QSEAL Certification Program Description

Version 2.1
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PPTA
Plasma Protein Therapeutics Association

PPTA QSEAL Certification Program Description, Version 2.1

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PPTA QSEAL Certification Program Description

Overview

Purpose

The purpose of this document is to describe the policies and processes that control and standardize the way in which Plasma Protein Therapeutics Association (PPTA) certifies plasma fractionation facilities. The certification program is known as "Quality Standards of Excellence, Assurance, and Leadership (QSEAL).

Contact

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Section A

PPTA QSEAL Certification of Plasma Fractionators

Overview

Vision and Mission

PPTA's Voluntary Standards Program provides global leadership for the plasma protein industry's goal of continuous improvement with a focus on safety and quality from the donor to the patient. The Standards program will be transparent, credible, innovative and responsive to stakeholder and industry needs.

Background

People around the world depend on therapeutics derived from human plasma proteins to treat conditions such as hemophilia, immune disorders and other diseases or injuries. The Plasma Protein Therapeutics Association (PPTA) represents the world's leading producers of these lifesaving medicines.

Safety of plasma protein therapies is the top priority of the plasma biotherapeutics industry. PPTA has adopted Voluntary Standards and other criteria that apply to the collection and fractionation of plasma used for manufacturing plasma protein therapies. These standards are in addition to formal regulatory requirements and are intended to promote the safety and quality of plasma protein therapies. The International Quality Plasma Protein (IQPP) voluntary standards address collection, processing and testing of Source Plasma. The Quality Standards of Excellence, Assurance and Leadership (QSEAL) program addresses the manufacture of plasma protein therapies, regardless of the source of plasma. The member companies also recognize the importance of demonstrating adherence to these standards. Thus, the PPTA QSEAL Certification program was established to provide independent certification of compliance.

Under this program, an independent, third party auditor evaluates a company's adherence to the PPTA QSEAL standards for facilities that manufacture products for therapeutic use. A facility is certified only if it meets all of the requirements. The program is open to all plasma fractionators.

Control of Program

Control and standardization of QSEAL Certification is important to maintain the quality and consistency of the certification program. Control and standardization of certification is achieved through four primary mechanisms:

- a standardized certification process,
- establishment of the global Voluntary Standards,
- qualified auditors, and
- periodic audits and timely correction of any deficiencies.

The Certification Process

Certification Definition

QSEAL Certification is a recognition by PPTA that a plasma biotherapeutics company operates its facilities that perform functions within the scope of the requirements in the QSEAL standards with adherence to PPTA's Voluntary Standards Program. Certification is based on the findings of an independent auditor's assessment of the company's policies, procedures, and facilities.

Eligibility

QSEAL Certification is available to plasma fractionators worldwide that have been licensed by a competent national regulatory body.

The company shall be fully operational. There may be no current governmental regulatory restraints against or sanctions on normal manufacturing operations.

General Rules

The following general rules apply to the PPTA QSEAL Certification process:

- Companies shall obtain certification for all of their facilities that perform functions within the scope of the requirements in the QSEAL standards.
- QSEAL Certifications are issued to a fractionation facility that performs functions within the scope of the requirements in the QSEAL standards.
- QSEAL Certifications are issued for a three-year period.
- As new Standards are implemented, their requirements will not be effective until three (3) months (one quarter) after the implementation date. Compliance with new requirements will be confirmed at the next scheduled audit. Extensions for the compliance timeline will be granted if companies require prior regulatory approval for changes to processes or SOPs.
- Applications and fees shall be received by PPTA before any audits are scheduled.
- Changes to either the QSEAL Certification process, the Voluntary Standards, or the auditor qualifications are made under procedures for change control which require PPTA Board and/or management approval.
- When ownership of a facility changes, the new owner shall make arrangements with PPTA to have any previously non-QSEAL certified facilities that perform functions within the scope of the requirements in the QSEAL standards audited. Successful completion of a QSEAL audit of all non-QSEAL certified facilities shall occur within one calendar year of the change of ownership.
- When ownership of a QSEAL-certified facility is transferred, the QSEAL certification and associated audit timelines will transfer to the new owner.

Regulatory Compliance

Upon receipt of the company's application for QSEAL Certification, all facilities in the company shall be fully operational. There may be no current governmental regulatory restraints or sanctions from normal manufacturing operations. In manufacturing therapies for therapeutic use, facilities may use plasma or intermediates only from suppliers that are in compliance with the requirements of the applicable competent national regulatory authority(ies) at the time of collection of the plasma or manufacture of the intermediates.

Government actions resulting in the voluntary or involuntary discontinuation of manufacturing and/or product release will result in withdrawal of QSEAL Certification. The facility is not eligible to be re-certified until government approval to resume is obtained.

If a facility is subjected to an FDA Consent Decree of Injunction (or comparable regulatory action by another government regulatory authority), but is allowed to continue operations under the terms of the Consent Decree, the company shall notify the QSEAL Administrator. Upon notification, the QSEAL Administrator will arrange for a QSEAL re-audit at the earliest possibility.

The Certification Process, Continued

Certification process overview

The following flow chart provides an overview of the process by which facilities achieve PPTA certification. Deviation from the PPTA Voluntary Standards Program will result in a decision not to certify as demonstrated on page 11.

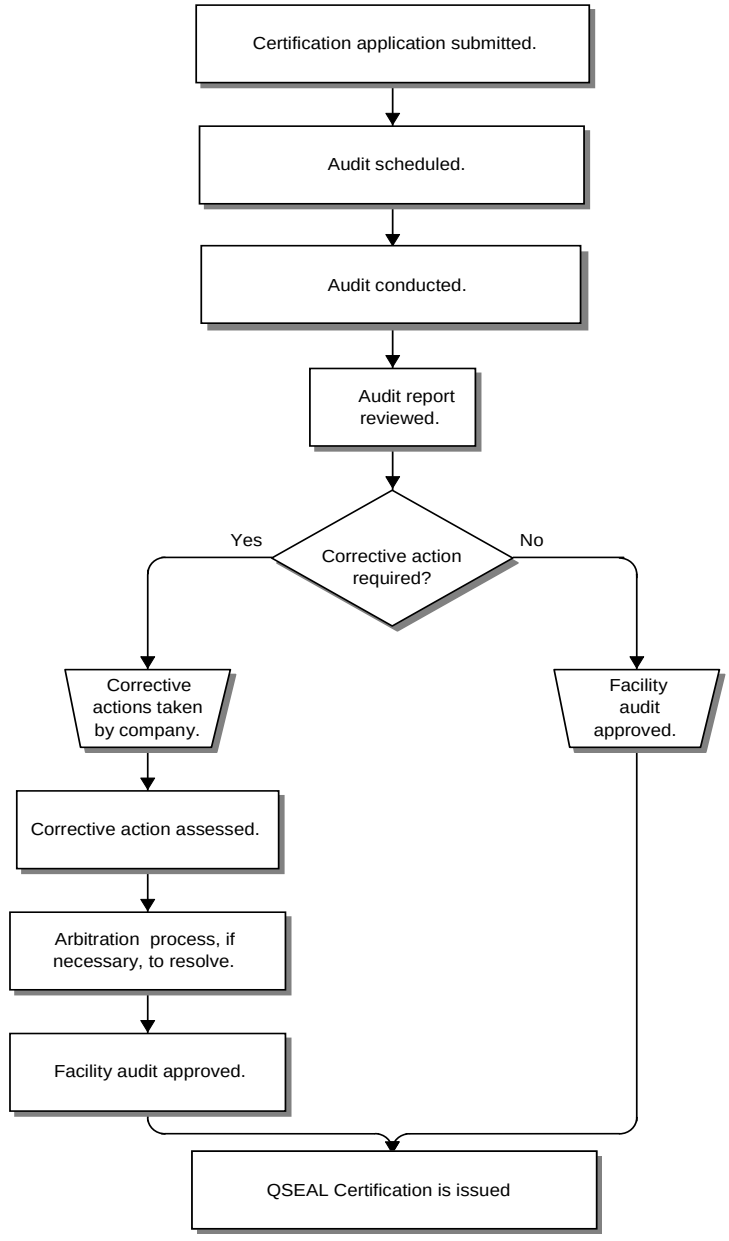

Figure 1 – Overview of Certification Process

The Voluntary Standards

The Voluntary Standards

QSEAL Certification recognizes a facility's adherence to PPTA's Voluntary Standards Program, posted online at: http://pptaglobal.org/safety-quality/standards/qseal. The QSEAL Voluntary Standards Program consists of the following:

- Controls on Incoming Plasma Standard
- IQPP Qualified Donor Standard
- IQPP Viral Marker Standard
- NAT Testing Standard
- Inventory Hold Standard
- Intermediates Standard
- Recovered Plasma Specification

Standards Development Process

The standards are developed in accordance with the PPTA Voluntary Standards Program Policies and Procedures.

PPTA Auditors

Auditor Qualifications

The PPTA auditor is essential to the QSEAL Certification process. Minimum qualifications for PPTA QSEAL Certification Auditors are:

- Advanced degree from an accredited college or university, preferably in a scientific or engineering discipline.
- Significant auditing experience, preferably in the pharmaceutical or plasma biotherapeutics industry.
- Professional certification by a recognized certifying agency is recommended. These may include ISO Lead Assessor, Examiner for the National Baldridge Award or a state award equivalent, certification by the American Society for Quality (ASQ), or other regional quality organization, and certification by the Regulatory Affairs Professional Society

At least five years experience inspecting/auditing pharmaceutical establishments is required.

Confidentiality and Conflict of Interest Agreements	As part of their agreement to perform QSEAL Audits on behalf of PPTA, auditors are required to execute both a Confidentiality Agreement and a Conflict of Interest Agreement. These agreements have been reviewed by PPTA's General Counsel and specifically prevent the auditor from communicating, disclosing, or retaining copies of Confidential Information. The Auditor is authorized to review documents, records, and/or facilities associated with QSEAL Standards and related documents only. The Auditor is also required to disclose any existing or potential conflict of interest to PPTA that may arise during the term of the Auditor's consultancy.
Auditor Training: Initial	Prior to becoming an official PPTA auditor, all candidates shall receive training in the following: • PPTA Voluntary Standards Program • the audit process • documentation of audits • PPTA's auditor agreement, including the confidentiality agreement PPTA shall implement a periodic survey of audited facilities to assess the effectiveness of the auditor training.
Auditor Training: Ongoing	PPTA is responsible to convene additional training workshops for official auditors. These are usually convened to introduce a new certification standard or to ensure consistent interpretations of current standards. Attendance at these workshops is mandatory.
Auditor Continuing Education	To maintain one's qualification as a PPTA auditor, each auditor shall participate in at least one continuing education event every three years. These events may include: • Industry or government workshops relevant to auditing, Quality Assurance, Quality Management, Good Manufacturing Practices, Validation, or government regulation. • Completion of courses required for maintenance of a professional certification. • Completion of one class at an additional advanced degree (Masters or Doctoral) level.
Number of Auditors	At least two qualified auditors are retained by PPTA to conduct QSEAL Certification audits.
Auditor's Objectives	QSEAL Certification auditors have only one very specific objective: • Assess a company's adherence to the PPTA Voluntary Standards and report this to the Association.

Audits and Audit Reports

Types of audits

QSEAL Certification is valid for a three-year period. All certified facilities are eligible for re-certification; re-certification audits will be scheduled by PPTA to occur at least 90 days prior to the tri-ennial anniversary of the facility's initial certification. Facilities being re-certified are expected to meet all current QSEAL Standards, including those implemented subsequent to the facility's previous audit.

Audit for Cause:

An audit for cause may be precipitated by suspected non-compliance with QSEAL requirements that PPTA or its auditors become aware of outside of the routine audit timing. At the discretion of the Association, any facility may be scheduled for a random audit. Failure to address observations found during a random audit may affect a facility's current certification status. A random audit does not substitute for an impending re-certification audit.

Focused Audit:

A focused audit may be scheduled to assure that corrective actions described by a company have been implemented in response to a previous "not-for-certification" audit report.

Discontinuous Recertification Audit:

This type of audit is conducted for the purpose of assessing adherence to QSEAL standards following the suspension of government regulatory restrictions from normal manufacturing operations. QSEAL Certification is withdrawn when a facility is restricted from normal operations due to government regulatory action; when those restrictions are suspended the facility is again eligible for QSEAL Certification. In this case, QSEAL Certification would be discontinuous from the previously withdrawn Certification.

Additionally, a Discontinuous Recertification Audit is required if a facility is subjected to an FDA Consent Decree or Injunction (or comparable regulatory action by another government regulatory authority), but is allowed to continue operations under the terms of the Consent Decree, the company shall notify the QSEAL Certification Manager. Upon notification. In this case, the QSEAL Certification Manager will arrange for a QSEAL re-audit at the earliest possibility.

Audit process The following flow chart provides an overview of the PPTA audit process.

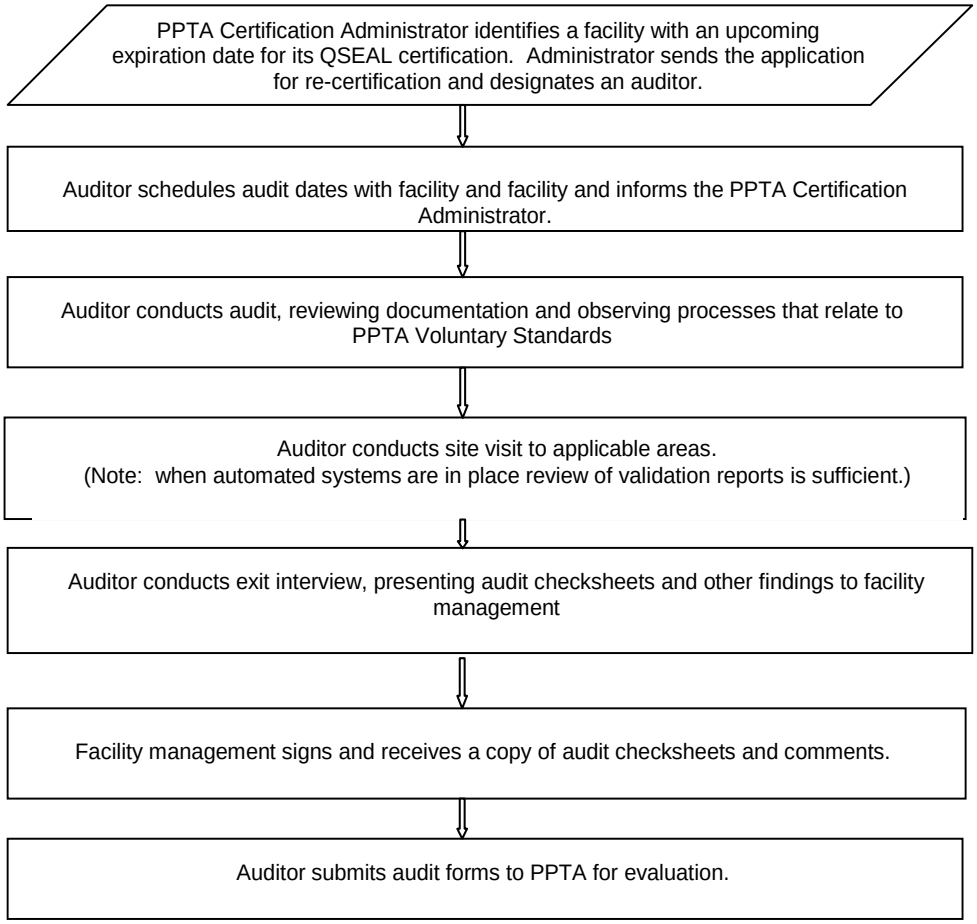

Figure 2 – Audit Process

The Audit

During the QSEAL audit, the auditor will review documentation and observe the processes that occur at the facility relating to the standards. The auditor will use the QSEAL Audit Checklist to assess a facility's compliance with the standards.

Audit findings

At the conclusion of the audit, the auditor will review the QSEAL Audit Checklist with the facility's management. The results will be presented as follows:

- Checklist Results – Auditor's assessment of a facility's adherence with the PPTA Voluntary Standards.

- Observations – Issues related to PPTA's Voluntary Standards identified by the auditor that may affect certification. Each observation noted by an auditor requires a response from the company before a facility is eligible for certification. When the auditor records "no" in answer to a question on the checklist, an observation will automatically occur. Additionally, observations for some audit questions on the checklist may be categorized as follows:

  Observation – event or condition that could prevent comprehensive adherence to an identified PPTA global voluntary standard. Examples include but are not limited to:
  - inadequate SOPs, and
  - inadequate documentation.

  Serious Observation – failure to implement a standard or any part of a standard; or an event or condition that indicates a lack of control over a system for implementing a standard, such as an actual failure of a system. Examples include but are not limited to:
  - a failure to implement required NAT testing for all viruses indicated in the standard, and
  - a failure in a system for ensuring only units from Qualified Donors are used, resulting in the use of a unit from an Applicant donor.

- Comments – Other issues related to PPTA's Voluntary Standards identified by the auditor that do not require a response from the company. A comment does not affect the certification.

- Initial Recommendation – The auditor's recommendation based on the situation at the facility at the time of the audit:

  - *For-certification* – the facility demonstrates compliance with the QSEAL Standards Program;
  - *Provisional-for-certification* – the facility demonstrates a need for improvement in its implementation of some aspects of the program;
  - *Not-for-certification* – Serious observations are identified in a facility's systems or corporate policy indicating non-adherence to the Voluntary Standards.

Evaluation of audit reports

All audit reports are evaluated by PPTA Management. The process for evaluating audit reports to determine if certification is to be awarded to a company follows.

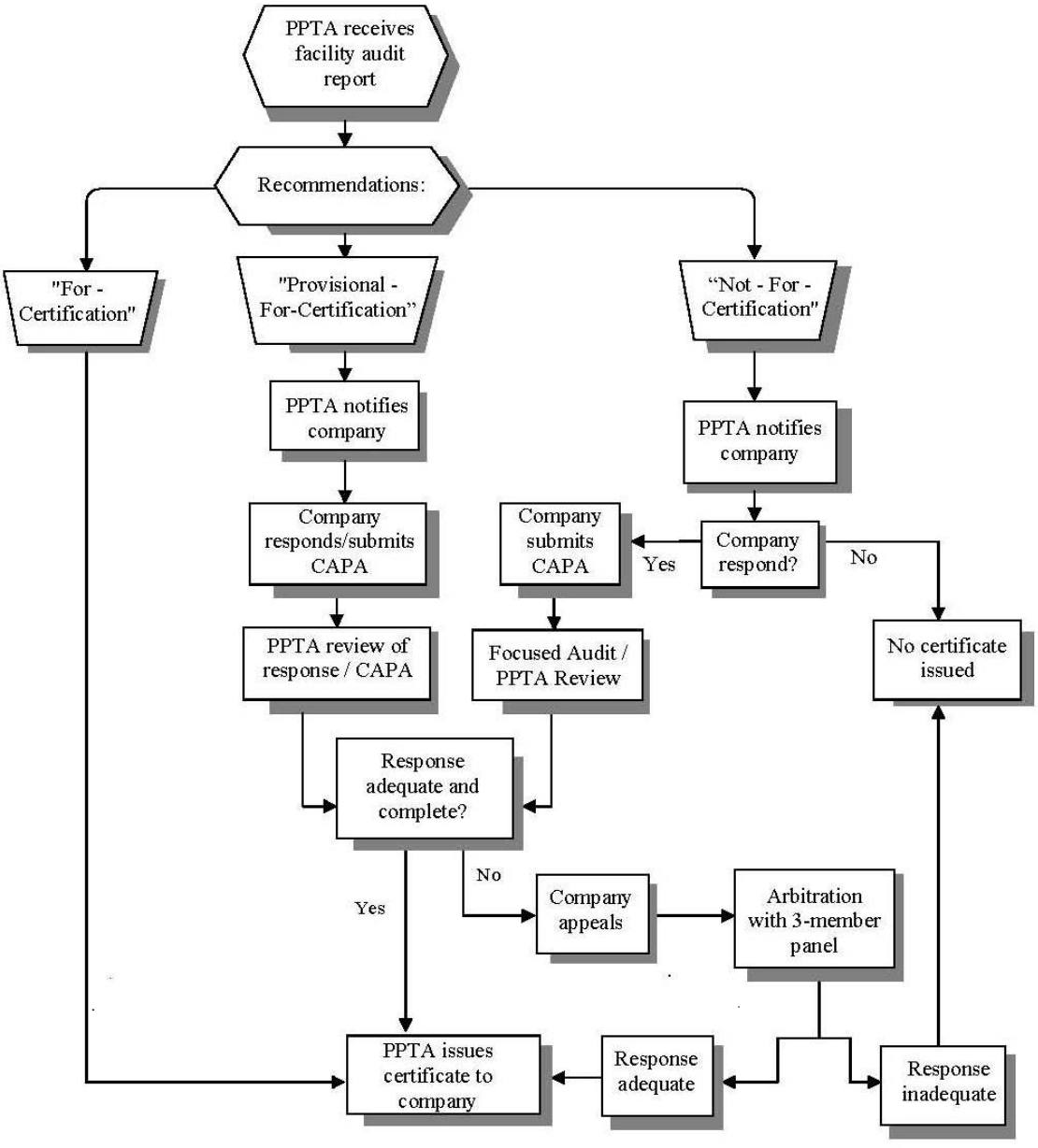

Figure 3 – Evaluation of Audit Reports

Corrective action plans

A written audit report will be forwarded to the company contact within 20 days of the completion of the audit. Companies receiving audit reports resulting in "*provisional-for-certification*" or "*not-for-certification*" recommendations are required to respond to observations, including a corrective action plan, within 30 days of receipt of the audit report. In *not-for-certification* situations, PPTA will also conduct a focused audit to assure the corrective actions were implemented and effective.

Upon receipt of the company response, the Association will reply to the company within 10 days regarding the acceptability of the response. Insufficient or unacceptable responses will require additional action prior to closure of the audit.

Audits for all company facilities must be closed in favor of *for-certification* before a certificate will be issued.

A *not-for-certification* recommendation must include justification for this determination. In these instances, the company will have the opportunity to attempt to correct the issue(s) that led to this recommendation in its response to PPTA. The PPTA QSEAL Administrator may choose to include the auditor in reviewing any response to a *not-for-certification* recommendation, and will provide a written reply to the company regarding the acceptability of the response within 30 days of receiving it. A focused audit, to take place within 90 days from receipt by PPTA of the written response, will be required to verify a company response.

Re-certification Audits

Observations noted in *provisional-for-re-certification* recommendations require a response from the company within 30 days of receipt of the audit report. Upon receipt of the company response, the PPTA QSEAL Administrator will respond to the company within 10 days regarding the acceptability of the response. Any outstanding issues must be resolved within 60 days of receiving the PPTA report, or the PPTA QSEAL Administrator may remove the certification status of the facility.

A *not-for-re-certification* recommendation shall include justification for this determination. In these instances, the company will have 30 days from the date of receiving the PPTA report to attempt to correct the issue(s) that led to this recommendation. The PPTA QSEAL Administrator may choose to include the auditor in reviewing any response to a *not-for-re-certification* recommendation, and will provide a written response to the company regarding the acceptability of the response within 30 days of receiving it. A focused audit will be required to verify a company response. Insufficient or unacceptable responses will result in removal of the certification status of the facility.

Conflict resolution

In the event that an audited company disagrees with any of the findings of an audit, the company may appeal the disputed observations to the QSEAL Administrator, setting forth its specific reasons for disagreement. The appeal shall be received in writing by PPTA no later than 30 days from the date on which the company receives written notification from PPTA of the results of the Audit. Acceptable bases for appealing audit observation(s) are:

a) One or more observations are factually inaccurate or incorrect; or

b) The facility's procedures, processes and/or practices do in fact meet the requirements of the standard.

Upon receipt of an appeal of audit findings, the PPTA QSEAL Administrator shall appoint a three-member panel to review the appeal. The review panel shall comprise:

a) One or two PPTA auditors, providing that the auditor who conducted the original audit cannot be a member of the review committee;

b) One PPTA Staff member qualified in accordance with the PPTA QSEAL Auditor Minimum Requirements contained herein; and

c) In the event that an auditor is available to serve on the review panel, a third party consultant qualified in accordance with the PPTA QSEAL Auditor Minimum Requirements contained herein.

The review panel shall meet no later than 30 days following the date on which the written appeal was received by PPTA. The panel shall review the Audit Checklist and Report, and the appeal submitted by the company. Additional fact-finding may be done at the discretion of the panel by interviewing the auditor and representatives of the company filing the appeal. The decision of the panel shall be by majority vote, and the panel shall communicate in writing its decision and its reasoning in detail to both the company filing the appeal and to the auditor.

Deadlines for responses and corrective actions related to an appealed issue shall be held in abeyance during the pendancy of the appeal. Deadlines shall be reset to the date the Dispute Resolution process is concluded as if that date was the conclusion of the audit; or, in the alternative, those deadlines shall be eliminated should the company's appeal be upheld by the panel.

The following matters are not subject to Dispute Resolution under this provision:

a) The merits or applicability of an adopted PPTA Standard;
b) The findings of a review panel under this provision; or
c) Any matter judged by PPTA to be unresolvable by this process.

Section B

How PPTA Administers the Certification Program

Overview

Control of program

Control and standardization of QSEAL Certification is important at the administrative level, as well as the audit level. Control and consistency at the administrative level is achieved through four primary mechanisms:

- a standardized administrative process,
- established rules which govern the administrative process,
- established authorities and responsibilities, and
- established procedures and document control system.

Administrative Process

Introduction

Administration of QSEAL Certification can be divided into two parts:

- coordination of the audits
- review of audit reports

Administrative process

The following flow chart provides an overview of the coordination of audits.

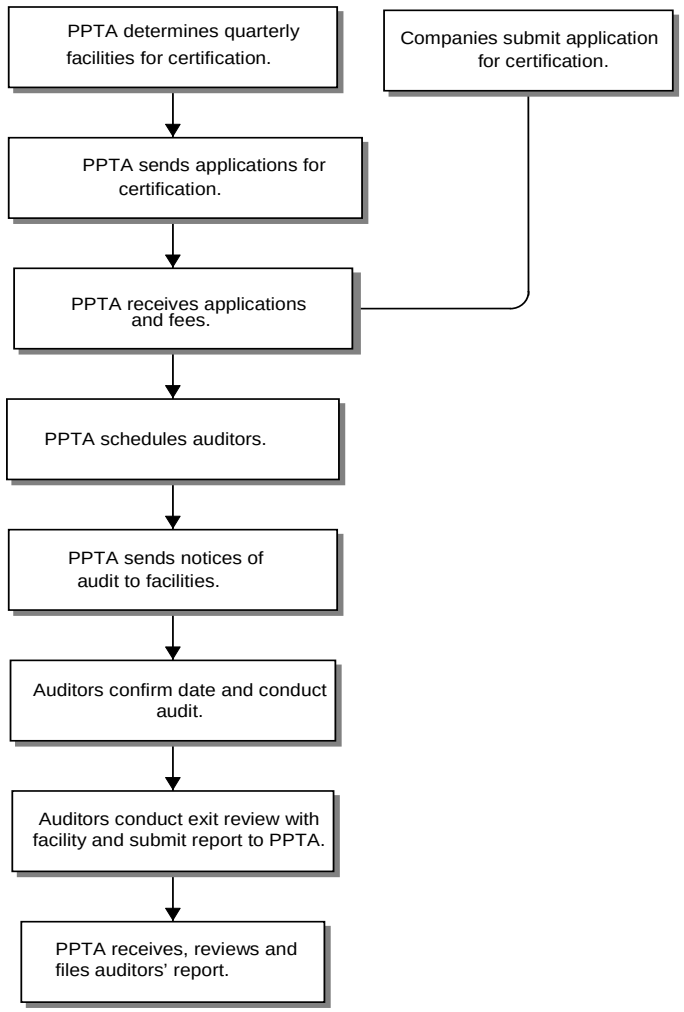

Figure 4 –Administrative Process

Rules

Introduction

A number of rules apply to the issuance and maintenance of QSEAL Certification. These include:

- eligibility for initial certification
- term for certification
- eligibility for recertification

Eligibility for initial certification

Facilities are only eligible for QSEAL Certification when they are licensed by a competent national regulatory authority (and maintain the license in good standing) and have submitted a complete QSEAL Certification application. The facility shall be fully operational. Initial certifications are usually scheduled to take place within 90 days of receipt of a completed application form.

Certification term

QSEAL Certification is valid for a three-year period.

Eligibility for recertification

PPTA tracks the date of initial certification. At least 120 days before the beginning of a quarter, all facilities that will observe their 3-year anniversary of certification are identified in PPTA's database as due for re-certification in the quarter. Audits must occur prior to the certification anniversary.

Change of Ownership

When ownership of a facility changes, the new owner shall make arrangements with PPTA, to have the previously non-QSEAL certified facilities that have been acquired audited for inclusion in their corporate Certification. Successful completion of the QSEAL audit of all non-QSEAL certified facilities that perform functions within the scope of the requirements in the QSEAL standards shall occur within one calendar year of the change of ownership.

Impact of Government Regulatory Authority Actions

Government actions resulting in the voluntary or involuntary discontinuation of manufacturing and/or product release will result in withdrawal of QSEAL Certification. The facility is not eligible to be certified until government approval to resume is obtained.

If a facility is subjected to an FDA Consent Decree of Injunction (or comparable regulatory action by another government regulatory authority), but is allowed to continue operations under the terms of the Consent Decree, the company shall notify the QSEAL Certification Manager. Upon notification, the QSEAL Certification Manager will arrange for a QSEAL re-audit at the earliest possibility.

PPTA will notify the industry through communications and Internet Webpage of suspended QSEAL Certifications.

Authorities and Responsibilities

Management structure

Authority and responsibility for administrating the PPTA QSEAL Certification Program is distributed in the management structure of PPTA, as follows:

Title	Responsibility
President & CEO	Board relations; Global Board of Directors
Staff	Policy development; Standards development
QSEAL Administrator (Staff)	Manager of Certification Program; Oversees auditors; Audit process implementation; Maintains program database

Governance structure

The following governing bodies provide guidance for the QSEAL Certification Program.

Governance Units	Comprised of	Responsibilities
QSEAL Standards Committee	High level representatives of a particular function in a company	Develops and maintains voluntary standards
Dispute Resolution Panel	1 PPTA Staff member, plus 2 auditors or 1 auditor and a third-party consultant	Reviews issues appealed as a result of a PPTA audit
Global Board of Directors		High-level policy approval, standards approval

Document Control

PPTA has a defined system for document control. Documents are numbered, indexed and stored to provide traceability and easy retrieval. Confidential files are kept in locked files and placed in archives after appropriate intervals.

End of Document