# PPTA Voluntary Standard
# Intermediates

## Background

The PPTA member companies are committed to taking all appropriate measures to ensure the quality and safety of plasma therapeutics. In 2000 the PPTA Board of Directors approved a recommendation to develop an industry-wide voluntary standard for intermediates, as a part of their overall strategy to have voluntary Industry-wide Standards that apply to all sources of starting material for plasma-based therapeutics. To achieve this objective, a specific task force (the PPTA Intermediates Task Force) was convened to develop appropriate quality standards to apply to intermediates.

As plasma is a human derived biological of limited supply worldwide, there is a moral imperative not to waste it or any of its derivatives. The exchange of intermediates allows manufacturers to concentrate on products for which they have an authorization or license while not wasting precious material that can benefit other patients if available for further fractionation by other fractionators with different authorizations.

The PPTA Voluntary standard is an industry initiative to further assure the consistency, quality and traceability of intermediate products being incorporated into final therapeutics by its member companies. While many of the elements described in the following proposal are required through current good manufacturing practice or through regulation, the Task Force agreed that the adoption of the standard would substantively [substantially] harmonize and improve the quality and traceability of the intermediate products, particularly those that may not have been subject to FDA or EMEA oversight throughout their production (for products manufactured in other jurisdictions). The adoption of this standard will also assure that products that may be of unverifiable or inconsistent quality or documentation will not be allowed to enter into the manufacturing chain of PPTA member companies. For QSEAL certified manufacturers adherence to this standard will be verified through the QSEAL audit process.

## Voluntary Standard: Intermediates

1. There must exist a contract chain between the supplier and the purchaser of the intermediate that specifies quality requirements which are verified through initial and subsequent regular quality assessments, e.g. audits.

**Mailing Address:** 147 Old Solomons Island Road · Suite 100 · Annapolis, MD 21401 USA
**Washington Office:** Washington Harbour · Suite 400 · 3050 K Street NW · Washington, DC 20007 USA
**Brussels Office:** Boulevard Brand Whitlock 114/5 · 1200 Brussels · BELGIUM
tel: 202.789.3100 · fax: 410.263.2298 · e-mail: ppta@pptaglobal.org · www.plasmatherapeutics.org

2. Intermediates must be manufactured from pools of plasma meeting national requirements of the country of collection and PPTA Voluntary Industry Standards valid at the time of pooling[1], e.g.:
    a. Qualified Donors
    b. Inventory Hold
    c. Viral Marker Standards
    d. NAT for HIV, HCV, HBV and Parvovirus B19.

3. The first Manufacturer (first homogeneous plasma pool) must provide adequate documentation of starting material, e.g. the Plasma Master File, to meet the requirements laid down in item 2.

4. The intermediate must have been produced and handled according to Good Manufacturing Practices (GMP). The current owner of the intermediate must demonstrate that the prior manufacturing processes used to produce the intermediate are able to consistently provide intermediates fulfilling the mutually agreed specifications. This should be certified by the supplier and verified through the regular quality assessment by the current owner of the intermediate.

5. If in the final product license application or in the registration dossier a claim was made for a Viral Removal/Inactivation step during the manufacturing process of the intermediate, the current owner of the intermediate must assure that the claim is valid.

6. The present owner of the intermediate must have a record of each previous owner of the intermediate or raw material with a link to the prior and the successive processes of the intermediate; see Table I.

7. Temperature of storage and shipping of the intermediate must comply with the specifications of the current owner and must be certified by supplier for all prior transactions and certified and verifiable for the most recent transaction.

8. Each intermediate must be accompanied by a release certificate from the Manufacturer's QA/QC Department.

9. Samples of the first homogeneous plasma pool must accompany the product at every transfer of ownership and their inclusion must be specified within the contract, unless pool testing certification is accepted by the buyer.

[1] Intermediates manufactured from recovered plasma must comply with the QSEAL standards for recovered plasma within one year of implementaion of the voluntary standard for recovered plasma.

10. In order to avoid release of potentially unacceptable therapeutic product and/or further processing of intermediates a robust reporting procedure must be in place and should be outlines in the contract chain between supplier and buyer.

    a. In the event that the manufacturer becomes aware of a Class A or B event (event notification), this manufacturer must inform the next owner of the intermediate as soon as possible but not to exceed:

        - five working days from receipt of the notification for a Class A event.

        - ten working days from receipt of the notification for a Class B event.

    These periods must be followed throughout the entire chain of manufacturers/owners of intermediates up to the final product. Confirmation of receipt of notification by the next owner must be received by the notifying party.

    b. Backup information to support a risk assessment must be provided as requested.

11. Intermediates may not be put into production prior to the acceptable completion of a quality assessment of the supplier by the customer. This is the responsibility of the purchaser of the intermediate.

12. Material sold for 'reagent use only' must be sold as such and permanently labelled as such. All documentation must reference that the material is deemed for reagent use only and that it will not be used for manufacture of therapeutic products.

13. There should be a maximum of 3 transactions (no more than 4 owners) from the first homogeneous plasma pool to finished product.

**Definitions**

**Owner:** Legal owner having physical possession of the intermediate and who can distribute the material at its sole discretion.

**Quality Assessment:** an objective qualification, by a systematic approach, of the ability of the supplier of the intermediate to meet the requirements of the purchaser as defined by specifications.

**First homogeneous plasma pool:** as defined by the Eu. Ph. Monograph on Plasma for Fractionation. The first homogeneous plasma pool represents the quality control check point at which the quality of the plasma is approved for manufacture.

**Intermediate:** A plasma derived raw material which must undergo further manufacturing steps before it becomes a final therapeutic product.

**Event Notification Class:**

Class A: Inclusion of a plasma unit from a donor probable or confirmed of vCJD or similar emergent pathogen-caused diseases transmitted by blood or plasma for which there is no test and no cure.

A Class A event is an event that occurs in the manufacture of an intermediate that will require notification and could result in a recall.

The time period for notification is as soon as possible but not to exceed five working days.

Class B: Inclusion of any unit in the first homogeneous plasma pool, excluding the class A items, that if inadvertently included would render the resulting intermediate unacceptable to the buyer as defined by the testing specification.

A manufacturing event that would render the intermediate adulterated, thereby not meeting the requirements of the specification.

The time period for notification is as soon as possible but not to exceed 10 working days.

**Toll fractionation:** Processing plasma or intermediates under another entity's label and ownership.

**Notes:**

- The standards described in this document apply to intermediates derived from both Source Plasma and Plasma Derived from Whole Blood[1].Toll fractionation is excluded from this standard. If the manufacturer takes ownership of any intermediate or final product derived from toll fractionation, this standard will apply.

[2] QSEAL standards for recovered plasma are in development and will be incorporated and covered by this standard when approved.

- This standard will apply to any intermediates manufactured from first homogeneous plasma pools created subsequent to the implementation date of this standard.

## References


- FDA Draft - Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics – August 1999.

- CPMP/BWP/269/95 rev. 3 – Committee for Proprietary Medicinal Products (CPMP) – Note for Guidance on Plasma-Derived Medicinal Products – 25 January 2001.

- Contribution to Part II of the structure of the dossier for applications for marketing authorization - Control of starting materials for production of blood derivatives Ad Hoc Working Party on Biotechnology/Pharmacy Sub-group on medicinal products derived from human blood or plasma. III/5272/94.

- Eur. Ph. Monograph 853 on human plasma for fractionation.

- Revision of Annex 14 to the EU Guide to Good Manufacturing Practice, 31 March 2000. ENTR/III/5717/99-en. Date of coming into operation : 1 September 2000.

# *HISTORY OF MANUFACTURE*
**[EXAMPLE]**

| Process Performed | Organization/Owner | Date | Site with full Address | Accompanying Documentation |
|---|---|---|---|---|
| Manufacturing Pool | Company A | Date 1 (Pooling date) | Site AX | Relevant information to the Plasma Master File or equivalent starting material documentation |
| First Fractionation Step | Company A | Date 2 (Date of first fractionation step) | Site AX | 1. Process Flow Sheet<br>2. Certification of Validation for Viral Removal/Inactivation if claimed by the buyer.<br>3. Temperature verification or certification for storage & transport<br>4. Shipping documentation<br>5. Release certificate or CoA in which the QA/QC department approves release of the intermediate<br>6. Certification that material is intended for therapeutic use. |
| Transfer of Ownership | Company A to Company B | Date 3 (Date of Ownership Transfer) | Site BY | 1. No process performed<br>2. Temperature verification or certification for storage and transport<br>3. Shipping documentation<br>4. Release certificate or CoA in which the QA/QC department approves release of the intermediate |
| Transfer of Ownership | Company B to Company C | Date 4 (Date of Ownership Transfer) | Site CZ | 1. No process performed<br>2. Temperature verification or certification for storage and transport<br>3. Shipping documentation<br>4. Release certificate or CoA in which the QA/QC department approves release of the intermediate |

| Process Performed | Organization/Owner | Date | Site with full Address | Accompanying Documentation |
|---|---|---|---|---|
| Second Fractionation Step | Company C | Date 5 (Date of second fractionation step) | Site CZ | 1. Process Flow Sheet<br>2. Certification of Validation for Viral Removal/Inactivation if claimed by the buyer.<br>3. Temperature verification or certification for storage & transport<br>4. Shipping documentation<br>5. Release certificate or CoA in which the QA/QC department approves release of the intermediate<br>6. Certification that material is intended for therapeutic use. |
| Transfer of Ownership | Company C to Company D | Date 6 (Date of Ownership Transfer) | Site DV | 1. No process performed<br>2. Temperature verification or certification for storage and transport<br>3. Shipping documentation<br>4. Release certificate or CoA in which the QA/QC department approves release of the intermediate |
| Further Fractionation Steps | Company D | Date 7 Date of further fractionation steps | Site DV | 1. Process Flow Sheet<br>2. Certification of Validation for Viral Removal/Inactivation if claimed by the buyer.<br>3. Temperature verification or certification for storage & transport<br>4. Shipping documentation<br>5. Release certificate or CoA in which the QA/QC department approves release of the intermediate<br>6. Certification that material is intended for therapeutic use |