

The Evolution of Pathogen Safety: A 25-YEAR PERSPECTIVE AND THOUGHTS FOR THE FUTURE

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The 2017 Plasma Protein Forum (June 13–14, Washington, D.C.) featured the 25th Anniversary of the industry association now known as PPTA, which beyond an opportunity for a splendid celebration gala also provided room to reflect on the Association’s history. It is indeed important to remember that the PPTA journey started with entrepreneurial

visionaries realizing that there was no room for competition when it came to topics around the safety margins of plasma protein therapies; on the contrary, joining forces laid the foundation for the enormous progress made over time. With our industry’s proclivity for innovation and sometimes forgotten lessons of the past,¹ it is of unchanged importance now to keep those learnings from the past fresh in our minds, and to utilize the concepts developed for mitigation of earlier concerns, to avoid future complications: Those who cannot remember the past are condemned to repeat it.²

The safety margins of plasma-derived products did undeniably need attention, at several points, in the now distant past. As problems were recognized though, available measures

were put in place to mitigate the risks. Those were initially in large part limited to the selection of lower-risk donors, i.e., the deferral of donor applicants at higher risk of carrying infectious disease agents, as well as the testing for detection of specific blood-borne pathogens. Yet as process science became more mature, manufacturing processes were improved to include steps specifically designed to inactivate (heat, treatment with solvent-detergent combinations) and remove (precipitation steps and later nanofiltration) viruses, cumulatively referred to as virus reduction steps. The relative effectiveness of these interventions, now commonly referred to as the safety tripod (Figure 1), was highlighted after the emergence of West Nile virus (WNV) in the U.S. in 1999 and the resulting blood transfusion transmissions described from 2002. The data collected from donor deferral and testing algorithms as applied to many millions of transfused blood donations³ allowed for the calculation of the relative quantitative contributions of these interventions.⁴ The selection of (apparently) healthy donors has, based on the absence of any symptoms in approximately 80 percent of those carrying the virus in their blood, provided a rather marginal contribution to transfused blood component safety margins, a reduction of risk by approximately 20

percent or 0.1 log. Application of what is still the most modern technology available for large-scale testing of blood donations, that is, nucleic acid testing (NAT), has reduced WNV transmissions through transfused blood components by approximately 90 percent or 1 log. For manufactured plasma derivatives, the inclusion of pathogen reduction steps, validated for WNV reduction after the first cases of blood transfusion transmission had been reported, demonstrated a risk reduction in the range of million-fold or higher per dedicated virus reduction step, or reduction of risk by more than 6 log per step.

As dedicated virus reduction steps are thus firmly established as the major contribution to virus safety margins of plasma-derived medicinal products, these have been universally deployed into their manufacturing processes. With the importance though came the burden of proof, and the endless supply of emerging infectious agents has, at the latest with confirmed transfusion-transmissibility of these infectious agents, always translated into concerns around the safety of plasma derivatives, too. In response to these challenges, it has become accepted best practice to generate “verification” data for these emerging agents to confirm that the expected virus reduction capacity of a manufacturing process would also apply for the new agent under discussion. These were, as soon as technically feasible, generated during only the past decade for WNV, the H5N1 “pandemic” influenza virus, Chikungunya virus, Hepatitis E virus, and, most recently, the Zika virus. Beyond providing peace-of-mind for plasma product users, they have also been of value in supporting the regulatory decision-making process.

While cell cultures in stainless steel fermenters can be infinitely better controlled than thousands of plasma donors, these proteins are still produced from living cells, and those can conceptually be exposed to opportunistic infectious agents. And while no human exposure to an infectious agent from this source has ever been reported, the production of recombinant plasma proteins utilize the same measures as applied for the production of plasma derivatives, i.e., the selection of well characterized cell banks and raw materials, the testing of those

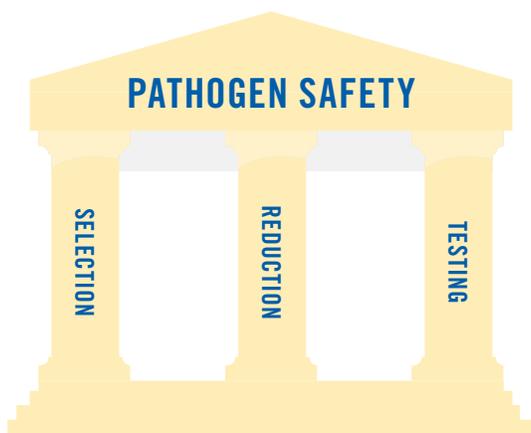
and eventually the bulk harvest derived from these cells, and finally embedding effective virus reduction steps into their downstream purification processes.

Currently, we witness the advent of Advanced Therapy Medicinal Products (ATMPs), a diverse class of products that holds the promise of affording treatment even to as yet orphan conditions. It cannot be forgotten though that these medicinal products are also derived from biological sources, and thus the final products need to be safeguarded against infectious agents. The task here is, however, quite a bit more complex. With the products themselves being virus-like (as for certain gene therapy approaches) or even whole living cells (as for cell therapies and tissue engineering), the application of the most effective intervention, i.e., virus removal or inactivation, becomes more challenging: While reduction of any adventitious viruses is desired, the product activity must not be compromised. As stipulated by leading regulators though, the task is not impossible, e.g., adeno-associated virus gene therapy vectors can be treated by solvent-detergent, which would inactivate any lipid-enveloped adventitious virus yet not impact the non-lipid enveloped vector, as well as nanofiltered through larger pore filters, which would remove larger adventitious viruses yet allow for passage of the vector.

Biotechnology has for a long time used upstream barriers to prevent access of microorganisms to fermenters, i.e., sterilizing grade filters. With advancements in filter technology, filters with average pore sizes in the nanofilters range can now be used for the purpose, such that beyond exclusion of bacteria even the much smaller viruses can be removed. This concept can equally be deployed for ATMPs to avoid any exposure of the manufacturing process to adventitious agents. If combined with functionally closed downstream systems, the approach may allow effective safe-guarding of these innovative therapies based on the well-proven concept of virus reduction capacity embedded into the manufacturing process.

It needs to be realized that many of the players now involved in the development of ATMPs are not familiar with the early history of biotechnology, and thus the potential for and consequences of exposure to biological agents. All the more important that the plasma protein community helps to convey these historical learnings, which can ultimately provide guidance on how to best mitigate the risk and which measures have been found most effective in addressing them. ●

Figure 1: The Safety Tripod



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