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Topic: The Safety of Intravenous and Subcutaneous Immune Globulin Products

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[This is an edited version of a live teleconference presentation.]

I want to start by acknowledging that blood products, in general, whether blood components for transfusion or plasma products, many years ago were associated with transmission of certain pathogens, in particle hepatitis B and C viruses and, following its introduction in the U.S., HIV in 1981. The issue was obviously a crisis for both the blood transfusion community and for plasma product manufacturers. In fact, patients were infected with hepatitis viruses and HIV back in those days when we had no specific measures or programs to address them. Beginning in the mid-1980s, both the U.S. Food and Drug Administration (FDA) and the industry got very serious about addressing this, and today, we're going to talk about those efforts.

Let me start by talking about the risks of blood components (not plasma products but actual transfused blood components), including red blood cells, platelets and fresh frozen plasma, that might be used to treat a hospitalized patient. When a patient receives one of those blood components, there is still a remote risk of infection with hepatitis B or C or HIV. But these days, the risks are extremely low. For hepatitis B, that risk is less than one in 200,000 — extremely low but still not zero. For hepatitis C or HIV, the risk is now below one in two million, which is lower than the risk of being struck by lightning. In fact, there hasn't been a report of an HIV infection from a blood product in several years, even though it is always theoretically possible. This is because of the number of measures that I am going to be talking about that have been applied to blood-transfused products. And, by the time I finish, you'll realize that the risk is lower yet for plasma products. That's one of the remarkable things about the measures that were taken more than two decades ago.

Last year, 2015, was something of a milestone that was reached for the plasma products industry, which comprises more than 30 companies and more than 150 unique plasma products derived from human plasma. Last year, we marked 20 years without a single reported transmission of any pathogen, whether virus, bacterium or otherwise, from any plasma product in the U.S. That is as good a safety record as you can get. The last event that occurred was in 1995 involving a single production lot of a factor VIII concentrate that was associated with a contamination that occurred in the bottling stage — not a plasma donor

or pooled plasma, but very likely someone who mishandled the product at the final stage. In the intervening years, measures have been put in place, and the risk of even this occurring again is extremely remote.

Let's talk about how we have accomplished this kind of safety record. It boils down to three pieces, known as the safety tripod. First is the selection of the starting material, the plasma itself. Second is testing for pathogens. And third is activation removal of pathogens.

When potential plasma donors arrive at collection centers, they go through a medical screening process, and they are asked a number of questions and evaluated for basic things like blood pressure, temperature and so forth to try to ensure they're in good health. The plasma that is donated is then collected and held in quarantine, and it isn't used until they come back a second time for a second collection, and it is tested again. This is a special measure for first-time plasma donors to make sure they have not been recently infected, because if they have, that first donation could possibly test negative for hepatitis B or C or HIV viruses. There is also a registry called the National Donor Deferral Registry. If anyone tests positive for a pathogen, they are listed in the registry, which is shared with all plasma collection centers so the donor would be deferred again.

This measure of selecting starting material has been in place for many years, and it is the very first leg of the tripod. It is nice, but as you can imagine, it's far from a complete measure. People can misreport their history. For example, they're asked among many questions if they've ever abused IV drugs. Someone might theoretically answer no, when in fact the answer is yes. So this is the first screening process, but it's not relied upon in any way, shape or form.

The next step is a two-part step, which is pathogen testing. The first phase of this is testing individual units of donor plasma. These tests include hepatitis A, B and C antibodies, HIV 1 and 2 antibodies and parvovirus 19. Following that, to try to discover any very low-level infections or early infections, a special procedure called nucleic acid testing is conducted in small pools of plasma. This procedure amplifies any viral RNA that might be present and allows detection of very very small quantities of viral material. So if anyone has just been infected and has very very low levels of virus, this is designed to detect that.

This two-part step is in itself really good, and that's where we stand with transfused blood components. But the difference between transfused blood products and plasma products is that plasma products are manufactured from large pools of thousands of units of donated plasma. So if there is just one unit of infectious plasma, in theory, that could prove to be a problem. It could cause an infection in people receiving manufactured products from that whole production lot.

In recognition of that, many years ago, FDA and the industry developed a variety of measures to both inactivate viruses and remove them if they happened to be present. Before mentioning what these are, I want to provide a little background and start with the first of all plasma products, human albumin, which was first manufactured during World War II and has been in continuous production since then. It's been noted by FDA and

industry that over the past 70 years, there hasn't been a single case of pathogen transmission by albumin products. And that actually is no accident. It's because albumin is subjected to heat treatment. A simple process of essentially heating or pasteurizing albumin has been adequate to protect people throughout all these years, including the years before we even identified HIV, when it was undoubtedly present in donors. Yet albumin never transmitted HIV to anyone.

Starting with that basis, industry has developed a host of pathogen inactivation measures that include pasteurization, dry heat treatment, low PH (a highly acidic environment), a special chemical called caprylate and, very importantly, a solvent detergent treatment that is focused specifically on lipid envelope viruses. Basically, these are viruses with a single layer of fat (a membrane) around them, which include hepatitis B and C and HIV. These viruses are all inactivated by solvent detergent treatment.

The second technique that's used typically in conjunction with one or more of these inactivation methods is a removal step, which can include precipitation steps during the purification process of the protein of interest, chromatography (another step that is used to purify proteins) and, finally, a more recent technology, which is the use of a very very fine filter, called nanofiltration. With nanofiltration, the therapeutic protein is passed through a filter with very tiny pores that doesn't allow viruses to pass through, but does allow the protein to pass through.

So, any very low levels of virus that could, in theory, escape detection during the screening process will be destroyed or removed during the manufacturing of the plasma product by inactivation and removal steps.

The point is that it's not an accident that we have had no cases of reported transmission of any virus or pathogen in more than 20 years by any product. It's the result of enormous amount of attention, research work and meticulous commitment to quality assurance. Rest assured, the industry is highly regulated and self-regulates. This track record of success in providing pathogen-free products is a result of many overlapping layers of redundancy and safety.

Having said this, there is always a theoretical possibility that if enough doses over enough hundreds or thousands of years were given that perhaps a virus might somehow escape or circumvent all of these steps. As such, the labeling (package insert) still includes a warning about the possibility of transmission of pathogens. It's a never-say-never issue. But after 20 years and countless millions of over 150 products later, I think we have a lot less to worry about with this than driving to the supermarket to pick up our groceries.