PPTA QSEAL Certification Program

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)."

Intended audience

The intended audience for this document includes:

- Regulatory agencies interested in applicable policies
- Association leadership responsible for high-level policy approval
- Fractionators seeking certification
- Association staff with responsibilities for steps in the certification process
- Other parties (e.g., patient groups) interested in the certification process

Contact

For further information about the PPTA Fractionator Certification Program, contact PPTA at (202)-789-3100 or in writing at:

QSEAL Certification
PPTA
147 Old Solomons Island Road Suite 100
Annapolis, MD 21401-3822
USA

In this document

In this document you will find information on the PPTA Fractionator Certification Program from two perspectives: the fractionator (Section A) and the administrator (Section B).

Topic	See Section
PPTA QSEAL Certification of Plasma Fractionators	A
How PPTA Administers the Certification Program	B

Section A

PPTA QSEAL Certification of Plasma Fractionators

Overview

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. Safety of plasma protein therapeutics is the top priority of the plasma fractionation industry. The Plasma Protein Therapeutics Association (PPTA), on behalf of its industry members, supports efforts by regulatory bodies to establish minimum requirements to ensure the safety of these products.

PPTA has adopted Voluntary Standards which go beyond regulatory requirements and help define the regulations as they apply to fractionation of plasma for plasma therapeutics. These Voluntary Standards relate to collecting, processing and testing of Source Plasma by member fractionators.

In 2000, PPTA established a certification program to provide independent certification of adherence by fractionators to the Voluntary Standards.

Purpose

The purpose of PPTA's QSEAL Program is to provide independent, third-party evaluation and recognition of a fractionator's adherence to PPTA's current and future global Voluntary Standards.

Control of program

Control and standardization of QSEAL Certification is important to assure PPTA, PPTA members, regulators, and patients about 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
- conduct of audits and review of audit reports.

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Overview, Continued

In this section This section contains information on the following topics.

The Certification Process

Certification: definition

QSEAL Certification is a recognition by PPTA that a plasma fractionation company operates its facilities with adherence to PPTA's Voluntary Standards, based on the findings of an independent auditor's assessment of the fractionator's policies, procedures, and facilities.

Eligibility

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

Upon receipt of the company's application for QSEAL Certification, the company must be fully operational. There may be no current governmental regulatory restraints or sanctions from normal manufacturing operations.

General rules

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

- QSEAL Certifications are issued to a company once all of the company's fractionation facilities have successfully completed an audit. Failure of any one of the facilities prevents certification of the entire company.
- Government actions resulting in the unscheduled voluntary or involuntary discontinuation of manufacturing and/or product release will result in withdrawal of QSEAL Certification. The facility, and company, are not eligible to be certified or recertified until government approval is obtained.
- QSEAL Certifications are issued for a two-year period.
- As new Standards are implemented, adherence will be confirmed within three (3) months (one quarter) of the implementation date.

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General rules, cont'd.

- Applications and fees must 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 Board, Global Management Committee and/or management approval.

- When ownership of a fractionation facility changes, the new owner must make arrangements with PPTA to have the previously non-QSEAL facilities audited for inclusion in their corporate Certification. Successful completion of the QSEAL audit of all non-QSEAL certified facilities must occur within one calendar year of the change of ownership.

Regulatory Compliance

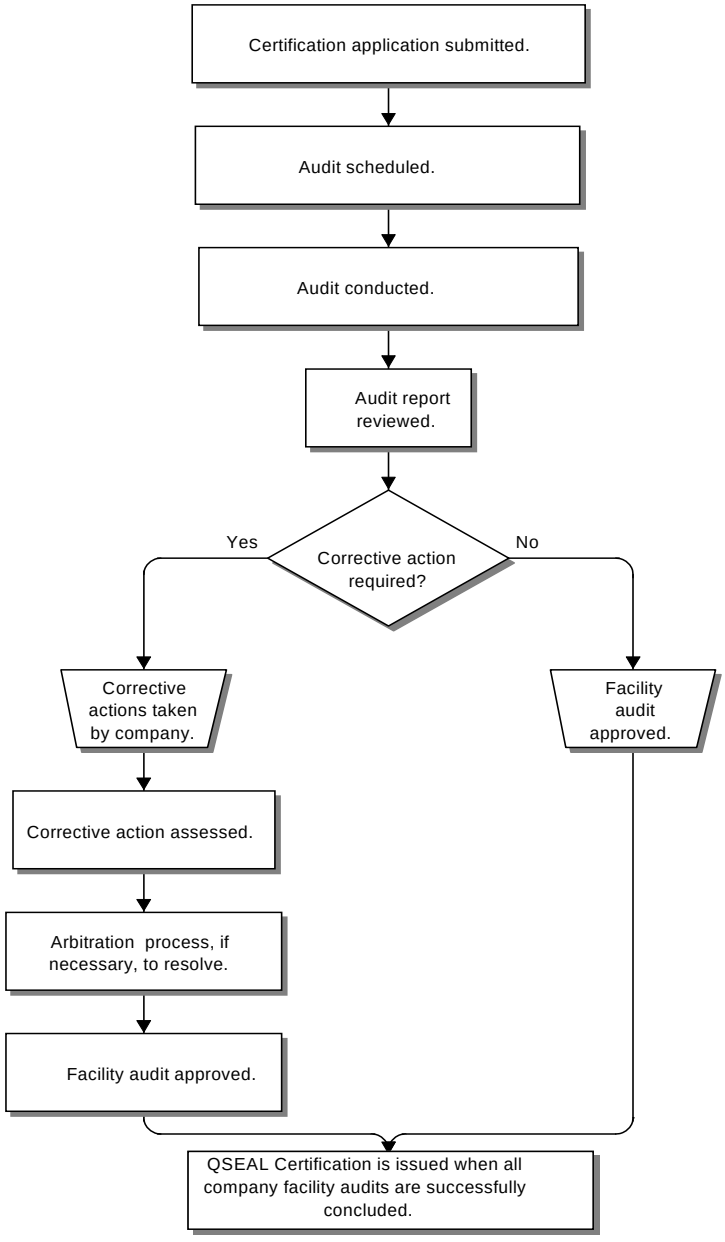
Upon receipt of the company's application for QSEAL Certification, all facilities in the company must be fully operational. There may be no current governmental regulatory restraints or sanctions from normal manufacturing operations.

Government actions resulting in the voluntary or involuntary discontinuation of manufacturing and/or product release will result in withdrawal of QSEAL Certification. The facility and company are 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 must notify the QSEAL Administrator. Upon notification, the QSEAL Administrator will arrange for a QSEAL re-audit at the earliest possibility.

Certification process overview

The following flow chart provides an overview of the process by which fractionators achieve PPTA certification. Deviation from the Voluntary Standards will result in a decision not to certify as demonstrated on page 12.



The Voluntary Standards

The voluntary standards

QSEAL Certification recognizes a fractionator's adherence to PPTA's global Voluntary Standards. Those Standards and their intent are:

- Qualified Donor Standard – to ensure a committed, healthy donor population
- Viral Marker Standard – to demonstrate the quality of the donor population
- NAT Testing Standard – to allow for the detection of certain viruses even earlier than current licensed serological screening technology
- Inventory Hold Standard – to allow for the retrieval of plasma prior to use if new post-donation information becomes available regarding the donor's health status
- Parvovirus B-19 – to assure that manufacturing pools do not exceed 10^5 IU Parvovirus B-19 DNA per ml.
- Intermediates Standards – to assure that intermediates are of the highest quality and safety.

Qualified Donor standard

The Qualified Donor Standard requires that Source Plasma donations from only Qualified Donors will be pooled for manufacturing of plasma derivatives.

Qualified Donors include all individuals who have been qualified for continued donations by passing two donor screenings and two sets of 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.

Viral marker standard

The Viral Marker Standard requires that Source Plasma units will be collected from collection centers that meet the Viral Marker standard as defined by PPTA.

The Voluntary Standards, **Continued**

NAT Testing standard

The NAT Testing Standard requires that all incoming Source Plasma will be tested for viral nucleic acid of the target viruses, HIV, HBV, and HCV using Nucleic acid Amplification Technology. The NAT must be carried out under conditions defined in PPTA's NAT Technical Guidance.

Inventory hold standard

The Inventory Hold Standard requires that all Source Plasma units must be held in inventory for a minimum of 60 days from the date of collection prior to pooling for manufacture.

Parvovirus B-19 Standard

All incoming plasma will be tested for Parvovirus B-19 DNA. Plasma that would result in a manufacturing pool exceeding 10^5 IU parvovirus B-19 DNA/mL will be removed.

Manufacturing pools will not exceed 10^5 IU Parovirus B-19 DNA/mL.

Intermediates Standard

PPTA's Voluntary Standard for Intermediates addresses an extensive list of quality requirements to which QSEAL certified manufacturers must adhere in their purchasing, processing and control of intermediates to be used in plasma protein therapeutics. For further description, please see the PPTA Voluntary Standard Intermediates.

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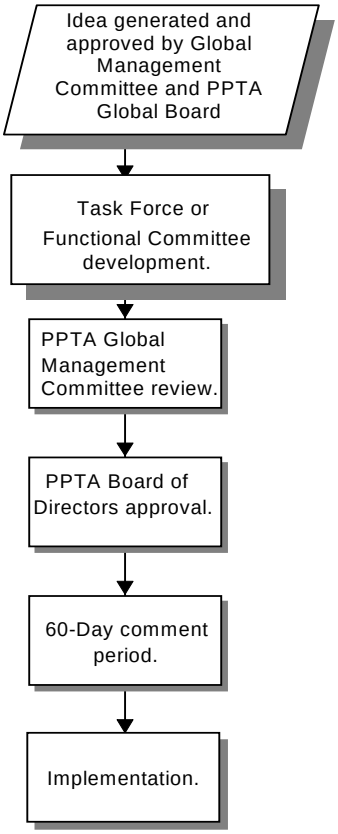
Standard development process - overview

The QSEAL Certification Program strives to be a dynamic reflection of current Industry Voluntary Standards. The following flow chart provides an overview of the process by which PPTA develops Standards.



Standard development process - discussion	The process for development of new standards starts with ideas for standards from a number of sources, including auditors, collection centers, fractionators, and government relations experts. The concept for the standard is reviewed by PPTA's Global Management Committee (GMC) and PPTA's Global Board of Directors. Other stakeholders will have a chance to provide their views on new proposals for new standards. The standard is assigned to a Task Force or Functional Committee which develops and reviews those ideas and is comprised of representatives from member companies. The GMC includes broader high level representation. A 60-Day Comment Period allows other stakeholders to review and provide input in the proposed standard. The proposed standard is also posted to the Association website, which allows interested parties to comment.

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 fractionation 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 Regulatory Affairs Professional Society, or at least five years experience inspecting/auditing pharmaceutical establishments.

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 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 must attend an official PPTA training workshop which includes the following topics:

- PPTA's Voluntary Standards
- the audit process
- documentation of audits
- PPTA's auditor agreement, including the confidentiality agreement

Auditor training: ongoing

PPTA periodically convenes 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 must participate in at least one continuing education event within each 2-year Certification Audit cycle. These events may include:

- Industry or government workshops relevant to auditing, quality assurance, quality management, good manufacturing practices, validation, or other relevant government regulation.
- Completion of courses required for maintenance of a professional certification.
- Completion of one class toward an advanced degree.
- Teaching a college-level course.

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 firm's adherence to PPTA Voluntary Standards and report this to the Association.

Audits and Audit Reports

Types of audits

The PPTA QSEAL Certification Program conducts four types of audits:

- Routine certification audits – conducted for the purpose of initial certification or continuous renewal of certification of a fractionator
- Random audits – scheduled at the discretion of the PPTA Certification responsible persons
- Focused audits – scheduled to assure corrective actions have been implemented in response to a previous "not-for-certification" audit report or following corrective actions in response to serious governmental regulatory compliance issues
- Discontinuous Recertification Audit--conducted for the purpose of assessing adherence to QSEAL standards following the suspension of government regulatory restrictions from normal manufacturing operations.

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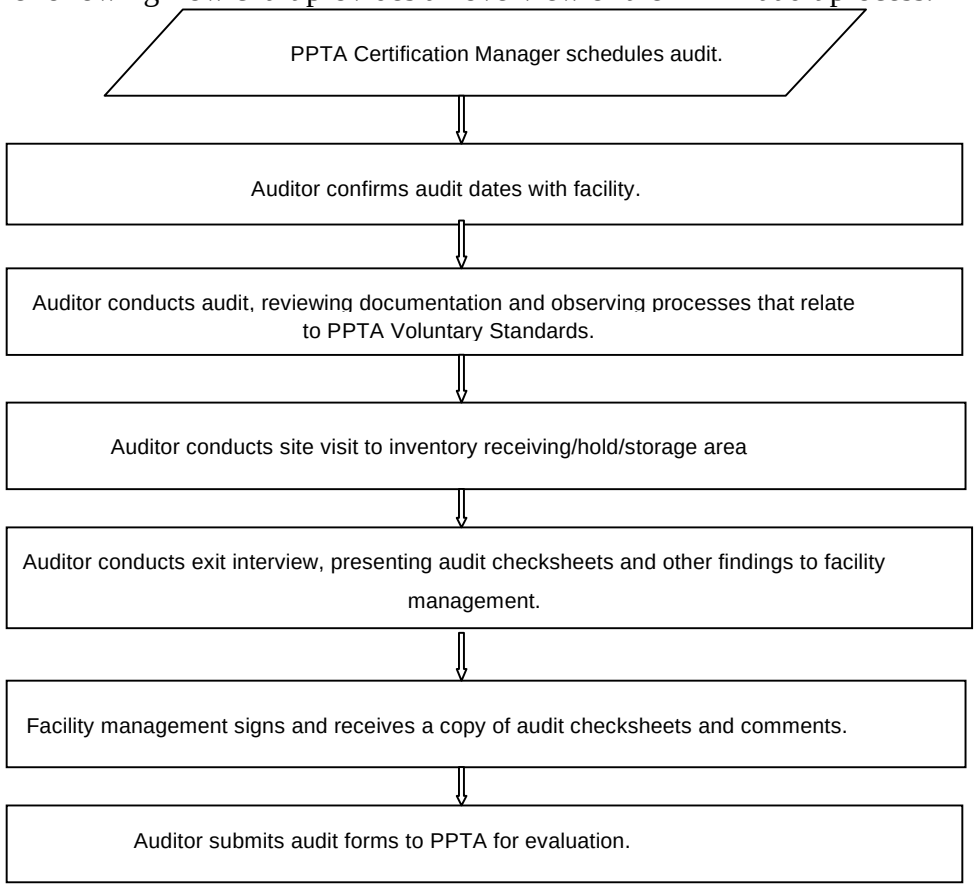
Audit process

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



Audit findings

Auditors may report their findings in the following ways:

Comments indicate the auditor has witnessed other issues related to PPTA's Voluntary Standards that do not require a response from the fractionator. A comment does not affect the certification.

Observations indicate the auditor has noted events or conditions that could prevent comprehensive adherence to an identified PPTA global voluntary standard. Examples include, but are not limited to, inadequate operating procedures or inadequate documentation. A response is required for all observations noted by an auditor.

Audit findings, cont'd.

Serious Observations indicate the auditor has noted events or conditions of a facility's failure to implement a standard or any part of a standard or that indicate 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 NAT testing for all viruses in the standard or a failure in a system for ensuring only units from qualified donors are used (resulting in use of a unit from an applicant donor). Serious observations result in a "Not For Certification" recommendation. A response is required by the fractionator.

Types of auditor recommen-dations

Audit reports may result in three types of recommendations by the auditors, based on their observations during the audit:

- For certification – the facility demonstrates adherence to the PPTA Voluntary Standards
- Provisional for certification – the facility demonstrates a need for improvement in its implementation of some aspects of the PPTA Voluntary Standards
- Not for certification – the facility demonstrates significant non-adherence to the PPTA Voluntary Standards

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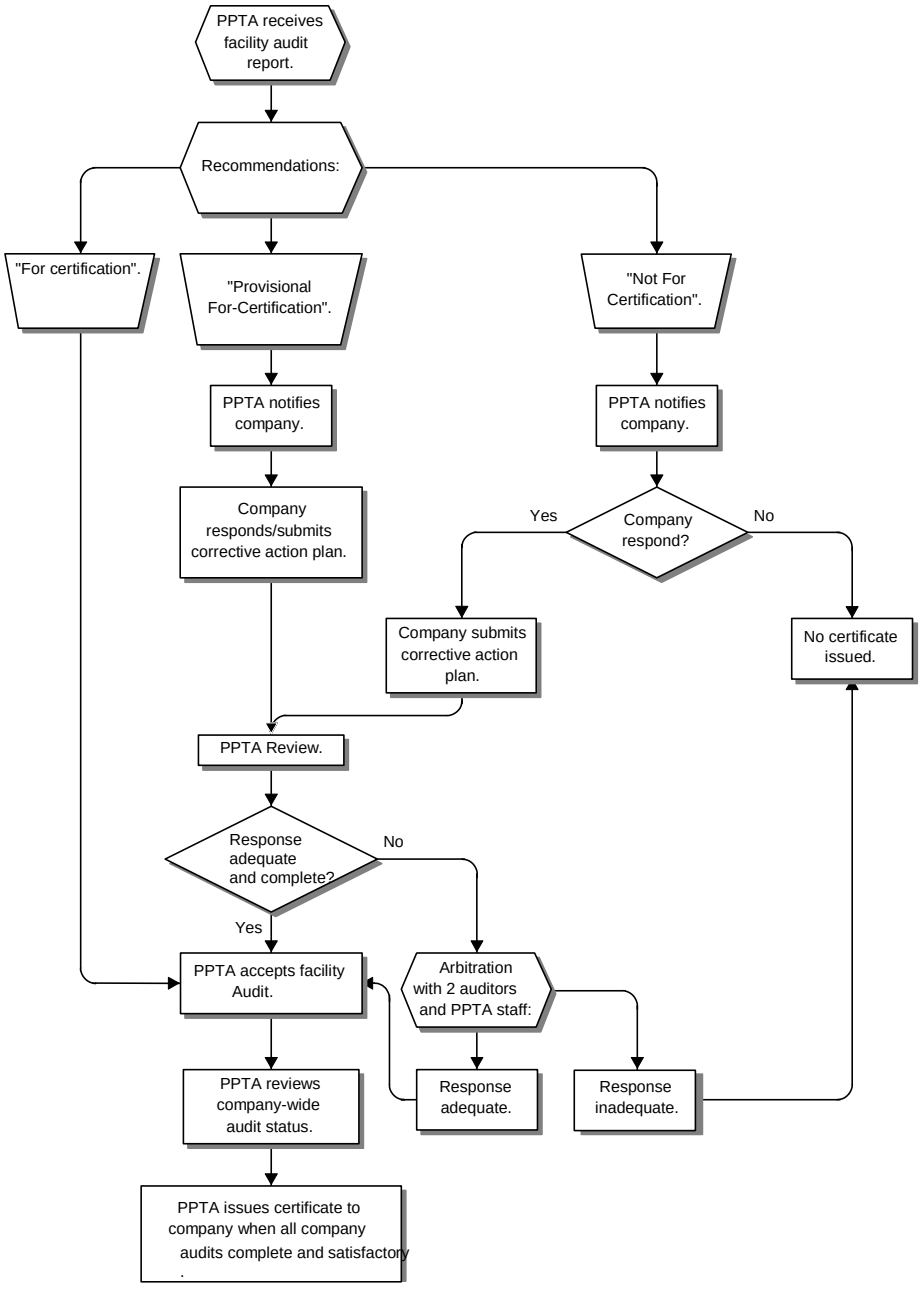
Evaluation of audit reports

All audit reports are evaluated by the PPTA Certification Manager. The process for evaluating audit reports to determine if certification is to be awarded to a fractionator is as follows.



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Audits and Audit Reports, Continued

Corrective action plans

The outcome of all audits are communicated to the fractionation company. Companies receiving facility audits resulting in "provisional certification" or "not for certification" recommendations are provided the opportunity to develop corrective action plans to correct the deficiencies. In "not for certification" situations, PPTA will conduct a focused audit to assure the corrective actions were implemented and effective.

Certification status may be removed by the PPTA in any situation where corrective actions to audit findings are not resolved within 60 days of the fractionator receiving the PPTA report.

Conflict resolution

In the event that a company disagrees with an audit report and PPTA review of that report, the company may enter into an arbitration and appeal process.

In the arbitration stage, two auditors and a PPTA staff member will jointly review the company's situation.

In the event that a disagreement involves policy or implementation issues not resolvable by arbitration, the company may choose to appeal the issue before the PPTA Global Management Committee and other qualified individuals it shall deem appropriate. This body will provide final resolution to the issue.

Section B

How PPTA Administers the Certification Program

Overview

Background

PPTA's QSEAL Certification Program is modeled after similar Industry certification programs, such as PPTA Source's International Quality Plasma Program (IQPP).

Processes and procedures that have been successfully used by other Industry certification programs are incorporated in the PPTA certification program.

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.

In this section

This section covers the following topics relating to the areas of control and standardization for the administrative processes of the Fractionator Certification Program.

Continued on next page

Administrative Process

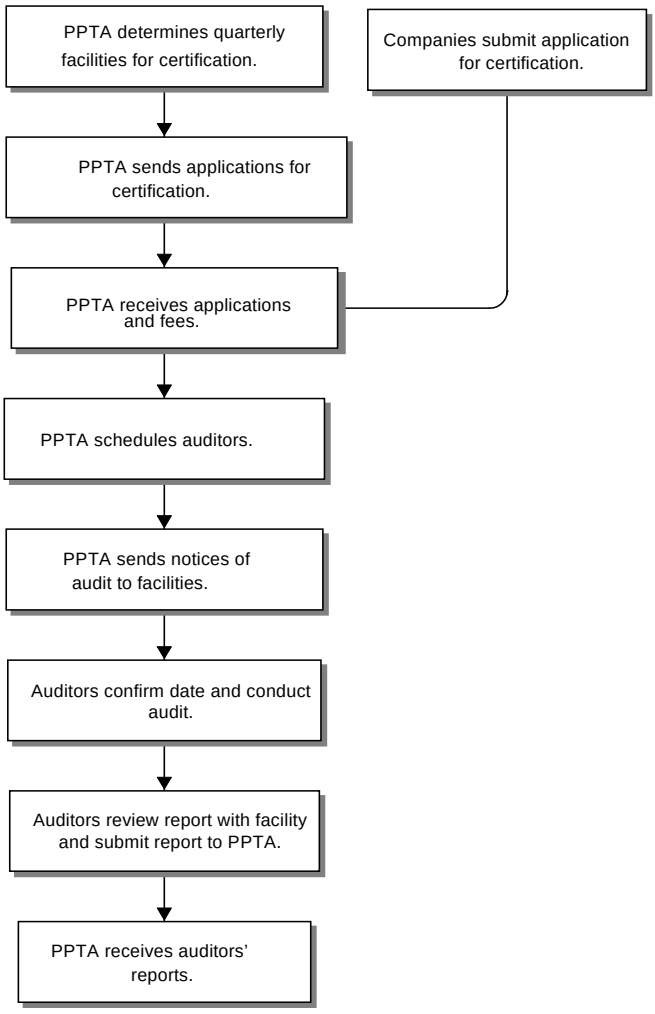
Introduction

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.



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 Certification application. The facility must 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 two-year period.

Eligibility for recertification

PPTA tracks the date of initial certification. At least 90 days before the beginning of a quarter, all facilities that will observe their 2-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 fractionation facility changes, the new owner must make arrangements with PPTA, to have the previously non-QSEAL facilities audited for inclusion in their corporate Certification. Successful completion of the QSEAL audit of all non-QSEAL certified facilities must 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 and company are 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 must 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:

Name	Title	Responsibility
Jan M. Bult	President	Policy development; Board relations; Global Management Committee
Michelle Mason	QSEAL Administrator	Manager of Certification Program; Oversees auditors; Audit process implementation; Maintains program database

Governance structure

The following governing bodies provide guidance for the PPTA Fractionator Certification Program.

Governance Units	Comprised of	Responsibilities
Functional Committees Or Task Forces	High level representatives of a particular function in a fractionation facility	Develops New Voluntary Standards
Review Committee	Global Management Committee, plus additional parties	Reviews issues appealed as a result of a PPTA audit
Global Management Committee	Executive representation	Final review of Voluntary Standards; approval and review of QSEAL Certification program
Board of Directors		High-level policy approval

Document Control

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.

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