Plasma Protein Therapeutics Association

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Dear Sir, Madam
Dear Committees,

On behalf of its member companies, PPTA would like to thank you for considering PPTA's request to exempt Triton-X 100 for manufacturing of plasma products from the list of substances of very high concern (SVHC), in accordance with Article 57 of the REACH Regulation (Art. 57(f)).

PPTA would like to highlight the importance of this agent for our industry and point out a multitude of unwarranted consequences and possible detrimental impact on safety and

availability of plasma-derived medicinal products (PDMP) in Europe, if no such an exemption was granted.

1. **Impact on pathogen inactivation process: Impact on Solvent/Detergent (S/D) treatment**

Human plasma is the source of a number of important therapeutic proteins such as immunoglobulins, albumin, clotting factors, fibrinogen and others, which are used by patients world-wide to treat a variety of rare diseases and serious medical conditions. These proteins are purified during a process known as plasma fractionation, which according to a number of regulatory requirements contains critical virus inactivation and/or removal steps. An established part of this process is the S/D treatment, and Triton-X is widely used and a well-recognized agent in the S/D treatment: Dichtelmueller et al. (1) investigated various different plasma manufacturing processes and found that approx. 35% of studies conducted use Triton-X for manufacturing of products as diverse as Factor VII, Factor IX, and intramuscular or intravenous immune globulins. Triton-X, in conjunction with other agents such as tri(*n*-butyl) phosphate (TNBP), polysorbate 80 (Tween 80) is, particularly due to its potent virus inactivation capacity, extensively mentioned in applicable guidelines for plasma fractionation by WHO (2), EMA (3), and European Pharmacopoeia (Ph. Eu.) (4), which specifically refer to its use to effectively inactivate a number of viruses potentially associated with human blood, such as Hepatitis B virus (HBV) (5), Hepatitis C virus (HCV), Human Immunodeficiency virus-1/-2 (HIV-1/ HIV-2), and other lipid-enveloped viruses, such as the West Nile virus (WNV), Yellow Fever and Japanese Encephalitis viruses (6, 7).

2. **Limited exposure to environment and public: Use of Triton-X is already tightly controlled**

The use Triton-X by our industry is tightly controlled. All handling and use takes place under well-established procedures, by use of closed systems and by specifically trained users. The quantities of Triton-X used in the S/D process are albeit crucial, relatively low. Any trace amounts of waste from the fractionation process is treated in accordance with all applicable measures and guidelines, including fractionators' individual, in-house containment programmes and applicable country-specific as well as EU regulations.

Considering the wide use of Triton-X across our industry it would be extremely challenging to substitute Triton-X which could perform as well as Triton. Any requirement to substitute Triton-X with another candidate agent(s) would necessitate extensive studies, potentially even clinical (re-) testing, and re-registration, with negative impact on the global supply of these medicinal products to patients. The impact would be substantial and disproportionate:

1. **Revalidation (and regulatory approval!) of the S/D treatment used for pathogen inactivation.**

In order to replace Triton-X, extensive studies would be required to screen candidate(s) to ensure no change in performance of the S/D process. This would include testing of a range of viruses mentioned above, to ensure the differences and variations between the pathogens, as well as the substitute products are sufficiently captured.

Since the introduction of the S/D treatment in the manufacturing process of plasma-derived medicinal products more than 20 years ago, no proven transmission of enveloped viruses by any S/D treated products has been reported (1). Therefore, patients who rely on these life-saving proteins can be assured of the high safety margin afforded by this processing step.

2. Revalidation, that following S/D treatment with a substitute the proteins present in plasma function equally well *in vivo, without any unintended interference with the plasma (as a biological substitute agent could potentially do).*

Revalidation would mean that the substitute reagent(s) would perform at last equally well in all instances listed above.

Considering S/D treatment alone:

The regulatory submission and applications for authorizations would represent a significant burden for our industry. Re-licensing of candidate substitute(s) in both EU and non-EU markets would inevitably lead to delays in approval time due to varying requirements of different regulatory agencies across the EU and world-wide, affecting the ability of European companies to perform in the EU, which in turn would impact on cost of plasma fractionation. Both, increased regulatory obstacles and costs may influence fractionators to perform plasma fractionation outside of Europe, with potential consequences for a supply of PDMPs within the EU.

Furthermore, considerable time and resources, which would need to be dedicated for implementation of candidate replacement(s) could be diverted from re-investment into further innovation and research of emerging pathogens and public health threats, such as Ebola, or most recently, the Zika virus (8).

We are aware of the possible serious impact of Triton-X on the environment and human health, which have been clearly put forward by various stakeholders during the ECHA consultation (9). We would like you to take into account the importance of this agent for our industry, the relatively small amounts used by our industry as well as the appropriate containment measures to limit the potential impact on the environment. Furthermore, the evidence to restrict the use of Triton-X is not based on its substance

properties, but on a possible link to its degradation products which are estimated to become a substance of very high concern.
However, no corresponding analysis and conclusion of Triton-X restriction on the possible detrimental effects and unintended consequences on the safety and availability of PDMPs for patients in Europe can be conducted.

In summary, we consider that enforcing the REACH restriction of Triton-X during the manufacturing processes is neither appropriate nor proportionate. Replacement of Triton X in the process with an alternative may not always be technically feasible, and if a suitable alternative found, re-development, re-validation and potentially even clinical (re-)evaluation followed by regulatory approval for alternative(s) will entail very significant (!) and disproportionate investments of time and resources. If Triton-X use in the manufacturing process would be restricted, it would have a severe impact on the European plasma manufactures' industry to provide safe and affordable PDMPs.

Therefore, we hope that EMA's committees and scientific working parties will support our request, considering that a primary focus of our manufacturers is human health.

We thank you in advance for your consideration, and if you have any questions, we would welcome a discussion of the subject at your convenience.

Yours sincerely,

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References:

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2. Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products; WHO Technical Report series no. 924, 2004.
3. Guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010)
4. European Pharmacopoeia_7.7_Human plasma pooled and treated for virus inactivation
5. Draft Reflection paper on viral safety of plasma-derived medicinal products with respect to hepatitis E virus (EMA/CHMP/BWP/723009/2014) and Workshop on Viral safety of plasma-derived medicinal products with respect to hepatitis E virus (EMA/CHMP/BWP/196177/2014)
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