Nat'l Library of Medicine, *available at* https://www.ncbi.nlm.nih.gov/books/NBK482253/.

[24] *Id.*

[25] Tziomalos *et al.*, *Treatment of Congenital Fibrinogen Deficiency: Overview and Recent Findings*, VASCULAR HEALTH AND RISK MANAG, 5:843-48 (2009) (Tab 1).

[26] Fibryga (STN 125612/67) Summary Basis for Regulatory Action (June, 2017) *at* 3, *available at* https://www.fda.gov/media/106074/download.

[27] *See* National Organization for Rare Disorders (NORD) website, *Congenital Afibrinogenemia: Affected Populations*, *available at* https://rarediseases.org/rare-diseases/afibrinogenemia-congenital/.

[28] Besser *et al.*, *Acquired Hypofibrinogenemia: Current Perspectives*, J. BLOOD MED; 7:217-25 (2016) (Tab 2).

[29] *See* Vilar R. *et al.*, *Fibrin(ogen) in Human Disease: Both Friend and Foe*, HAEMATOLOGICA; 105(2):284-96 (2020) (Tab 3).

[30] *See e.g.* Franchini, M. and Lippi, G., *Fibrinogen Replacement Therapy: A Critical Review of the Literature*, BLOOD TRANSFUS.; 10(1): 23-27 (2012) (Tab 4); *see also* Fibryga (STN 125612/67) Clinical Review Document *at* 6, *available at* https://www.fda.gov/media/145117/download.

fibrinogen replacement options include fresh frozen plasma, cryoprecipitate, and licensed human fibrinogen products.[31]

B. Fibryga

Fibryga is a human fibrinogen concentrate manufactured by Octapharma. Fibryga has been licensed since June 2017 for treatment of acute bleeding episodes in adults and children with congenital fibrinogen deficiency, including both afibrinogenemia and hypofibrinogenemia.[32] Fibryga is not indicated for dysfibrinogenemia. It is also not licensed for treatment of acquired fibrinogen deficiencies.

Fibryga is manufactured by separating plasma proteins using a combination of processes involving centrifugation, adsorption, filtration and ultrafiltration, viral inactivation using solvent detergents, and temperature changes resulting in the formation of precipitates.[33] Based on the combination of these processes, FDA has determined that Fibryga's manufacturing process requires more than mere "physical or mechanical means," and thus regulates Fibryga as a blood derivative.

Because Fibryga is regulated as a blood derivative, Octapharma was required to, and did, conduct clinical studies to assess the safety and efficacy of Fibryga in treating acute bleeding episodes in patients with congenital fibrinogen deficiency: FORMA 01 and FORMA 02.[34] FORMA-01 was a Phase 2 crossover pharmacokinetic (PK) and efficacy study in 22 subjects ≥12 years old in the non-bleeding state.[35] FORMA-02 was an uncontrolled Phase 3 primarily efficacy and safety study of Fibryga for the treatment of acute bleeding (major and minor bleeding episodes) and perioperative management of bleeding for major and minor surgery in patients ≥ 12 years old.[36]

Fibryga was also subject to rigorous post-approval study requirements.[37] Most recently, Octapharma completed a clinical study in children less than 12 years old with congenital

---

[31] *See* Fibryga (STN 125612/67) Clinical Review Document *at* 6.

[32] *See* Section 1, Fibryga Prescribing Information.

[33] *See* generally, Fibryga Chemistry, Manufacturing, and Controls (CMC) Review Memorandum, *available at* https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/fibryga; *see also* Section 11, Fibryga Prescribing Information.

[34] *See* Fibryga (STN 125612/67) Summary Basis for Regulatory Action *at* 8.

[35] *See id. at* 5.

[36] *See id.*

[37] *See* Fibryga Approval Letter (June 7, 2017) *at* 5.

fibrinogen disease who had been treated with Fibryga for at least ten major bleeding events.[38] It was only after that required clinical study that Fibryga was licensed for use in patients less than 12 years of age with congenital fibrinogen disease.[39] Moreover, at the time Fibryga was licensed for treatment of congenital fibrinogen disease in adults and adolescents, FDA determined that mere analysis of spontaneous post-marketing adverse events or the maintenance of a pharmacovigilance system would not be sufficient to "assess signal of a serious risk of thromboembolic events" following treatment with Fibryga. As a result, FDA required that Octapharma conduct *another* prospective observational study in patients with congenital afibrinogenemia and hypofibrinogenemia treated with Fibryga for at least ten major bleeding events to further characterize the risk of thromboembolic events.[40] Octapharma is currently conducting this study and anticipates completing it by 2027.

Notwithstanding all of the studies described above in congenital fibrinogen deficiency patients, Fibryga is still not licensed for treatment of a subset of congenital fibrinogen deficiency conditions—dysfibrinogenemia.[41] Further, FDA recently determined that Octapharma will be required to complete yet more clinical studies, in addition to studies already submitted to FDA, to support use of Fibryga for treatment of acquired fibrinogen deficiency. In making this determination, FDA also declined to recognize acquired fibrinogen deficiency as a single new indication; instead, FDA is requiring separate clinical trials for *each setting* in which a patient becomes fibrinogen-deficient, such as cardiac surgery or surgery to treat pseudomyxoma peritonei cancer.

C. INTERCEPT Blood System for Pathogen Reduction

The INTERCEPT Blood System is a medical device manufactured by Cerus Corporation (Cerus) that is used for reducing pathogens in transfused blood or blood products.[42] The INTERCEPT

[38] *See* Fibryga Supplement Approval Letter (Dec., 2020) *at* 1, *available at* https://www.fda.gov/media/144964/download.

[39] *See id.*

[40] *See* Fibryga Approval Letter (June 7, 2017) *at* 5. FDA initially requested that this study be conducted in patients 12 years and older, but later amended the request to include all patients.

[41] *See* Section 1, Fibryga Prescribing Information.

[42] *See* Cerus Webpage, INTERCEPT Fibrinogen Complex, Pathogen Reduction *at* https://INTERCEPT-cryoprecipitation.com/pathogen-reduction/ (last visited Nov. 23, 2022).

Blood System achieves this pathogen-reducing result through a combination of physical and chemical treatments of blood plasma.

INTERCEPT's pathogen reduction process begins by mixing plasma with a photochemical known as amotosalen (S-59, a psoralen derivative), which is capable of binding to nucleic acids in pathogens.[43] The photochemical-processed plasma is then subjected to ultraviolet (UV) light while being agitated.[44] The UV light activates the amotosalen, resulting in the formation of a covalent chemical bond between the photochemical and the nucleic acids in any pathogens present in the plasma and preventing further replication of the pathogens.[45] INTERCEPT's manufacturer Cerus also has acknowledged that amotosalen is capable of binding to targets in addition to the specific target pathogen DNA, stating that amotosalen "is not selective for genomic material from any one organism."[46] Residual amotosalen creates risks to the safety, purity and potency of the final product which require clinical trials to assess. It is precisely such unknown risks from chemical manipulations that undergird the regulatory definition of blood components and that limits their processing to physical or mechanical means.

The processed plasma is then subjected to a compound adsorption device (CAD) intended to remove unreacted amotosalen and free photoproducts.[47] Despite subjecting the plasma to adsorption—a process by which atoms, ions, or molecules adhere to a surface—to remove unreacted amotosalen, the resulting plasma product is contraindicated in "patients with a history of hypersensitivity reaction to amotosalen or other psoralens."[48] Amotosalen-treated plasma has been shown to cause cardiac events including angina pectoris, cardiac arrest, bradycardia,

---

[43] *See* INTERCEPT Blood System for Plasma Package Insert *at* 1, *available at* https://wayback.archive-it.org/7993/20190208123656/https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM427365.pdf.

[44] *See id.*

[45] *See* Cerus Webpage, INTERCEPT Fibrinogen Complex, Pathogen Reduction *at* https://INTERCEPT-cryoprecipitation.com/pathogen-reduction/ (last visited Nov. 23, 2022).

[46] Cerus Webpage, Amotosalen Mechanism of Action, *available at* https://INTERCEPTbloodsystem.com/en/blood-center/INTERCEPT/mechanism-action-amotosalen (last visited Dec. 8, 2022).

[47] *See* INTERCEPT Blood System for Plasma Package Insert *at* 1, *available at* https://wayback.archive-it.org/7993/20190208123656/https://www.fda.gov/—downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM427365.pdf.

[48] *See id. at* 5.

tachycardia, and sinus arrhythmia.[49] And "several reports point towards a reduced platelet function after Amotosalen/UVA exposure," concerns that were validated in a 2017 study.[50]

D. Blood Center Products Produced Using the INTERCEPT Blood System

Cerus has contracted with three blood centers—the Gulf Coast Regional Blood Center, the Central California Blood Center, and the Community Blood Center of Appleton[51]—to use the INTERCEPT Blood System to produce pathogen reduced fibrinogen products which FDA has licensed for distribution in interstate commerce as "Pathogen Reduced Cryoprecipitated Fibrinogen Complex products."

The Blood Center products are produced from plasma that has been initially subjected to physical and chemical treatment through the INTERCEPT Blood System, including treatment with the photochemical amotosalen and UV radiation.[52] The resulting plasma from the INTERCEPT Blood System is then further subjected to repeated rounds of thawing, centrifugation at cold temperatures, pooling (which is optional), and cryoprecipitation to irreversibly precipitate out the fibrinogen to form the Blood Center products.[53]

Despite these overt chemical manipulations to the Blood Center products and their similarity to the processes used to manufacture Fibryga, FDA currently regulates the products as blood components. This in turn means that the Blood Center products are not subject to the rigorous pre-approval and post-approval requirements that are imposed on products treated as blood derivatives, such as Fibryga. In particular, no *in vivo* clinical studies or safety studies have been carried out on the products.[54]

---

[49] *See* INTERCEPT Blood System for Plasma Package Insert *at* 5.

[50] Stivala, S. *et al.*, Amotosalen/ultraviolet A Pathogen Inactivation Technology Reduces Platelet Activatability, Induces Apoptosis and Accelerates Clearance, 102 Haemotologica 102(10): 1650-60 (2017)("The study herein clearly demonstrates that platelet treatment with Amotosalen/UVA causes an alteration of platelet function.") (Tab 5).

[51] *See* FDA List of Products and Establishments, *at* 16, 19, and 29, *available at* https://www.fda.gov/media/76356/download.

[52] *See* INTERCEPT Blood System for Cryoprecipitation Package Insert for the Manufacturing of Pathogen Reduced Cryoprecipitated Fibrinogen Complex (INTERCEPT Blood System for Blood Center Products Package Insert) *at* 21, *available at* https://www.fda.gov/media/143996/download.

[53] *See* INTERCEPT Blood System for Blood Center Products Package Insert *at* 17-18.

[54] *See* INTERCEPT Blood System for Blood Center Products Package Insert *at* 21 ("There are no specific clinical studies for Pathogen Reduced Cryoprecipitated Fibrinogen Complex.").

Nevertheless, FDA licensed the Blood Center products for use in *all* acquired and congenital fibrinogen deficiencies.[55] According to the *Circular*, the Blood Center products are broadly indicated for:

1. Treatment and control of bleeding, including massive hemorrhage, *associated with fibrinogen deficiency*;
2. Control of bleeding when recombinant and/or specific virally inactivated preparations of Factor XIII or Von Willebrand factor are not available;
3. Second-line therapy for Von Willebrand disease; *and*
4. Control of uremic bleeding after other treatment modalities have failed.[56]

In March 2022, FDA accepted the most recent version of the *Circular* providing the labeling instructions for use of the Blood Center products for these indications.[57] The broad licensure for use in treatment of fibrinogen deficiency means that the Blood Center products are licensed for treatment and control of *any* bleeding associated with fibrinogen deficiency, including dysfibrinogenemia and *all* instances of acquired fibrinogen deficiency. That is to say, the Blood Center products are licensed for use in a variety of patient populations and for a variety of fibrinogen deficiency conditions for which neither the Blood Centers nor Cerus has demonstrated "safety, purity, and potency."

ARGUMENT

I. THE BLOOD CENTER PRODUCTS ARE BLOOD DERIVATIVES.

The regulatory definition of blood components does not permit the Blood Center products to be regulated as blood components. The Blood Center products are manufactured by a combination of physical and chemical manipulations that exceed the scope of "physical or mechanical" processes intended by the regulation. FDA's regulation of these products as blood components is also a departure from the agency's established practices in distinguishing between blood components and blood derivatives. Because the Blood Center products have been misclassified as

[55] *See* FDA Guidance, Manufacture of Blood Components Using a Pathogen Reduction Device in Blood Establishments: Questions and Answers, (Nov. 2021) *at* 6-7, *available at* Manufacture of Blood Components Using a Pathogen Reduction Device in Blood Establishments: Questions and Answers; Guidance for Industry (fda.gov).

[56] *Circular at* 38.

[57] *See* FDA Blood Circular Guidance *at* 2.

"blood components," and thus not subject to the same critical study and labeling requirements applicable to blood derivatives, FDA must set aside their BLAs.

FDA must also refrain from approving any additional similarly manufactured INTERCEPT Blood System fibrinogen products as blood components.

A. The Regulation does not Support Classification of INTERCEPT Fibrinogen Complex Products as "Blood Components."

As discussed above, FDA defines the term "blood component" as a "product containing a part of human blood separated by physical or mechanical means."[58] The Blood Center products are licensed as "Pathogen Reduced Cryoprecipitated Fibrinogen Complex" products.[59] And true to their name, the manufacturing process used to prepare the Blood Center products—and other INTERCEPT fibrinogen complex products—involves complex chemical manipulations. By regulating the Blood Center products as blood components, FDA has embraced an interpretation of blood component that stretches beyond the definition's plain meaning and strays from FDA's past consistent interpretation of the term.

The manufacturing process for the Blood Centers' fibrinogen products includes photochemical and ultraviolet pathogen reduction and multiple cycles of freezing, thawing, and centrifugation at low temperatures in order to concentrate the fibrinogen and produce the final product.[60] The photochemical treatment of the plasma and the formation of chemical bonds are chemical manipulations that clearly fall outside the scope of mere "physical or mechanical" separation, and FDA has previously found such manipulations to trigger regulation as a blood derivative.[61] Moreover, FDA has historically interpreted the phrase "physical or mechanical means" to exclude viral inactivation steps using chemicals.[62] FDA's conduct in regulating the Blood Center products and other INTERCEPT fibrinogen complex products as blood components therefore violates the plain language of its own regulation.

---

[58] 21 CFR 606.3(c).

[59] *See* FDA List of Products and Establishments *at* 16, 19, and 29.

[60] *See* INTERCEPT Blood System Package Insert *at* 2-4.

[61] *See, e.g.,* Package Insert for Octaplas (describing clinical trials required for plasma that is pathogen-reduced using solvent/detergent chemical treatments).

[62] *See, e.g., id.*.

B. The INTERCEPT Fibrinogen Complex Products Have Not Been Established to be Safe, Pure, and Potent Through Clinical Studies.

The PHSA prohibits the introduction of a biological product into interstate commerce unless a biologics license is in effect for that product.[63] Among other things, the statute directs FDA to approve a biologics license if the applicant demonstrates that the biological product is safe, pure, and potent.[64] The statute further grants broad authority to FDA to establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses.[65] Accordingly, FDA has the authority to set aside the licensure of the Blood Center products and to refrain from approving any additional INTERCEPT fibrinogen complex products because they have simply not been established to be safe, pure, and potent as required by the statute.

FDA's purpose in regulating blood components and blood derivatives differently is undermined when chemically modified blood products such as the Blood Center products are included under the umbrella of blood components. The addition of amotosalen, treatment with UV radiation, and the use of newer chemical separation methods introduce unstudied elements into the final Blood Center products. It is not enough that Cerus studied the safety and effectiveness of the precursor plasma drug substance treated with the INTERCEPT Blood System.[66] FDA should have required Cerus to perform clinical testing on the final fibrinogen products to confirm that the activity of amotosalen is not detrimental to the safety, purity, and potency of those final products. FDA has typically—and justifiably—determined that these untested modifications require additional *in vivo* studies. By failing to classify and regulate the Blood Center products appropriately, FDA has shunted a new, chemically treated blood product into a category in which it clearly does not belong.

FDA's more lenient regulatory requirements for INTERCEPT fibrinogen complex products, and the corresponding absence of clinical study data demonstrating the safety, purity, and potency of these products, presents a risk to public health. Currently, the Blood Center products are being advertised for use in various emergency situations, including obstetrics hemorrhage, without accompanying studies confirming that the products are safe, pure, and potent—all without assessing the effect of amotosalen in the final Blood Center products, among other deficiencies in the process. By contrast, as described further below, FDA is forcing Octapharma to perform

[63] *See* 42 USC 262(a)(1)(A).

[64] *See* 42 USC 262(a)(2)(C)(i)(I).

[65] 42 USC 262(a)(2)(A).

[66] *See* INTERCEPT Blood System Package Insert *at* 14-15.

clinical trials to establish that Fibryga is a safe, pure, and potent treatment for acquired fibrinogen deficiency in these same emergency scenarios.

II. FDA VIOLATED BASIC PRINCIPLES OF ADMINISTRATIVE LAW BY REGULATING SIMILAR PRODUCTS DISSIMILARLY.

It is black-letter law that "an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so."[67] Unexplained inconsistency "is an arbitrary and capricious change from agency practice"[68] and an agency's inconsistent interpretation must be set aside.

FDA's actions with regard to regulation of Fibryga and the Blood Center products are arbitrary and capricious. The agency has provided no explanation for treating Fibryga and these other fibrinogen complex products dissimilarly despite the material similarities in the process of manufacture. Both products are manufactured by subjecting human plasma to chemical treatment, pooling, adsorption, freezing, cryoprecipitation, thawing, and centrifugation cycles. There is no logical basis for treating these competing products differently.

By classifying Octapharma's Fibryga as a blood derivative, the agency held Octapharma's BLA to a more stringent standard of review, requiring premarket approval supported by clinical trials, full drug user fees, and pediatric assessments in compliance with PREA. In contrast, by classifying the Blood Centers' fibrinogen products as blood components, FDA subjected the BLAs to a much lower regulatory burden.

Further, FDA's classification of the Blood Center products as blood components is a major departure from the agency's historic practice of characterizing any products subjected to complex chemical processes for reducing the risk of pathogens as blood derivatives. Such conduct defies logic, lacks a reasoned basis, and lacks support in the administrative record.

---

[67] *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) (citation omitted) (Tab 6); *see also County of Los Angeles v. Shalala*, 192 F.3d 1005, 1022 (D.C. Cir. 1999) ("A long line of precedent has established that an agency action is arbitrary when the agency offer[s] insufficient reasons for treating similar situations differently.") (Tab 7).

[68] *Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 222 (2016) (Tab 8); *see also Republic Airline Inc. v. Dep't of Transp.*, 669 F.3d 296, 300 (D.C. Cir. 2012) ("One of the core tenets of reasoned decision-making is that an agency [when] changing its course . . . is obligated to supply a reasoned analysis for the change.") (internal quotation marks and citations omitted) (Tab 9).

FDA's actions are causing concrete and imminent harm to Octapharma. FDA licensed the Blood Centers' fibrinogen products for a broad range of indications, including treatment and control of any bleeding associated with fibrinogen deficiency, whether congenital or acquired.[69] And unlike for Fibryga, FDA made no distinctions among the various settings in which patients can acquire fibrinogen deficiency. The Blood Center products thus are licensed for indications that overlap with those indications for which Fibryga is licensed. The products are therefore directly competing in the marketplace for treating the same type of fibrinogen deficiency, and yet subject to far different regulatory standards. Indeed, recently, when Octapharma attempted to obtain licensure for acquired forms of fibrinogen deficiency—an indication for which the Blood Center products are already licensed without any clinical studies—FDA required Octapharma to conduct additional studies for this indication, and changed its own definition of the indication itself, deeming each setting in which a patient acquires fibrinogen deficiency to be a new indication requiring a new clinical trial. Approving the Blood Centers' competing products subject to a more lenient standard creates an uneven playing field between these competing products.

III. FDA'S ACTION IS CAUSING POTENTIAL HARM TO THE PUBLIC

FDA's action in regulating the Blood Center products as blood components rather than blood derivatives is potentially harmful to the public. Octapharma requests that the agency put patient safety first by holding the Blood Centers and other sponsors of fibrinogen products manufactured by the INTERCEPT Blood System to the same high standard as Octapharma.

FDA regulates certain blood products as blood components in part because these products have been established to be safe, pure, and potent (including effective) for their intended uses for decades. When manufacturing processes carried out on blood products exceed the scope intended for blood components, then the effect of such processes on the blood product as well as the safety, purity, and potency of the products can no longer be assumed. This is why FDA requires that such products—with more than physical and mechanical manipulation—be tested through clinical studies to ensure that the products' process of manufacture have not rendered them unsafe, impure, or not potent.

FDA licensed the Blood Center products for a broad range of indications, including treatment and control of any bleeding associated with fibrinogen deficiency, whether congenital or acquired,

[69] *See* INTERCEPT Blood System for Blood Center Products Package Insert *at* 2; *see also Circular at* 38.

without confirming the safety, purity, and potency of these products through clinical studies.[70] And unlike for Octapharma's Fibryga, FDA made no distinctions among the various settings in which patients can acquire fibrinogen deficiency. Thus, given the importance and widespread use of the Blood Center products, including in emergency situations, FDA must ensure that patient safety is put first and similarly require a higher standard for licensure of the Blood Center products.

CONCLUSION

FDA's regulation of the Blood Center products as blood components is contrary to the plain language of the agency's regulation and the agency's established practices in clarifying the difference between blood components and blood derivatives. The process of manufacturing the Blood Center products involves complex chemical manipulations not included within the narrow definition of blood components. Moreover, these products have not been established to be safe, pure, and potent for their intended uses, including for treatment and control of bleeding associated with all forms of fibrinogen deficiency. FDA cannot lawfully license the Blood Center products as blood components, while approving a similarly manufactured Fibryga as a blood derivative.

For these reasons, Octapharma respectfully requests that FDA grant the actions requested in this citizen petition and set aside the licensure of the Blood Center products and refrain from licensing any similarly manufactured products as blood components. Alternatively, we request that FDA give equal treatment to Fibryga by regulating it as a blood component.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

ECONOMIC IMPACT

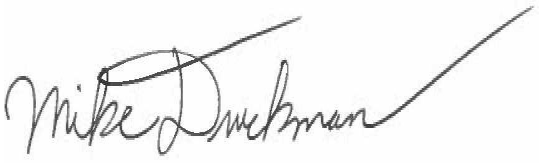
Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

[70] *See* INTERCEPT Blood System for Blood Center Products Package Insert *at* 2; *see also Circular at* 38.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



Mike Druckman, Partner
Hogan Lovells US LLP
555 Thirteenth Street, NW
Washington, DC 20004
(202) 637-5635
mike.druckman@hoganlovells.com
Counsel for Octapharma