

**Patients Who Depend On Plasma Protein Therapies
Need Legislative Protection From Unpredictable Risks To Which
An Abbreviated Product Approval Pathway Could Expose Them**

Prepared for the Plasma Protein Therapeutics Association
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The Question:

Congress is now debating how to reduce healthcare costs by creating an abbreviated approval pathway for biologics. Currently circulating legislation seeks to abbreviate the pathway by allowing a manufacturer to show that its product is similar enough to an already-licensed biologic for FDA to conclude that no meaningful clinical differences will exist between the two when used in people. The cost savings would be realized if manufacturers are able to make that showing completely or at least to a large extent with biochemical assays and animal testing, rather than having to prove their biologics to be safe, pure, and potent through expensive human clinical trials.

The key question, then, based on the circulating legislation, is: how can FDA be sure that biochemical testing and animal data can detect all clinically meaningful differences between a licensed biologic and one that follows it? 1/

The Conundrum:

Congress's desire to reduce the cost of healthcare in this country is laudable. Congress must be sure, however, not to pass legislation that will jeopardize patients' health by exposing them to unpredictable risks. Any legislation that creates an abbreviated approval pathway by relying on biochemical testing and animal data in lieu of substantial evidence from well-designed clinical trials must contain mechanisms to ensure that FDA answers the critical question above for each abbreviated biologic application before approving it.

FDA will face a conundrum when trying to answer that question for plasma protein therapies. The nature of these therapies, of the patients using them, and of the rare but serious adverse events that they can cause make it impossible to rule out all clinically meaningful differences in a second manufacturer's follow-on product without testing the follow-on thoroughly in people, as discussed below.

Plasma protein therapies generally treat patients whose health is severely compromised by chronic, debilitating, and rare^{2/} diseases and medical conditions,

1/ See, e.g., Janet Woodcock, et al., *The FDA's assessment of Follow-on Protein Products: a Historical Perspective*, 6 NATURE REVIEWS 437, 438 (June 2007) ("A major scientific issue in evaluating follow-on protein products is determining how much and what kind of data are needed to establish whether differences between similar – but not identical – protein products produced by different manufacturers are clinically insignificant.").

2/ Among the diseases treated by plasma protein therapies that meet National Institute of Health Office of Rare Diseases' definition of rare disease, according to

such as hemophilia A, primary immune deficiency, and alpha1-antitrypsin deficiency. Some plasma protein therapy products are derived from human plasma, which is rich in complex, therapeutically useful proteins. ^{3/} Other plasma protein therapy products are produced using DNA recombinant technology. ^{4/}

Among the plasma-derived products are all brands of immune globulin and alpha1-proteinase inhibitor, as well as albumin and many brands of coagulation factor products. To extract selected proteins from plasma, manufacturers exploit different proteins' varying solubility (ability to dissolve in solution) under different conditions, such as alcohol concentration, pH, ionic strength, and temperature. ^{5/} By gradually altering those properties of the plasma, they cause different groupings of proteins in the plasma (called fractions) to separate. After completing that fractionation process, they use other manufacturing processes to isolate particular proteins. ^{6/}

Plasma protein therapies made through recombinant DNA technology include the blood clotting proteins Factor VII, Factor VIII, and Factor IX. ^{7/} The process involves inserting the DNA from the clotting protein into a nonhuman

the agency's database, are: alpha1-antitrypsin deficiency, B-cell chronic lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, hemophilia A, hemophilia B, hyperimmunoglobulinemia E syndrome, idiopathic thrombocytopenic purpura, Kawasaki syndrome, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, multiple sclerosis, myasthenia gravis, primary immune deficiency disease, staphylococcal toxic shock syndrome, and von Willebrand disease. See Office of Rare Diseases, U.S. Dep't of Health & Human Servs., *Rare Diseases and Related Terms*, <http://rarediseases.info.nih.gov/RareDiseaseList.aspx?PageID=1> (last visited May 18, 2009).

^{3/} See Thierry Burnouf, *Plasma Proteins: Unique Biopharmaceuticals – Unique Economics*, in 7 PHARMACEUTICALS POLICY AND LAW, BLOOD, PLASMA AND PLASMA PROTEINS: A UNIQUE CONTRIBUTION TO MODERN HEALTHCARE 209 (J. L. Valverde ed., 2006).

^{4/} See S.W. Pipe, *The Promise and Challenges of Bioengineered Recombinant Clotting Factors*, 3 J. OF THROMBOSIS AND HAEMOSTASIS 1692, 1692 (2005).

^{5/} See Georg Lemm, *Composition and Properties of IVIg Preparations that Affect Tolerability and Therapeutic Efficacy*, 59 NEUROLOGY S28, S29-S30 (2002); Basil Golding, MD, Director of Plasma Derivatives, U.S. Dep't of Health & Human Servs., *Clinical Trial Endpoints for Immune Globulin Intravenous (IGIV)* (Mar. 26, 1999), <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3504t2.pdf> [hereinafter "Golding Presentation"], at 16.

^{6/} *Id.*

^{7/} Pipe, *supra* n.4, at 1692.

mammalian cell line. 8/ The cell line is a single layer of cells derived from either Chinese hamster ovaries or baby hamster kidneys, which are cultivated in a cell culture flask. 9/ The DNA causes the cell line to express (produce) the clotting factor protein into the culture medium. 10/ The protein in the culture is then purified into the final product. 11/

Plasma protein therapies pose a fundamental conundrum for those interested in abbreviating their approval process for the following reasons:

1. Adverse events that plasma protein therapies cause often result from an interaction between patient and product characteristics.
2. Rare but severe adverse events can occur with these products, and some of them can result in the need for lifelong treatment.
3. The potentially relevant patient characteristics are numerous and highly variable.
4. The potentially relevant product characteristics are too numerous to test for all of them, or even to discover all of them.
5. Small changes in the manufacturing process for these plasma protein therapies can produce product characteristic changes that interact with particular patient characteristics in ways that are clinically meaningful, but beyond our ability to detect, measure, or recognize as meaningful without safety data from actual clinical experience.

Real Life Examples of the Conundrum

A few examples of adverse events in plasma protein therapies will help illustrate the conundrum that plasma protein therapies pose for anyone trying to abbreviate their approval process.

Factor VIII immunogenicity reactions:

Factor VIII (FVIII) is one of many proteins in the blood that play a role in blood clotting. It is the active ingredient in 11 different brands of Antihemophilic Factor products that are used to treat patients suffering from hemophilia A, a

8/ *Id.*, at 1693.

9/ *Id.*

10/ *Id.*

11/ *Id.*

bleeding disorder caused by deficiency or absence of the FVIII protein. ^{12/} One major adverse reaction to FVIII is that patients sometimes develop an antibody that attacks the FVIII protein molecule itself. ^{13/} That immune system response (called an immunogenicity reaction) immediately inhibits the Antihemophilic Factor's clotting effect, returning those patients to their original state of high bleeding risk. ^{14/} Treating patients who develop such antibodies (commonly called inhibitors) is difficult because each reacts differently to various treatments. ^{15/} One treatment is to infuse the patient with a high dose of FVIII to familiarize the patient's system with FVIII to the point that the immune system recognizes the molecule and stops producing the inhibitor antibody (achieving "tolerance" for the FVIII molecule). ^{16/} While many patients achieve tolerance within 6 to 9 months, 25% of patients treated require tolerance treatment regimens for the rest of their lives. ^{17/}

Unfortunately, many variables relating to the characteristics both of the patient and of the product influence the risk that a patient will have this immune reaction. As to patient characteristics, previously untreated patients are at the highest risk, but both genetic factors (severity of hemophilia, type of mutation, ethnicity, family history of inhibitors, and HLA genotype) and non-genetic factors (age at first treatment, intensity of treatment, continuous infusion, and multiple product switches) play a role in determining the risk. ^{18/}

The product characteristics of the FVIII molecule are that it is a very large, single polypeptide gene protein with a tertiary (three dimensional) structure with multiple domains (portions of the protein sequence that can function and fold independently of the rest of the protein chain) ^{19/} To interact effectively with other

^{12/} Andrew Chang, Assoc. Dir, Div. of Hematology, U.S., Dep't of Health & Human Servs., *Licensed Therapeutic Protein Products with Known Structural Modifications, Address Before the Blood Products Advisory Committee* (Nov. 4, 2005) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4190t2.rtf>), at 121-22 [hereinafter "Chang Presentation"].

^{13/} See Jenny Goudemand, et al., *Influence of the Type of Factor VIII Concentrate on the Incidence of Factor VIII Inhibitors in Previously Untreated Patients with Severe Hemophilia A*, 107 BLOOD 46, 49 (2006); Pipe, *supra* n. 4, at 1696.

^{14/} Pipe, *supra* n. 4, at 1693.

^{15/} See THE MARKETING RESEARCH BUREAU, INC., THE PLASMA FRACTIONS MARKET IN THE UNITED STATES 2007 149 (2008) [hereinafter "MRB Report"]

^{16/} *Id.*

^{17/} *Id.*, at 149-50.

^{18/} Goudemand, *supra* n. 13, at 46, 48-49.

^{19/} See Betty W. Shen, et al., *The Tertiary Structure and Domain Organization of Coagulation Factor VIII*, 111 BLOOD 1240, 1241-42, fig. 1 (2008).

proteins in blood, the domains must be intact and correctly positioned. [20/](#) The tertiary structure of the molecule, however, can be affected by particular manufacturing steps, such as by combining pasteurization with other viral inactivation methods like solvent detergent treatment, to the extent that the change could increase the risk that certain patients will develop inhibitors. [21/](#)

How exactly that manufacturing-induced change interacts with particular patient characteristics to determine the risk of developing an inhibitor is unknown. Too many variables are in play, with too few patients to isolate them all. [22/](#)

And that is just one product characteristic affected by one manufacturing step. Other manufacturing differences known to affect FVIII products' characteristics, to name just a few, include: the cell line used in recombinant versions [23/](#); the pH level [24/](#); and, fundamentally, whether the product is made through DNA recombinant processes or is plasma derived. That last factor has been shown to affect inhibitor risk in previously treated patients. [25/](#) Specifically, one study found inhibitors to be 2.5 to 3 times more likely in recombinant FVIII patients than in those treated with plasma-derived FVIII. [26/](#) As to previously-treated patients, the European Medicines Agency (EMA) recently concluded that a trend of developing low levels of inhibitors exists for patients previously treated for more than 100 days with one recombinant FVIII product who switch to another. [27/](#)

Intravenous Immune Globulin:

Intravenous Immune Globulin (IVIG) is made by isolating a particular antibody (also known as an immunoglobulin) -- immunoglobulin G (IgG) -- from plasma pooled from hundreds to thousands of patients. [28/](#) IVIG was first used as

[20/](#) See Angelica Fatouros, et al, *Recombinant Factor VIII SQ – Influence of Oxygen, Metal Ions, pH and Ionic Strength on Its Stability in Aqueous Solution*, 155 INT'L J. OF PHARMACEUTICS 121, 129 (1997).

[21/](#) Pipe, *supra* n. 4, at 1693-94 (citing reports that patients developed inhibitors after switching to plasma-derived FVIII virally inactivated by pasteurization in conjunction with solvent detergent treatment or other processes).

[22/](#) See Goudemand, *supra* n.13, at 50.

[23/](#) See M.A. Jankowski, et al., *Defining 'Full Length' Recombinant Factor VIII: A Comparative Structural Analysis*, 13 HAEMOPHILIA 30, 32 (2007).

[24/](#) See Fatouros, *supra* n. 20, at 129.

[25/](#) See Goudemand, *supra* 13, at 49.

[26/](#) *Id.*

[27/](#) See Press Release, The European Medicines Agency, *EMA Completes the Review of Recombinant Factor VIII Products and Inhibitor Development* (July 31, 2007), at <http://www.emea.europa.eu/pdfs/human/press/pus/31022507en.pdf>.

[28/](#) See Lemm, *supra* n. 5, at S29.

replacement therapy for patients with antibody deficiencies, but now is used to treat a wide variety of immune diseases. [29/](#) Variations in different manufacturers' fractionation methods and subsequent processes for purification, stabilization, and virus inactivation result in significant differences among products, such as in chemical structure, antibody content and structure, and amount of contaminants. [30/](#) Those differences can affect the products' efficacy and safety, depending on particular patients' characteristics. [31/](#)

For example, older patients and patients with cardiovascular disease experience an increase in infusion-related adverse events from IVIG with high osmolality (a high concentration of particles dissolved in the solution). [32/](#) Those adverse events include renal complications and thromboembolic episodes (where a blood clot forms in a blood vessel, breaks loose, and plugs another vessel, such as one in the lungs). [33/](#) Major contributors to osmolality include sugars, sodium, and amino acids, which vary in amount among the different IVIG products. [34/](#) For example, some manufacturers add sugars to their preparations to prevent IgG molecules from aggregating (attracting to each other). [35/](#) Similarly, sodium content varies widely in different IVIG preparations, and can be affected by the manufacturing process as well as other factors, such as efforts to reconstitute lyophilized (freeze-dried) preparations in higher concentrations in an attempt to reduce volume load on patients. [36/](#)

Thus, subtle differences in manufacturing processes can have significant impacts on IVIG safety. Other known variables that can affect the final product in clinically significant ways include:

- *Very small changes in pH during one of the steps of fractionation that can increase the concentration of plasminogen (an anticoagulant protein) in the final product. Increased plasminogen can have “a devastating effect on the stability and efficacy of the immune globulins.” [37/](#)*
- *Unspecified manufacturing differences that increase the amount of Immunoglobulin A (IgA), [38/](#) an antibody that protects against infections of the mucous membranes lining the mouth, airways, and digestive tract, in the*

[29/](#) *Id.* at S28.

[30/](#) *See id.* at S28, S30; *see also* Golding Presentation, *supra* n. 5, at 16-17.

[31/](#) Lemm, *supra* n. 5, at S30; Golding Presentation, *supra* n. 5, at 17-18.

[32/](#) *Id.* at S30, S31.

[33/](#) *Id.* at S30.

[34/](#) *Id.*

[35/](#) *Id.*

[36/](#) *Id.*

[37/](#) Golding Presentation, *supra* n.5, at 16.

[38/](#) Lemm, *supra* n. 5, at S31; Golding Presentation, *supra* n.5, at 18.

final product. In most patients the IgA level is not problematic, but patients with selective IgA deficiency (whose bodies do not produce the IgA antibody) are at risk for an anaphylactic reaction because their bodies recognize the molecule as foreign and produce antibodies against the IgA antibody itself. [39/](#) Using an IVIG product that is low in IgA does not always prevent a reaction, however. [40/](#)

- *Differences in excipients.* For example, some IVIG manufacturers add albumin to the product during manufacturing. In one case, the manufacturer added albumin after manufacturing the bulk IVIG and then subjected the intermediate product to chemical treatments. Those treatments changed the albumin, and were later found to induce allergic reactions. [41/](#)

Other plasma protein therapies:

All plasma protein therapies, because they are so complex, vary in manufacturing process and product characteristics from manufacturer to manufacturer. For example, alpha1-proteinase inhibitor, which is generally administered weekly to patients with a congenital deficiency in the alpha1-proteinase inhibitor protein who have clinically evident emphysema, are “somewhat heterogeneous in terms of protein composition and chemical structures.” [42/](#) Specifically, the agency notes that although alpha₁-proteinase inhibitor protein is the active agent in all formulations in the marketplace, each formulation “contain[s] different amounts of other plasma proteins and . . . chemical modifications which arise during manufacturing and occur at minor to substantial levels varying from product to product.” [43/](#)

Similarly, Von Willebrand factor is a complex molecule that undergoes serious post-translational modifications intracellularly (changes to the protein after it is translated from DNA coding into a protein molecule), and it forms multi-molecule complexes. [44/](#) The characteristics of these multi-molecular complexes and the specific activity of the final therapy depend on the manufacturing process. [45/](#)

Only through real experience in patients is it possible to know with confidence whether the biochemical differences between different manufacturers’

[39/](#) *Id.*

[40/](#) Lemm, *supra* n. 5, at S31

[41/](#) Golding Presentation, *supra* n.5, at 17.

[42/](#) Ctr. for Biologics Evaluation & Research, U.S. Dep’t of Health & Human Servs., *Heterogeneity of Alpha-1 Proteinase Inhibitor (Human) Products*, <http://www.fda.gov/cber/infosheets/alph1pi.htm> (updated May 7, 2007), at n1.

[43/](#) *Id.*

[44/](#) Chang Presentation, *supra* n. 12, at 116.

[45/](#) *Id.*

plasma protein products have a material impact on clinical safety and effectiveness. Moreover, the biochemical differences among products discussed above are only those *known* to exist. Plasma “is a very complex protein solution consisting of hundreds, maybe thousands of different proteins” [46/](#) Consequently, it is impossible to test for all of them in final products through biochemical assays, and even if it became possible, it would not be practical to do so. It would be similarly impracticable to identify, strictly through biochemical assays, all other differences between a new plasma protein therapy and already-licensed one, let alone to determine how they might react with particular patient characteristics.

When a manufacturer makes a change to its already-licensed product, the manufacturer and FDA have a baseline of clinical experience on which to make judgments about the likely effect that the change will have, if any, on the product, keeping all other variables constant. When a new manufacturer produces a plasma protein therapy through its own, unique manufacturing process, all variables are not being held constant. The new manufacturer, who does not have access to the already-licensed manufacturer’s trade secrets and proprietary manufacturing data, has no way to know the ways that its process differs from that of the licensed manufacturer. Moreover, as a practical matter, for the reasons discussed above, FDA would not be able to discern all the subtle differences that could be material, simply by comparing the manufacturing processes as described in the two companies’ biological license applications (BLAs). As CBER Division Director Dr. Basil Golding stated, “variations in the process can have far-reaching effects on both safety and efficacy. So, our conclusion is that each product should be regarded as unique, and immune globulins should not be treated as a single generic biologic.” [47/](#) The same reasoning applies to all plasma protein therapies.

The Conundrum’s Implications

The bottom line is that to know all the relevant biochemical factors that are clinically meaningful for plasma protein therapies, we would need to test each product characteristic in patient populations with each relevant patient characteristic. Furthermore, there can always be unknown or unanticipated product characteristics, patient characteristics, or combinations that create serious safety risks.

Advocates for moving ahead aggressively notwithstanding those unknowns sometimes point to the success that biologics manufacturers have had in determining the comparability of protein products produced before and after changes they make in their own manufacturing processes, without having to

[46/](#) Golding Presentation, *supra* n.5, at 16.

[47/](#) *Id.* at 19.

undertake new clinical trials. [48/](#) Indeed, FDA has adopted -- as its own Guidance -- an ICH document, "Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process." [49/](#) That document lays out recommendations about all the factors a manufacturer should consider when attempting to demonstrate that its own product, following a manufacturing change, is comparable its product before the change. [50/](#)

Significantly, that document applies only to "[p]roducts where manufacturing process changes are made by a single manufacturer," and not to manufacturers trying to compare their product to another manufacturer's biologic. [51/](#) That limitation reflects, in part, the critical importance of manufacturing process considerations, including "a well-defined manufacturing process with its associated process controls [that ensure] that acceptable product is produced on a consistent basis." [52/](#) In other words, showing comparability requires an established, reliable baseline and the ability to hold all variables constant except for the change or changes in question.

Holding all variables constant and identifying all differences between two manufacturing processes is extremely difficult, even when one has full access to all records on both processes, when the product is a plasma protein therapy. As CBER's Dr. Golding has explained:

So, what I have been telling you is that the manufacturing is a multi-step process. It is different from one manufacturer to the other, and, in fact, to me the most striking example is [when] . . . one manufacturer tried to change its manufacturing by just moving from one plant to another plant, they were using the exact same process as far as they could tell, but they were unable for many months at the new plant to manufacture the product in the same way as that manufacturer before. [53/](#)

Even though the processes appeared to be identical based on the records, some undetected difference about either the new plant location or the personnel carrying out the process obviously made a material difference. Indeed, the ability to recognize all the variables that must be kept constant, let alone to keep them constant, invariably depends to a great degree on "the manufacturer's knowledge of

[48/](#) See, e.g., Woodcock et al., *supra* n.1, at 438.

[49/](#) Available at <http://www.fda.gov/cber/gdlns/ichcompbio.htm>.

[50/](#) *Id.*, at 2-3.

[51/](#) *Id.* at 2-3.

[52/](#) *Id.* at 9.

[53/](#) See Golding Presentation, *supra* n.5, at 18.

and experience with the process” [54/](#) Thus, a new plasma protein therapy manufacturer, with its own plant and its own manufacturing process, who does not have access to details about the reference product’s manufacturing process, has little hope of duplicating that process, without introducing some material differences. That conclusion is inevitable for plasma protein products because even the most subtle changes to the product are difficult to detect, and because predicting how those changes might affect patients is extremely challenging.

Indeed, even the European Union (EU), which has been the quickest in the world to approve abbreviated biologics applications based on similarity to previously-licensed biologics (or, in EU parlance, to grant biosimilar marketing authorisations based on reduced dossiers), has recognized the conundrum that plasma protein therapies pose in this area. In its guideline on biosimilar products, the European Medicines Agency (EMA) makes clear that applicants will have to submit the same amount of safety and efficacy data to obtain marketing authorisation for a biologic, whether they employ the biosimilar pathway or not. [55/](#) The guideline states:

In view of the complex and variable physico-chemical, biological and functional characteristics of the products listed in the [guidelines on blood and plasma-derived products and their recombinant alternatives], it will not be acceptable to submit a reduced clinical dossier when claiming similarity to a reference medicinal product. As a result, applications for such similar products will need to satisfy the safety and efficacy requirements describe in [those] guidelines for “new products.” [56/](#)

Why Does Congress Need to Address this Issue, Rather than Delegating it to FDA?

A bill that Representative Henry Waxman and other Members introduced to create an abbreviated approval pathway for biologics [57/](#) requires all follow-on

[54/](#) See Guidance: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, *supra* n. 49, at 9 (Manufacturing Process Considerations).

[55/](#) See Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency, *Guideline on Similar Biological Medicinal Products*, CHMP/437/04 (Oct. 2005), at 7.

[56/](#) *Id.*

[57/](#) H.R. 1427, the “Promoting Innovation and Access to Life-Saving Medicine Act.” Senator Schumer and colleagues introduced a companion bill into the Senate, S.726, with an identical title. For simplicity, all references will be to the House bill.

biologic applicants (called “biosimilar” applicants in the bill) to make a showing that no clinically meaningful differences between the biosimilar and the already-licensed product (called the “reference” product) would be expected in terms of safety, purity, and potency if treatment were initiated with the biosimilar rather than the reference product. [58/](#) The bill recognizes the risk of immunogenicity reactions to biologics, which would include the risk that plasma protein therapy patients will develop inhibitors. [59/](#) But the bill addresses that risk insufficiently, in a manner that raises significant safety concerns for patients who depend on plasma protein therapies.

Specifically, the bill only addresses immunogenicity in the context of interchangeability. Interchangeability is defined to mean that a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity. [60/](#) The bill contains no similar express provision regarding biosimilarity itself. That omission suggests that FDA might be able to approve an abbreviated BLA without any data directly addressing the biosimilar’s immunogenicity risk.

In fact, whether clinical trials are necessary at all is left completely up to FDA's discretion. Specifically, in stating what information an applicant must submit to demonstrate biosimilarity to the reference product, the bill requires clinical study data only if, “in the discretion of” the Secretary of the Department of Health and Human Services (which would be delegated to FDA), the data are “necessary.” [61/](#) Omitting any mention of immunogenicity in relation to biosimilarity implies that immunogenicity is not as important a consideration in determining biosimilarity as in determining interchangeability. Moreover, neither determination, biosimilarity or interchangeability, requires human clinical trial data, under the bill.

The decision about whether (and, if so, how much) increased risk of immunogenicity reactions or other adverse events is acceptable as a trade-off for cost savings is a value judgment. Science cannot make that judgment. Consequently, the legislators representing the American people either must make the judgment, or must establish mechanisms through which the interests of appropriate stakeholders – most importantly, affected patients -- can be taken into account. That is particularly true where approval decisions will expose patients like those who rely on plasma protein therapies to risks that cannot be measured or anticipated.

[58/](#) H.R. 1427, proposed Public Health Service Act (PHSA) section 351(k)(1).

[59/](#) *Id.*, proposed subsection (k)(2) (definition of interchangeability).

[60/](#) *Id.*

[61/](#) *Id.*, proposed subsection (k)(3)(B)(ii).

As explained above, those plasma protein therapy patients' risks from products approved without actual human clinical experience cannot be predicted or measured because no one has solved the conundrum that plasma protein therapies pose. Namely, the interaction between the products' many potentially relevant characteristics and the patients' own potentially relevant characteristics are too varied and complex to nail down without testing the products in people. The rarity and unpredictability of relevant patient characteristics are such that manufacturers could not even set a baseline for each characteristic by performing clinical trials on a characteristic-by-characteristic basis. Thus, manufacturers have no way to show that they have identified and analyzed all potentially relevant product characteristics.

Congress must make it clear, through legislation, that until the plasma protein therapy conundrum is solved, FDA may not approve a biosimilar applicant's abbreviated application for a plasma protein therapy relying on prior products' approval, without an equivalent showing of safety, purity, and potency through full clinical trials.

Representative Eshoo has recognized the need for such Congressional direction, and incorporated such direction in a bill that she and other colleagues introduced, H.R. 1548, which would create the "Pathway for Biosimilars Act." The bill also establishes mechanisms for obtaining public input, through the FDA guidance process, to guide FDA decisions that implicate the value judgment about increasing risks to patients in exchange for cost savings.

First, unlike H.R. 1427, H.R. 1548 requires biosimilar applicants to provide clinical trial immunogenicity data independently showing that their products are safe, pure, and potent for every indication for which the reference product is approved. [62/](#) Granted, FDA may waive that requirement. [63/](#) But it may do so only after receiving and considering public comment on a draft guidance and after publishing a final guidance. [64/](#) The guidance must advise that, with respect to a particular product class, scientific knowledge has made it feasible to determine immunogenicity without clinical trials, and the guidance must explain the data that will support such a determination. [65/](#) Thus, the bill would effectively require FDA to solve the conundrum that plasma protein therapies pose for biosimilars regarding immunogenicity reactions, and would require FDA to explain the solution before approving a biosimilar application.

[62/](#) H.R. 1548, proposed Public Health Service Act (PHSA) section 351(k)(2)(A)(i)(III).

[63/](#) *Id.*, proposed PHSA section 351(k)(2)(B)(i).

[64/](#) *Id.*, proposed PHSA section 351(k)(2)(B)(ii).

[65/](#) *Id.*

Second, the bill also recognizes that the very criteria for establishing biosimilarity must vary from product class to product class. Accordingly, the bill requires FDA to issue a guidance spelling out the criteria it will apply when determining biosimilarity for each product class before it approves any biosimilar in that product class. [66/](#) That requirement is separate and apart from the requirement that FDA issue guidance on assessing immunogenicity for each product class, as well as for assessing interchangeability. [67/](#)

Finally, as to interchangeability, the bill both directs what the general standards should be and establishes a mechanism for tailoring specific standards to the particular product class. As to the general standards, FDA must determine that the biosimilar can be expected to produce “the same clinical result as the reference product in any given patient for each condition of use prescribed, recommended, or suggested in the labeling of the reference product.” [68/](#) Furthermore, the bill sets a standard that requires FDA to determine that the risk of switching between the biosimilar product and the reference product is not greater than risk that patients current face with the licensed reference product. [69/](#)

As to specific standards, the bill requires FDA, before determining any particular biologic to be interchangeable with another, to issue a guidance determining that scientific knowledge is adequate to determine interchangeability within the specific product class and explaining what data are necessary to make that interchangeability determination. [70/](#) Thus, under H.R. 1548, FDA would not be able to find two plasma protein therapies to be interchangeable before solving the conundrum that minor manufacturing process differences can produce product characteristic changes that can interact with patient-specific characteristics in ways that create different clinical results.

Absent legislative direction and mechanisms, like those in the Eshoo bill, that will protect patients who rely on plasma protein therapies, Congress should create an express exception for plasma protein therapies in any legislation authorizing abbreviated biologics licensure. Understandably, some in Congress might prefer to create a general legal framework that can capture all future technological advances, including the possibility that one day scientists will solve the conundrum that plasma protein therapies pose for biosimilar applicants. The danger is too great, however, that absent an express legislative directive or mechanism protecting patients from unpredictable risks, FDA might succumb to

[66/](#) *Id.*, proposed PHSA section 351(k)(9)(E), (F).

[67/](#) *Id.*, subparagraph (F).

[68/](#) *Id.*, proposed PHSA section 351(k)(4)(A)(i)(II) (emphasis added).

[69/](#) *Id.*, proposed PHSA section 351(k)(4)(A)(ii).

[70/](#) *Id.*, proposed PHSA section 351(k)(4)(B).

outside pressures and prematurely approve an abbreviated application for a follow-on plasma protein therapy. Without provisions like those in the Eshoo bill, Congress must exclude any abbreviated biosimilar applications for plasma protein products in order to protect the patients that rely on those therapies. One way or another, Congress must make clear that FDA may not approve an abbreviated application for a follow-on plasma protein therapy until the conundrum has been solved.