PPTA
Plasma Protein Therapeutics Association

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Subject: PPTA comments on GMP Chapter 5: Production and Chapter 7: Outsourced Activities

Dear Madam/Sir,

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analogue therapies, collectively referred to as plasma protein therapies.

Thank you very much for the opportunity to participate in the revision of GMP Chapters 5 and 7. We have a number of observations which we would like to share with you.

Chapter 5:

- In sections 5.1. and 5.15 the term "competent person" should be better defined.

- The term "starting materials" (which is defined per the Glossary as *"any substance used in the production of a medicinal product, but excluding packaging materials."*) is obviously not correctly used throughout several statements of the new and revised sections. Requirements e.g. for GMP, traceability, supply chain, or purchasing from approved distributors of active substances can only be applied for certain starting materials. Therefore we recommend to replace the term "starting materials" in sections 5.25, 5.26 (including the footnote 1), and 5.31 by the term "active substances, certain excipients considered to be high risk materials, and critical packaging materials".

- In the footnote 1 to section 5.26 the reference to the DUNS number has to be removed. The PIC/S Explanatory notes on the preparation of a Site Master File is only requesting an *"Identification number of the site as e.g. GPS details, D-U-N-S number [...] of the site or any other geographic location system"*. This is required for the specific site described by the Site Master File itself. For any contractors listed in the SMF, the addresses and contact information is considered sufficient. Therefore to align requirements of PIC/S and EU-GMP-Guide the requirement in the footnote should only focus on name and address.

- In section 5.27 a new requirement is included, i.e. *"supply chain traceability should be established and documented"*. This may provoke a question for documenting the traceability of each delivered container of any starting materials. Indeed it is important to understand the supply chain of supplied starting materials, but this has to be built on written Agreements with the suppliers, an established system to notification of changes by the supplier, a system for supplier qualification and supplier auditing, etc. but cannot be required and performed on each delivered container.

- The third bullet-point of 5.31 requires the certificate of analysis to be signed by a designated person with appropriate qualification and experience. Nowadays the use of electronic systems should also be allowed. Therefore we suggest including a statement, that use of a validated electronic system to generate and approve a certificate of analysis is also acceptable.

- The requirements stipulated in the fourth bullet-point of 5.31are extremely onerous and would disadvantage smaller companies that do not have the resources in comparison to bigger competitors. Therefore we would like to propose the following wording:

"Finished product manufacturer should either have a Certificate of Analysis of a reliable manufacturers, or should perform a full analysis at appropriate intervals. Possessor of a Certificate of Analysis issued by the supplier could compare their own testing results with those provided by the supplier in order to check its reliability. …."

Furthermore the fourth bullet point would require rejection of a certificate of analysis from the supplier in case of a discrepancy in testing. Discrepancies in testing do not automatically result in Out-of-Specification results and therefore further investigation might be sufficient. Therefore we would like to propose the following wording:

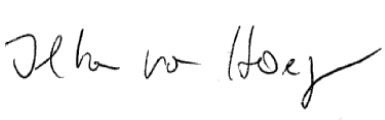
"Should this testing identify discrepancies an investigation should be performed and appropriate measures implemented based on quality risk management."

Chapter 7:

On the cover page under *"reason for changes"* it is made clear that only *"outsourced GMP regulated activities"* are now also in the scope of this document. In order to prevent misunderstanding or misinterpretation (since a number of activities related to GMP-manufacture of testing are outsourced, but not per se are many of these activities GMP regulated processes, e.g. maintenance or repair of equipment, calibration of certain measuring devices, etc.) we highly recommend to include the statement from the cover page also in the main text under the section *"Principle"* and therefore introduce the text *"GMP regulated"* after the first word *"Outsourced"* in this section.

We hope that you will find our comments constructive and helpful and remain at your disposal for further discussions.

Sincerely Yours,



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