Plasma Protein Therapeutics Association

QSEAL AUDIT REPORT
COVER SHEET

Auditor _____

Facility _____

Address _____

_____

Telephone _____ Telefax _____

Facility Audit Coordinator _____

_____

Government Authority Identification _____

Date of Audit _____ Start Time _____

(approx.) End Time _____

Auditor notes unrelated to QSEAL Standards _____

Auditor Recommendation:

[ ] For Certification

[ ] Provisional for Certification,

Section(s)Page(s)_____

[ ] Not for Certification, due to issues listed on report form,

Section(s)/Page(s)_____

PPTA Office Review_____Date Reviewed_____

Auditor's Statement

As an auditor for PPTA QSEAL Certification, I shall not, either directly or indirectly, for myself or for the benefit of or in conjunction with any other person, corporation, partnership, association, agency, department, or other legal entity, use, communicate or otherwise disclose, or permit to be disclosed, any Confidential Information relating to this audit or facility without prior written consent of such facility; provided, however, Auditor may, only to the extent reasonably necessary or appropriate to the performance of Auditor's duties, disclose such Confidential Information to PPTA or an employee of PPTA for use in the QSEAL Certification or a person to whom disclosure is otherwise required by applicable state or federal law or regulation.

All information obtained during audit will be forwarded to PPTA to be made a part of the facility's permanent QSEAL certification file.

As a consultant appointed by PPTA to perform this facility's QSEAL audit, I hereby attest that to the best of my knowledge no conflict of interest exists between my current clients and the audited facility and/or PPTA.

As a consultant for the purposes of performing the QSEAL audit of said facility, I certify that the attached audit findings and comments are true and accurate findings based on my observations and record review during the audit.

Auditor Signature _____ Date _____

POST AUDIT REVIEW

I acknowledge that the auditor has reviewed the observations listed in this report. My signature does not constitute concurrence or denial of any of the observations made by the auditor.

Company Representative _____ Date _____

Title _____

Facility Name/Location _____

QSEAL Audit Checklist

I. Qualified Donor Standard – Source Plasma donations from only Qualified Donors will be pooled for manufacturing of plasma derivatives.

[Qualified Donor: All individuals who have been qualified for continued donations by passing two donor screenings and serological viral testing for HIV, HBV, and HCV within six (6) months, with a minimum interval between the screenings according to national recommendations or requirements. (USA = 2 days, Germany/Austria = 2 days, Europe = 14 days]

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
1. Does the facility have a policy/specification that requires Source Plasma pooled for manufacture of plasma derivatives to be exclusively from Qualified Donors?				
2. Are contracts between the facility and suppliers in place to assure compliance with the Qualified Donor Standard?				
3. If the facility uses Source Plasma from IQPP-certified collection centers:				
a. Is there an established procedure to assure the facility that the plasma collection center's IQPP certification is current?				
b. Is this procedure adequate to assure that plasma is received only from IQPP Certified facilities (see Question 9)? *[i.e., Recertification every 2 years, corrective action plan to observations within 30 days, notice of status change within 30 days.]*				

Comments:

I. Qualified Donor Standard (continued)

Question:	Documentation (procedures)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
4. If the facility uses Source Plasma from non-IQPP-certified collection centers, is there a system in place to assure that the Source Plasma suppliers comply with the Qualified Donor Standard which includes the facility conducting supplier audits to assess compliance with the Qualified Donor Standard [*I.e., audits no less frequently than every 24 months for all suppliers*]?				
5. Are procedures in place during the receiving inspection which include checking incoming Source Plasma shipments for compliance with the Qualified Donor Standard?				
6. Does the facility have a system to segregate Source Plasma units which do not comply with the Qualified Donor Standard from those which do comply? (e.g., Applicant Donor units)				
7. Does the facility have a system whereby Applicant Donor (a.k.a. "orphan") units are: • quarantined until donor qualification records are received from the supplier, • destroyed, and/or • identified and segregated for use in research or production of non-therapeutic plasma products?				

Comments:

I. Qualified Donor Standard (continued)

Question:	Documentation (procedures)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
8. Is there a system to ensure that only Source Plasma Units from Qualified donors are pooled for manufacture of plasma derivatives?				
9. If the check to assure that incoming plasma comes from centers that adhere to the Qualified Donors Standard is done by computer:				
a. Is there a procedure to keep the list current and correct?				
b. Has this function been tested under challenge conditions?				

Comments:

II. Viral Marker Standard – Source Plasma units will be collected from collection centers that meet the Viral Marker standard as defined by PPTA: the PPTA Source's IQPP Viral Marker Standard.

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
1. Does the facility have a policy/specification that requires Source Plasma units be collected from collection centers that meet the Viral Marker Standard as defined by PPTA?				
2. If the facility uses Source Plasma from non-IQPP-certified collection centers, is there a system in place to assure that the Source Plasma suppliers comply with the Viral Marker Standard, including:				
a) Specifications &/or procedures for Source Plasma collection center viral marker requirements are in the contract between the facility and plasma supplier.				
b) The current PPTA Source's viral marker standard is used to evaluate viral marker data.				
c) Viral marker data are reviewed at least every six months.				
d) There is an alert system in place by which the facility monitors a collection center.				
e) Viral marker data of suppliers are reviewed and accepted or rejected by the company – & in an appropriate timeframe.				
f) The facility audits suppliers to assess compliance with the Viral Marker Standard.				

II. Viral Marker Standard (continued)

Question:	Documentation (procedures)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
3. Does the facility have a system to segregate Source Plasma units from collection centers that do not comply with the Viral Marker Standard from those which do comply?				
4. Does the facility have a system whereby shipments from collection centers which do not meet the Viral Marker Standard are: • destroyed, and/or • identified and segregated for use in research or production of non-therapeutic plasma products?				
5. Is there a system to ensure that only Source Plasma units from collection centers that meet the Viral Marker Standard are pooled for manufacture of plasma derivatives?				
6. If the check to assure that incoming plasma comes from centers that adhere to the Viral Marker Standard is done by computer:				
a. Is there a procedure to keep the list current and correct?				
b. Has this function been tested under challenge conditions?				

Comments:

III. NAT Testing Standard - All incoming plasma is tested for HIV, HBV, HCV, and Parvovirus B19 viral nucleic acid using a Nucleic Acid Amplification Technology test. Plasma reactive for HIV, HBV, HCV or Parvovirus B-19 nucleic acid is segregated and not pooled for production[1].

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO[2]	Implementation (records, physical plant)	Rating: A/O/SO	See Note
1. Does the company have a written, approved document requiring that plasma collected for the manufacture of plasma derivatives is tested for viral nucleic acid of HIV, HBV, HCV, and Parvovirus B19 using NAT methods?	☐ Yes, Document Number or Title _____ _____ ☐ No				☐
2. Does the company audit its provider of NAT testing to assess compliance with the NAT Technical Standard[3]?	☐ Yes, Document Number or Title _____ _____ ☐ No		☐ Yes ☐ No		☐

Comments:

[1] The Parvovirus B-19 Standard applies to all starting material: source plasma, recovered plasma and intermediates.
[2] Rating: A=Acceptable/O=Observation/SO=Serious Observation
[3] Technical Considerations for the Performance of Nucleic Acid Amplification Technology (NAT)

III. NAT Testing Standard (continued)

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO	See Note
3. Are contracts in place between the facility and supplier to assure compliance with the requirements defined in the NAT Technical Standard, specifically: A. Written, approved specifications and procedures to ensure 1) That NAT specimen identity is retained at all times 2) That NAT specimens are stored at appropriate temperatures.	☐ Yes, Document Number or Title _____ _____ ☐ No		☐ Yes ☐ No		☐
B. Facilities adequate to ensure 1) That NAT specimen identity is retained at all times 2) That NAT specimens are stored at appropriate temperatures.	☐ Yes, ☐ No		☐ Yes ☐ No		☐
C. The supplier's approved, written training program includes NAT training as appropriate.	☐ Yes Document Number or Title _____ _____ ☐ No		☐ Yes ☐ No		☐
4. Are the quality requirements described above verified through initial and regular quality assessments?	☐ Yes, Document Number or Title _____ _____ ☐ No		☐ Yes ☐ No		☐

III. NAT Testing Standard (continued)

Plasma Quality Operations

Question:	Documentation (procedures)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO	See Note
5. Does the company have a written, approved system to identify and retrieve units that are rejected based on NAT test results?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No		☐ Yes ☐ No		☐
6. Does the company have a written, approved system whereby those rejected units are: destroyed, and/or identified and segregated for use in research.	☐ Yes, Document Numbers or Titles _____ _____ ☐ No		☐ Yes ☐ No		☐
7. Is there a written, approved system to ensure that only plasma units that meet all acceptance criteria, including NAT test results are pooled for manufacture of plasma derivatives?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No		☐ Yes ☐ No		☐
8. Is there a written, approved system in place to ensure that manufacturing pools do not exceed 10^5 IU/mL Parvovirus B19 DNA?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No		☐ Yes ☐ No		☐
9. Does the written, approved training program include NAT training as appropriate?	☐ Yes ☐ No		☐ Yes ☐ No		☐

III. NAT Testing Standard (continued)

Pooling Center Location of Pooling Center:_____

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO	See Note
10. Are there written, approved specifications and procedures to ensure specimen identity is retained at all times and that specimens are stored at appropriate temperatures?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No		☐ Yes ☐ No		☐
11. Are the facilities adequate to ensure specimen identity is retained at all times and that specimens are stored at appropriate temperatures?			☐ Yes ☐ No		☐
12. Are there written, approved specifications and procedures that provide an appropriate environment for pooling donation samples?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No		☐ Yes ☐ No		☐
13. Do the facilities provide a appropriate environment for pooling donation samples?			☐ Yes ☐ No		☐
14. Does the pooling process assure that the identity of each individual donation in any pool is adequately documented?	☐ Yes ☐ No		☐ Yes ☐ No		☐

III. NAT Testing Standard (continued)

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO	See Note
15. Is there a written, approved system to prevent, monitor and remedy cross contamination events?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No		☐ Yes ☐ No		☐
16. Are there written, approved specifications and procedures to ensure that pools for NAT testing will retain their identity and will be kept at appropriate temperatures?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No		☐ Yes ☐ No		☐
17. Does the written, approved training program include NAT training as appropriate?	☐ Yes ☐ No		☐ Yes ☐ No		☐

Comments:

III. NAT Testing Standard (continued)

NAT Testing Laboratory

The NAT Testing Laboratory review must address the entire NAT test, including but not limited to preparation of reagents, isolation of nucleic acids from specimens, amplification of the target sequence, and detection of amplicons. The NAT standard for open test systems requires a separate area for amplicon detection.

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO	See Note
18. Is the NAT test system an open or closed system?	☐ OPEN ☐ CLOSED		☐ OPEN ☐ CLOSED		☐
19. Is there a written, approved validation report or reports for the NAT test system to ensure sensitivity and specificity in accordance with ICH and other applicable guidelines?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No				☐
20. Are there written, approved specifications and appropriate procedures for the conduct of the NAT tests as appropriate for the open or closed test system being used?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No				☐
21. Is the laboratory design appropriate for the open or closed test system being used?			☐ Yes ☐ No		☐
22. Are the engineering controls and work practices appropriate for the open or closed test system being used?	☐ Yes, ☐ No		☐ Yes ☐ No		☐

Comments:

III. NAT Testing Standard (continued)

NAT Testing Laboratory (continued)

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO	See Note
23. Are assay controls used in accordance to the NAT Technical Standard to monitor assay performance and/or sensitivity?	☐ Yes ☐ No		☐ Yes ☐ No		☐
24. Are positive assay controls, negative assay controls, and internal controls used and are they appropriate?	☐ Yes ☐ No		☐ Yes ☐ No		☐
25. Are positive assay controls calibrated against WHO International Standards when available or other well-characterized, commonly accepted reagents if not available?	☐ Yes ☐ No		☐ Yes ☐ No		☐
26. Are test results interpreted by criteria at least as stringent as prescribed in the NAT Technical Standard?	☐ Yes ☐ No		☐ Yes ☐ No		☐
27. Is there a written, approved procedure to link each NAT result to its individual donation?	☐ Yes ☐ No		☐ Yes ☐ No		☐
28. Does the written, approved training program include NAT training as appropriate?	☐ Yes ☐ No		☐ Yes ☐ No		☐
29. Is there a reagent QC/monitoring program in place? If yes, does it include: • Traceability • Functional QC • Specific reagent QC to address overall reagent quality	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No		☐ Yes ☐ No		☐

Inspection notes are attached as indicated.

III. NAT Testing Standard (continued)

Donation Collection Center(s)

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO	See Note
30. Are there written, approved specifications and procedures to ensure specimen identity is retained at all times and that specimens are stored at appropriate temperatures?	☐ Yes, Document Numbers or Titles _____ _____ ☐ No		☐ Yes ☐ No		☐
31. Are the facilities adequate to ensure specimen identity is retained at all times and that specimens are stored at appropriate temperatures?			☐ Yes ☐ No		☐
32. Does the written, approved training program include NAT training as appropriate?	☐ Yes ☐ No		☐ Yes ☐ No		☐

Comments:

IV. Inventory Hold Standard – All Source Plasma units must be held in inventory for a minimum of 60 days from the date of collection.

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
1. Does the facility have a policy/specification that requires Source Plasma pooled for manufacture of plasma derivatives be held for a minimum of 60 days from the date of collection before pooling?				
2. a. Is there a system to ensure that only Source Plasma Units which have been held for a minimum of 60 days are pooled for manufacture of plasma derivatives? b. If this system is controlled by a computer, has the system been tested under challenge conditions?				
3. Is there a system for receipt of Post Donation Information from Source Plasma collection centers?				
4. Is there a system to identify, retrieve, and remove Look Back units reported during Inventory Hold?				
5. Is there a procedure established by which to ensure segregation and appropriate disposition of units related to Post Donation Information received during the 60-day hold.				

Comments:

IV. Inventory Hold Standard (continued)

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
6. Inventory Hold facility tour: a. Is the general space adequate?				
b. Is the receiving area adequate?				
c. Is the storage area adequate?				
d. Is the separation between quarantine and released areas adequate?				
e. Is the flow of materials adequate to prevent bottlenecks, accidents, or mix-ups?				
f. Is the area where quality control checking, data transfer, and archiving operations take place adequate and conducive to adherence to the Standard?				

Comments:

V. Integration Summary--Assess the integration of the Voluntary Standards into the manufacturing process by conducting a case study.

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
Starting from finished product, verify adherence to Voluntary Standards:				
1. Source Plasma must be held in inventory for a minimum of 60 days from the date of collection.				
2. Incoming Source Plasma will be tested for viral nucleic acid of the target viruses HIV, HBV, HCV and parvovirus B-19 using Nucleic Acid Amplification Technology and found acceptable.				
3. Source Plasma units will be collected from collection centers that meet the Viral Marker standard as defined by PPTA: the ABRA IQPP Viral Marker Standard.				
4. Source Plasma donations from only Qualified Donors will be pooled for manufacturing of plasma derivatives.				

Comments:

VI. Intermediates Standard Summary – To further assure the consistency, quality and traceability of intermediate products being incorporated into final therapeutics.

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
1. Does this owner receive intermediates from another company? If no, continue to next question. If yes: a. Is there a contract between this owner and the supplier of the intermediates? b. Does the contract specify quality requirements for the intermediates? c. Are the quality requirements verified through initial and regular quality assessments?				
2. a. Are the national requirements of the country of collection of plasma used in the manufacture of intermediates readily available on site? b. Is there documentation verifying that the pools of plasma used to make these intermediates met the national requirements valid at the time of pooling? c. Is there documentation verifying that the pools of plasma used to make these intermediates met QSEAL requirements valid at the time of pooling? e.g: • Qualified Donor • Inventory Hold • Viral Marker Standard • NAT for HIV, HCV, HBV, parvovirus B19 d. Is there a specification for the above?				
3. a. Does the current owner receive adequate documentation of the starting material (e.g., Plasma Master File) to meet the requirements of 2 above? b. Is there a specification for the above?				

VI. Intermediates Standard (continued)

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
4. a. Can the current owner of the intermediate verify that the intermediates were produced and handled under current GMP conditions? b. Can the current owner of the intermediate verify, by way of • a certificate from the supplier AND • the regular quality assessment of the supplier that includes an audit report that shows the prior manufacturing processes used to produce the intermediate are able to consistently provide intermediates fulfilling the mutually agreed upon specifications? c. Is there a specification for the above?				

5. a. Is there a record listing and linking the following data items: • Each owner of each intermediate and/or raw material? • The period of ownership? • The nature of the material in question? b. Are the following documents for intermediates available: • Plasma Master File information? • Process Flow Sheet? • Certification of Validation for Viral Removal/Inactivation if claimed by the buyer? • Temperature records of storage and transport? • Shipping documentation? • Release certificate or CoA in which the QA/QC department approves release of the intermediate? c. Is there a specification for the above?				

VI. Intermediates Standard (continued)

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
6. a. Has the current owner established and provided requirements for temperature during storage and shipment of the intermediates? b. Are there records provided by the supplier whereby: • The supplier certifies that these temperature requirements have been met in all prior transactions? • The current owner has verified the temperature conditions on the most recent transaction?				
7. Does the current owner either: a. specify in the contract with the supplier that samples of the first homogeneous plasma pool must accompany the product, OR b. accept certification of pool testing?				
8. a. Does the current owner have a written procedure regarding lookback? b. Does that procedure require that the current owner inform the next owner of the intermediate about a Class A or B event within the following time frames: • 5 working days from receipt of notification of a Class A event and • 10 working days from receipt of notification of a Class B event? c. Does the current owner require confirmation of receipt of the notification from the next owner? d. Can the current owner provide back up information to support a risk assessment?				

VI. Intermediates Standard (continued)

Question:	Documentation (policy, procedures, specifications, etc.)	Rating: A/O/SO	Implementation (records, physical plant)	Rating: A/O/SO
9. Does the current owner put the intermediate into production? If no, continue to next question. If yes: a. Does the current owner conduct an assessment of the supplier's quality system prior to use of the intermediate in production, through initial and regular quality assessments? b. Does the current owner have a procedure describing its supplier management system?				
10. Are materials sold for reagent use only? If no, go to next question. If yes: a. Are the materials labeled as such? b. Do documents reference that the materials are for reagent use only? c. Is there a specification for the above?				
11. For final products made at this facility: c. Have there been no more than three (3) transactions (no more than four owners) of the plasma intermediates including the first homogeneous plasma pool? **d.** Is there a policy or procedure limiting the number of transactions?				
CASE STUDY: Review of records for 3 batches of intermediates, from receiving through manufacturing (record batch records reviewed below; see notes in column 4 for specific record to review)				

Batch records reviewed during CASE STUDY: