IM-EN-PR43VAC-A

Appendix

to PR-43 Instruction Manual for Vaisala K-PATENTS® Products Intended for Use in Vaccine Production

Vaisala K-PATENTS® Pharma Refractometer PR-43-PC

VAISALA

Do not underestimate or neglect the laboratory and factory safety rules:

- Before you start, assess the workplace to determine if hazards are present, or are likely to be present, which necessitate the use of personal protective equipment, e.g.:
  - protective clothing and shoes
  - safety goggles
  - protective gloves
  - respiratory shields and devices
- Locate the nearest safety equipment, extinguishers, eyewash, and emergency shower

Contents

1 Vaisala K-PATENTS® products for vaccine production and sucrose gradient ultracentrifugation

This instruction manual appendix covers Vaisala K-PATENTS Pharma Refractometer PR-43-PC when used in the production of viral vaccines. The vaccines are either produced by inoculating viruses into specific pathogen-free eggs or in animal cell culture based process. The allantoic fluid of these processes is harvested and purified by centrifugation and stabilised with buffer containing sucrose. The centrifugation process typically uses density gradient continuous flow ultracentrifuge for the purification of the virus particles. The particles are separated and the virus is isolated based on the particle size differences or buoyant densities differences. The Pharma Refractometer PR-43-PC is used for accurate measurement of the sucrose densities of the gradient used for centrifugation. The measurement signal is reliable for timely determination of the product peak in the density gradient (0 to 60% w/w sucrose), and the subsequent collection of the virus rich fraction (Figure 1.1.).

Pharma Refractometer PR-43-PC can be installed in the vaccines fractionation unit for in-line process control. The output of the transmitter is a 4 to 20mA DC output signal proportional to sucrose solution density or Brix. Process data can also be downloaded to a computer via an Ethernet cable.

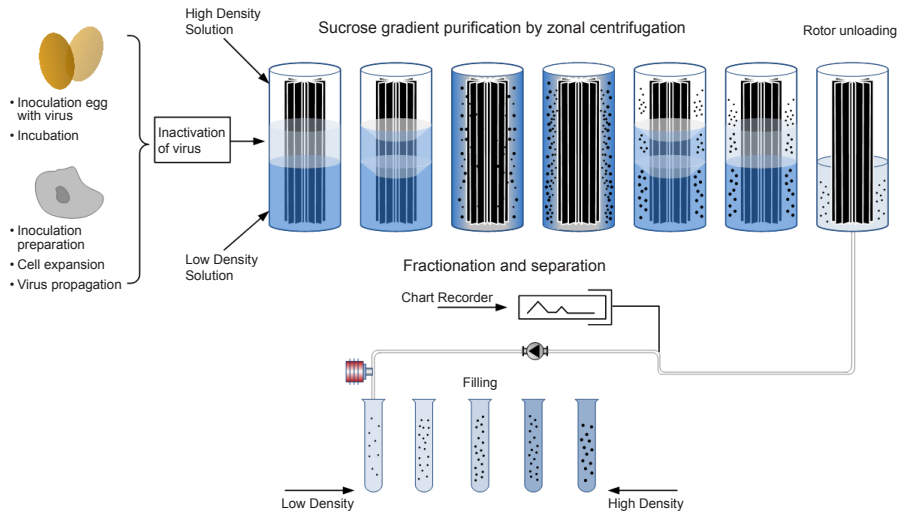

Figure 1.1 Ultracentrifugation density gradient purification process steps.

1.1 Design qualification

Design Qualification (DQ) typically consists of manufacturer's documentation to verify that the proposed design of the Vaisala K-PATENTS Refractometer is suitable for the intended purpose.

Pharma Refractometer PR-43-PC is an in-line real-time instrument that is designed to meet the pharmaceutical industry standards and guidelines including PAT, GMP, CIP/SIP and validation. Pharma Refractometer PR-43-PC wetted parts materials comply with the contact-compatibility of a substance with pharmaceutical materials. Gasket materials conform to the FDA requirements 21 CFR 177.2600 and to biocompatibility standards according to USP Class VI. Meeting the FDA and USP criteria guarantees that the seal material is acceptable for sanitary process applications and the material, or extracts from the material will not be harmful to human health. No animal derived ingredients (ADI) have been used in the machining and polishing processes.

The refractometer has an Ethernet communications solution. It uses the IP protocol to communicate over the Ethernet to any type of computer. This eliminates human error and allows for easy capture of the refractometer generated measurement and diagnostic data for storage, analysis and reporting. Access to the refractometer and the generated data can be restricted to authorized personnel using password.

Vaisala K-PATENTS refractometers are designed, manufactured and serviced under ISO 9001 quality system and procedures that guarantee the accuracy and repeatability of the measurement results. Each refractometer is provided with a calibration certificate comparing a set of standard liquids to the actual refractometer output. Vaisala verifies the calibration of all delivered instruments according to the procedure similar to the one described in the PR-43 series refractometer manual, **Section 9**.

The quality system is ISO 9001 certified by Det Norske Veritas. The quality performance is improved by critical self-assessment, internal auditing and feedback system. The chain of quality starts from the subcontractors with whom Vaisala maintains a quality contracting and regular auditing system. The internal quality functions, from verification of incoming products to packing and delivery, are based on defined procedures. Vaisala provides full traceability of the wetted parts materials. Certificates of Origin, and any other required quality documentation is available upon request at time of order.

Vaisala K-PATENTS process refractometers and support services are available to customers anywhere in the world. Application, installation and technical assistance are provided both locally by the representatives and by the headquarters in Finland and branches in the U.S. and China.

Vaisala warrants that all products made by Vaisala shall be free of defects in material and workmanship. Vaisala agrees either to replace or repair free of charge any such product or part thereof which shall be returned to the nearest authorized Vaisala K-PATENTS repair facility within two (2) years from the date of delivery.

2 The Pharma Refractometer PR-43-PC

2.1 System description

The recommended system for the vaccines production process comprises of a Pharma Refractometer PR-43-PC and a Pharma Mini Flow Cell PMFC-HSS that allows the refractometer connection to the ultracentrifuge rotor unloading and fractionation phase.

The PR-43-PC Refractometer has a built-in web server with an instrument homepage. The homepage enables the configuration, monitoring, verification and diagnosis of the refractometer via an Ethernet connection. In addition, the standard Ethernet communication solution allows for simultaneous data logging and continuous monitoring of the measurement values and diagnostic data from refractometer via an Ethernet connection.

2.2 System components

2.2.1 Checklist of components for a stand-alone refractometer

☐ 1	Pharma Refractometer PR-43-PC calibrated with raw measurement data refractive index (n_D) and temperature (T)
☐ 2	Split cable PR-8444
☐ 3 ☐ 3a ☐ 3b	Table top stand PR-7605-SS with an integral support rod and 2.5” Sanitary Clamp for the Pharma Refractometer PR-43-PC-73-H25-P15 contains a M5x16 A4 DIN 912 screw
☐ 4	Pharma Mini Flow Cell PMFC-HSS
☐ 5	PR-9244-USP O-ring for the Pharma Mini Flow Cell, 22.2x3.0 EPDM
☐ 6	Two sets of PR-9235 0.5” Sanitary Clamp for the Pharma Mini Flow Cell connection
☐ 7	Two sets of PR-9236-USP Sanitary gasket EPDM for the 0.5” Sanitary Clamps
☐ 8	Two sets of PR-9237 0.5” Sanitary ferrule (length 1.5 cm) for the inlet and outlet hose connections and Pharma Mini Flow Cell
☐ 9	Universal sample holder PR-1012
☐ 10	R.I. Liquid set PR-2300, consists of Cargille Certificate for the liquids

2.2.2 Checklist of components for a system with Compact user interface CI

☐ 1	Pharma Refractometer PR-43-PC calibrated with raw measurement data refractive index (n_D) and temperature (T)
☐ 2 ☐ 2a	Compact user interface CI PR-8350 Power cable for CI
☐ 3	Table top stand PR-7611 for CI
☐ 4	PR-8430-010 Platform 4 cable
☐ 5	PR-8330 Ethernet cable for interfaces
☐ 6 ☐ 6a ☐ 6b	Table top stand PR-7605-SS with an integral support rod and 2.5” Sanitary Clamp for the Pharma Refractometer PR-43-PC-73-H25-P15 contains a M5x16 A4 DIN 912 screw
☐ 7	Pharma Mini Flow Cell PMFC-HSS
☐ 8	PR-9244-USP O-ring for the Pharma Mini Flow Cell, 22.2x3.0 EPDM
☐ 9	Two sets of PR-9235 0.5” Sanitary Clamp for the Pharma Mini Flow Cell connection
☐ 10	Two sets of PR-9236-USP Sanitary gasket EPDM for the 0.5” Sanitary Clamps
☐ 11	Two sets of PR-9237 0.5” Sanitary ferrule (length 1.5 cm) for the inlet and outlet hose connections and Pharma Mini Flow Cell
☐ 12	Universal sample holder PR-1012
☐ 13	R.I. Liquid set PR-2300, consists of Cargille Certificate for the liquids

2.2.3 Checklist of components for a system with Multichannel user interface MI

☐ 1	Pharma Refractometer PR-43-PC calibrated with raw measurement data refractive index (n_D) and temperature (T)
☐ 2 ☐ 2a	Compact user interface MI Power cable for MI
☐ 3	Table top stand PR-7610 for MI
☐ 4	PR-8430-010 Platform 4 cable
☐ 5	PR-8330 Ethernet cable for interfaces
☐ 6 ☐ 6a ☐ 6b	Table top stand PR-7605-SS with an integral support rod and 2.5” Sanitary Clamp for the Pharma Refractometer PR-43-PC-73-H25-P15 contains a M5x16 A4 DIN 912 screw
☐ 7	Pharma Mini Flow Cell PMFC-HSS
☐ 8	PR-9244-USP O-ring for the Pharma Mini Flow Cell, 22.2x3.0 EPDM
☐ 9	Two sets of PR-9235 0.5” Sanitary Clamp for the Pharma Mini Flow Cell connection
☐ 10	Two sets of PR-9236-USP Sanitary gasket EPDM for the 0.5” Sanitary Clamps
☐ 11	Two sets of PR-9237 0.5” Sanitary ferrule (length 1.5 cm) for the inlet and outlet hose connections and Pharma Mini Flow Cell
☐ 12	Universal sample holder PR-1012
☐ 13	R.I. Liquid set PR-2300, consists of Cargille Certificate for the liquids

2.3 Pharma Refractometer

2.3.1 Refractometer model code

Model and Description	Model
PR-43 = Refractometer	PR-43
Refractometer model	
-PC = Pharma Refractometer, compact	-PC
Refractive Index range limits	
-73 = R.I. 1.320....1.530 (0-100 Brix)	-73
Process connection	
-H25-P15 = Sanitary 3A-clamp, 2 ½ inch	-H25-P15
Refractometer wetted parts material	
-SS = AISI 316 L	-SS
Electrical classification	
-UN = Unclassified area, General purpose, Ordinary location	-UN
-AX = Ex and IECEx certified Ex II 3G, Ex nA IIC T4 Gc (up to zone 2)	-AX
-IA = ATEX and IECEx certified Ex II 1G, Ex I M1, Ex ia IIC T4 Ga, Ex ia I Ma (up to zone 0)	-IA
-CU = CSA certified Class I, Div.2/Zone 2, Groups A, B, C, D, T4	
Polishing	
-EP = Electropolished refractometer wetted parts (Ra 0.38µm, 15 µ inch)	-EP
EHEDG option	
-EH = EHEDG Type EL Class I Certified Model	-EH

2.3.2 Pharma Mini Flow Cell model code

The wetted parts materials for the Pharma Mini Flow Cell are AISI 316 stainless steel standard Ra 0.38 µm, 15 µ inch and EPDM (ethylene propylene diene monomer) for the O-ring sealing.

Model and Description	Model
PMFC = Pharma Mini Flow Cell	PMFC
Refractometer connection	
-H = Sanitary 3A-clamp, 2 ½ inch	-H
Material of Construction	
SS = AISI 316	SS
Process connection	
-H = Sanitary mini fitting	-H
Pipe section diameter	
04 = 4 mm	04
05 = 5 mm	05
06 = 6 mm	06
Options	
-EP = Electropolished process wetted parts (Ra 0.38 µm, 15 µ inch)	-EP

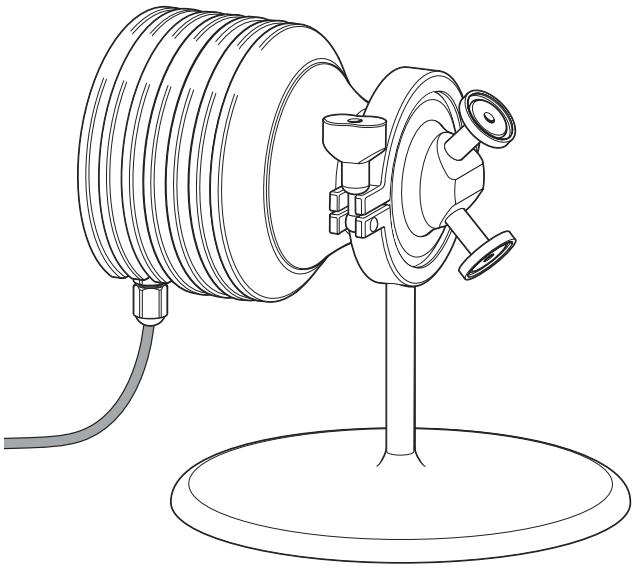

Figure 2.1 Pharma Refractometer PR-43-PC and Pharma Mini Flow Cell PMFC-HSS-EP with PR-7605-SS table top stand.

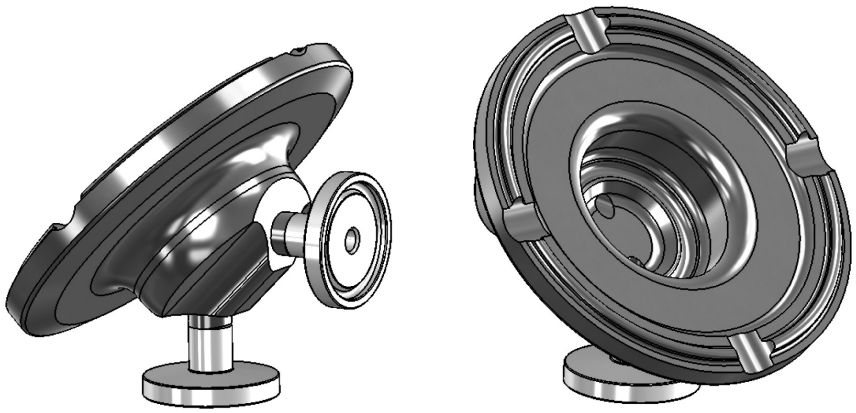

Figure 2.2 Pharma Mini Flow Cell PMFC-HSS-EP.

2.4 Compact user interface CI

Compact user interface is a specialized computer designed to process and display data received from the refractometer. It contains a front panel with touch screen.

2.4.1 Compact user interface model code

Model and Description	Model
CI = Compact user interface, Power supply 24 V DC	CI
Enclosure type	
-AA = Anodized Aluminium enclosure -EC = Epoxy coated with display shield	-AA -EC

2.5 Multichannel user interface MI

Multichannel user interface is a specialized computer designed to process and display data received from the refractometer. It contains a front panel with touch screen. The door can be locked with a padlock to prevent unauthorized access.

2.5.1 Multichanneld user interface model code

Model and Description	Model
MI = Multichannel User Interface, Stainless steel enclosure	MI
Cable connection for power	
-U = ½ inch NPT-type conduit hubs -M = M20x1.5 metric cable glands	-U -M
Electrical classification	
-UN = Unclassified area, General Purpose, Ordinary location	-UN
Power supply	
-AC = Power supply 100-240 VAC 50/60 Hz -DC = Power supply 24VDC	-AC -DC

2.6 Pharma vaccines accessories

Vaisala recommended accessories for the vaccines production application contain PR-8444 Split cable (for stand-alone refractometer), PR-8330 Ethernet cable for interfaces (for CI) or PR-8441 Ethernet cable for interfaces (for MI), IQ and OQ documentation (this document) and parts for verification and usage of Pharma Refractometer and CI/MI mounted on a table top or a trolley via metal support stands. **The recommended accessories and corresponding part numbers are**:

- **PR-7611 Table stand for CI** for Compact user interface
- **PR-7610 Table stand for MI** for Multichannel user interface
- **PR-7605-SS Table top stand** with the integral support rod and 2.5” Sanitary Clamp for the Pharma Refractometer PR-43-PC (contains a screw)
- **PR-8444 Split cable** for Ethernet connection between a stand-alone refractometer and a computer
- **PR-8330 Ethernet cable for interface** for Ethernet connection between CI and computer
- **PR-8441 Ethernet cable for interfaces** for Ethernet connection between MI and computer
- **Parts for off-line instrument verification:**
  PR-1012 Sample holder
  PR-2300 R.I. liquid set 5 x ¼ fl.oz.; Including: 1.33; 1.37; 1.42; 1.47; 1.52
- **IM-EN-PR43VAC** Instruction Manual for use in Vaccine Production for Refractometer PR-43-PC including IQ and OQ Documentation for Equipment qualification)

3 Installation of PR-43 Pharma Refractometer

3.1 Hardware and software requirements

PR-43 software is included in the refractometer system and it comprises the following functions:

- Automatic temperature compensation
- Ethernet connection for data download
- Refractometer diagnostics and verification

3.2 Mechanical and electrical requirements

Power supply for stand-alone refractometer and for the refractometer system with CI is 24 VDC. For refractometer system with MI power supply is either 24 VDC or 100-240 VAC. Power requirement is indicated on MI nameplate.

3.3 Refractometer installation for use in pharmaceutical batch manufacturing

Laboratory table top or trolley installation and key considerations for the site preparation

1. Physical dimensions of the instrument and accessories: make sure there is enough space to accommodate them.
2. Suitable recommended operational environment for the instrument and for the Cargille Refractive Index Liquids should be maintained between 20 – 30 °C (68 – 86°F).
3. Utilities: 24 VDC or 100-240 V AC power supply as required by your refractometer/ interface, and computer network connection.

Attaching table top stand PR-7605-SS for Refractometer and Mini Flow Cell
Attach the 2.5” Sanitary clamp and the support rod to the base plate. The supplied screw (M5x16 A4 DIN 912) for attaching the stand is inserted from the bottom of the base plate through the bottom hole (Figure 3.1). To assemble the Pharma Mini Flow Cell first locate the PR-9244-USP O-ring 22.2x3.0 EPDM inside the Mini Flow Cell (Figure 3.2). Then insert the 2.5” Sanitary clamp for the refractometer and Mini Flow Cell.

Finally insert the two PR-9236-USP Sanitary EPDM gaskets and the two PR-9237 0.5” Sanitary ferrules for the inlet and outlet connections using the two PR-9235 0.5” Sanitary Clamps.

Refractometer can now be connected to flexible hoses and used as a free standing tabletop unit, see Figure 3.4.

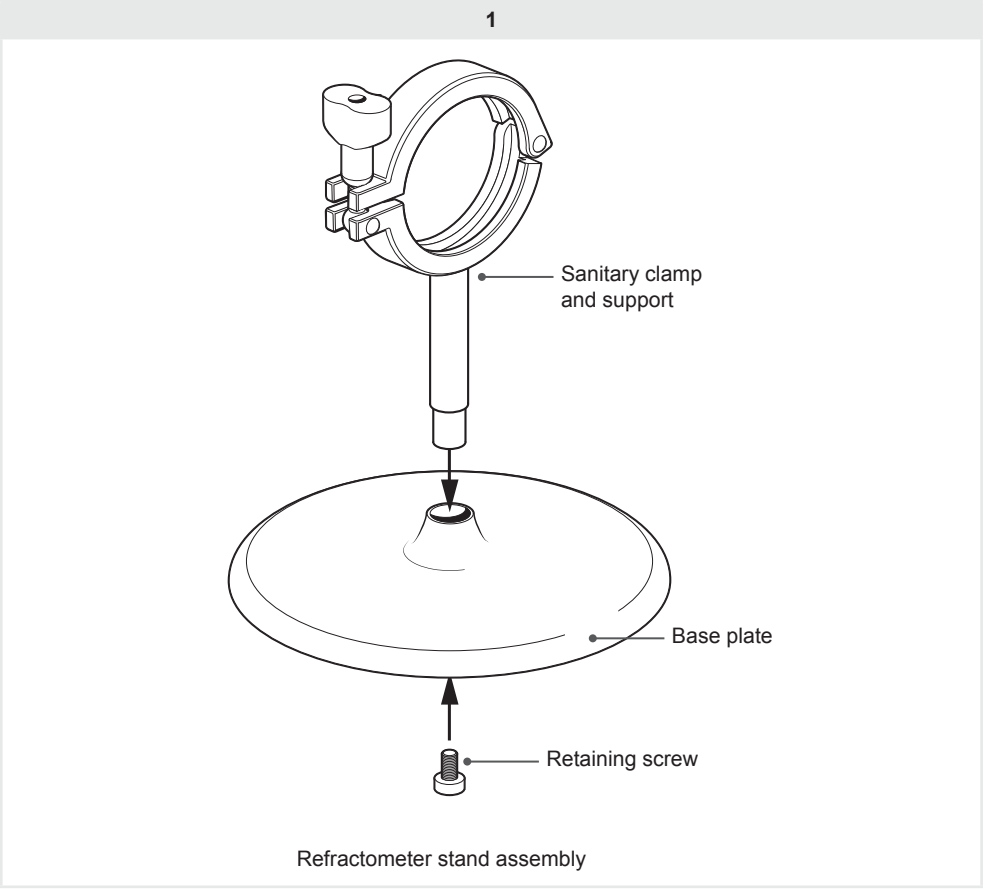

Figure 3.1 Refractometer stand assembly: Attaching the clamp and support rod to the base plate.

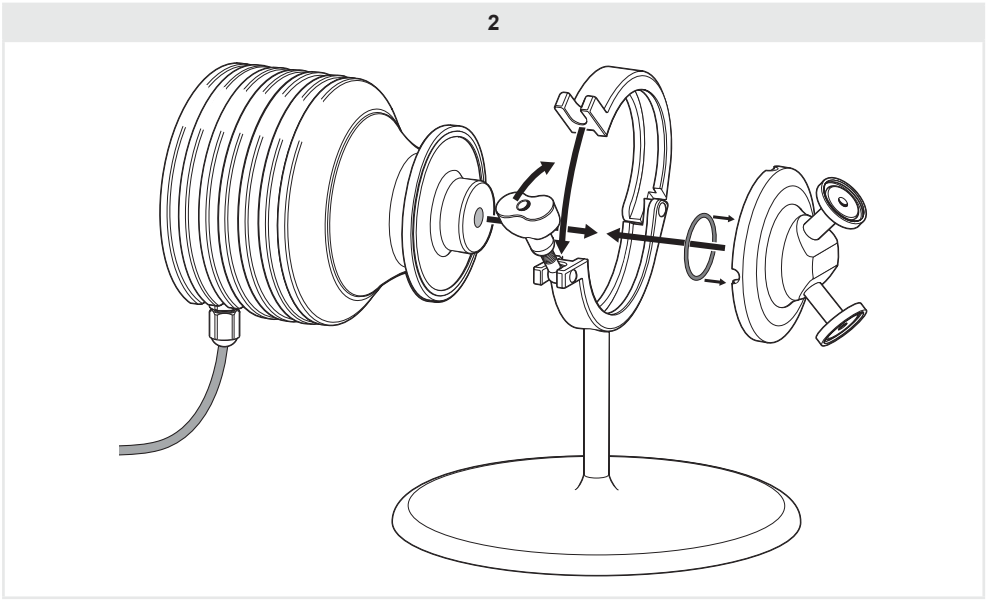

Figure 3.2 Refractometer stand assembly: Installing the refractometer and Mini Flow Cell to the stand.

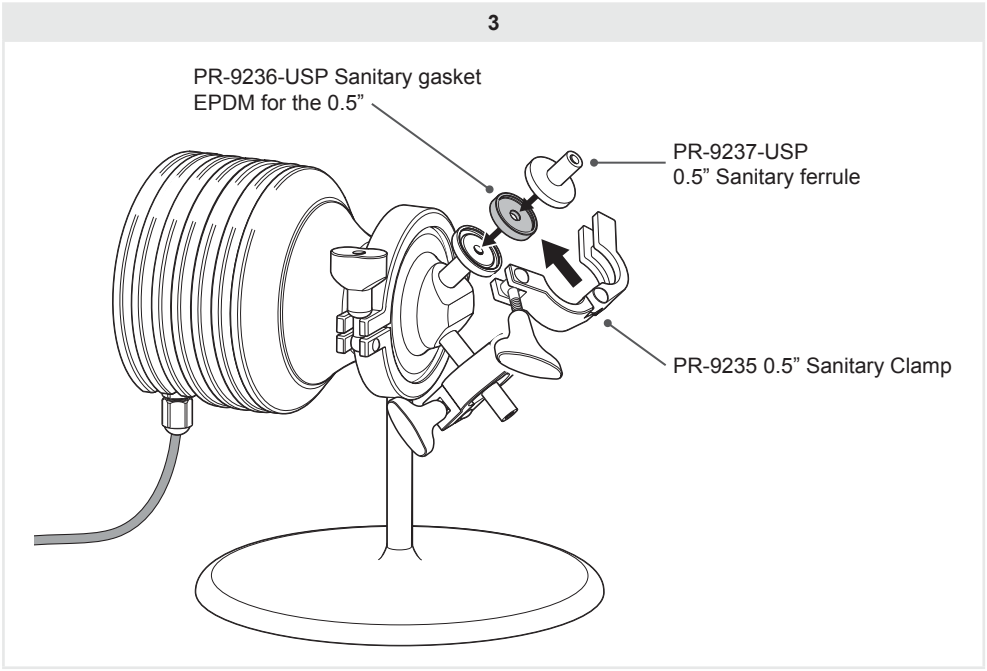

Figure 3.3 Refractometer assembly: Attaching the ferrules for the feed pipes.

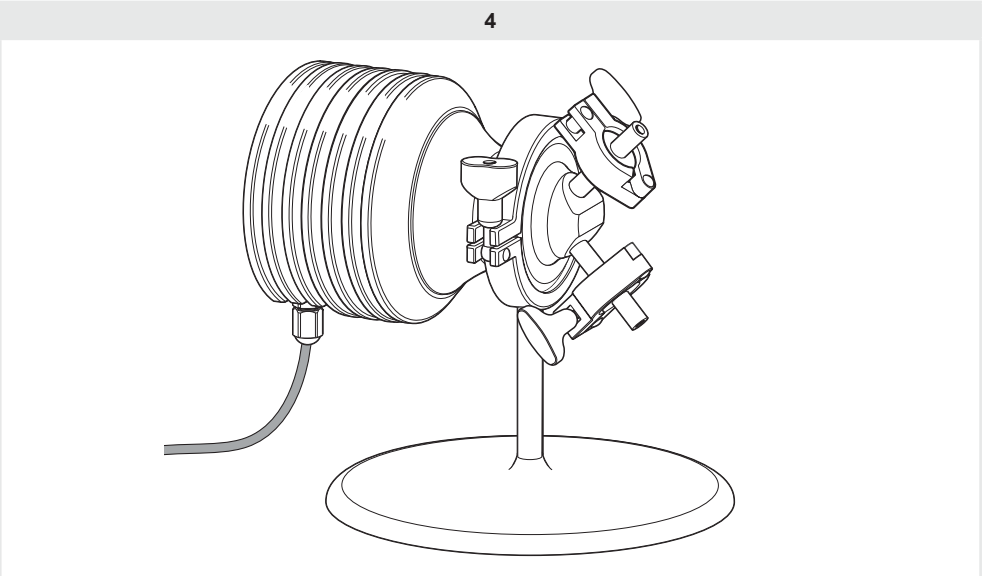

Figure 3.4 Refractometer stand assembled.

3.4 Compact user interface CI installation for use in table top

Place table stand PR-7611 on the table. Insert CI into the slots, Figure 3.5.

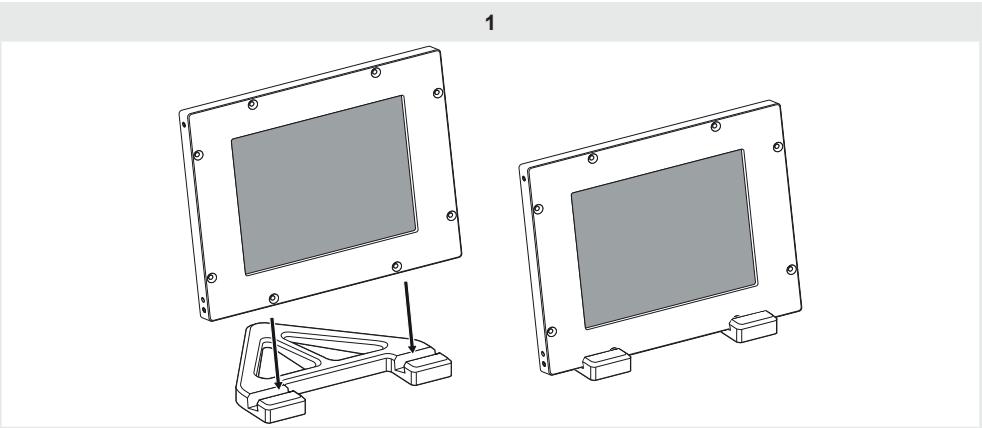

Figure 3.5 Attaching the table top stand to the CI for use in the laboratory.

3.5 Multichannel user interface MI installation for use in table top

Bring the table stand PR-7610 on both sides of the MI. Using the screws provided with the stand, securely fasten the MI, Figure 3.6.

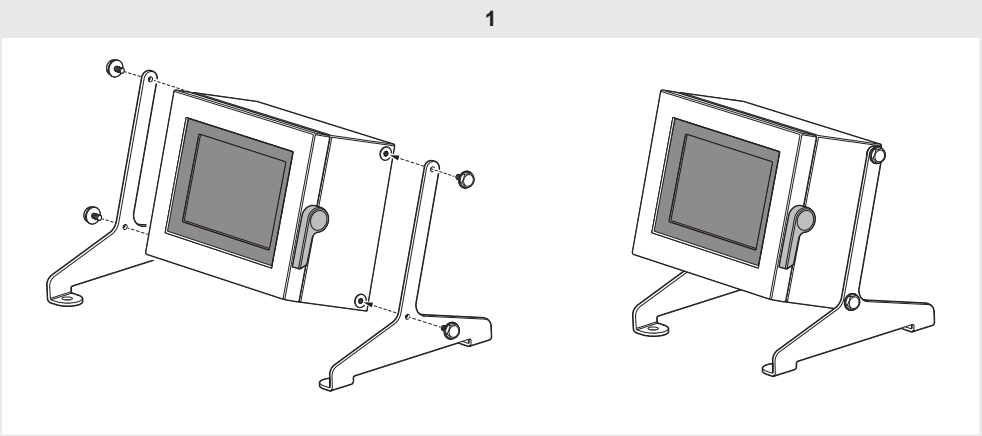

Figure 3.6 Attaching the table top stand to the MI for use in the laboratory.

3.6 Connections

For connections see PR-43 series instruction manual (stand-alone refractometer), Compact user interface CI instruction manual or Multichannel user interface MI instruction manual. When the connections have been made refractometer calibration and verification can commence.

3.7 Refractometer instrument verification

The operational procedure checking the refractometer calibration accuracy, linearity and short-term repeatability and reproducibility consists of verification tests using Cargille standard refractive index n_D liquids.

The verification of the refractometer calibration is performed whenever a new Vaisala laboratory refractometer is qualified as a part of the validation process, and also if any of the following occurs:

- There is a replacement of optical parts (prism and prism gasket).
- Refractometer readings reflect an unusual shift, or are outside of the acceptable limits, and other means of assessing and correcting unacceptable control values fail to identify and correct the problem.

Verification is recommended to be performed once every 12 months (or more frequently if specified in the client's own quality system) as a routine quality control check. Verification is carried out using the Sample Holder PR-1012 and the set of Cargille standard refractive

index n_D liquids. A set (R.I. Liquid Set PR-2300) is supplied by Vaisala. The Sample Holder PR-1012 consists of a sample receptacle with O-ring seal around the bottom aperture.

Before commencing the verification process make sure that your refractometer and sample holder are at normal room temperature. Preferably take all components to the laboratory already one day prior to the verification. Check the condition and expiry date of your standard refractive index liquids and that you also have the required cleaning solution (e.g. Isopropyl alcohol) and cleaning tissue to clean the refractometer wetted surfaces and the sample holder.

If verifying a stand-alone refractometer via refractometer website, choose Verification on refractometer main page to start the guided verification process. In a CI and a MI, the guided verification process can be found in Diagnostics display, see CI/MI user manual.

4 Electronic data capture and storage

4.1 Ethernet connection

In addition to software operation via the hardware, the refractometer, a CI or a MI can be considered as a web server and is accessible via a web-browser (e.g. Internet Explorer, Firefox, Chrome etc.). The Ethernet connection enables data download from the refractometer or a user interface to a computer and replaces the traditional paper-based data collection methods and streamlines data collection. The connection works both directly between the instrument and a computer, or via a hub or a switch, local area network (LAN), wireless network (WLAN) or fiber Ethernet.

For connecting and operating instructions of the Ethernet connection see PR-43 series manual **Sections 2, 3 and 8.** For CI see CI instruction manual **Section 3.5** and for MI see MI instruction manual **Section 4.5.**

5 Complying with documentation and validation regulations

5.1 Documentation

When a pharmaceutical company purchases new measuring instruments, they must take into account the documentation requirements covered by national and international laws and directives, for example, the US Food and Drug Authority's Code of Federal Regulations (CFR). FDA's validation requirements leave it up to the manufacturer to determine what data is essential to prove control over their processes. Therefore, the requirements vary from company to company, and each pharmaceutical company is responsible for defining and maintaining its own documentation requirements list. Some areas to consider and their Vaisala K-PATENTS solutions are presented in the sections below.

5.2 Qualification

The qualification action consists of proving and documenting that the equipment and ancillary systems are properly installed, operating correctly, and producing verified results. Qualification is a part of the validation process, but the individual qualification stages alone do not constitute process validation.

Installation Qualification, Operational Qualification and Performance Qualification protocols are normally required to document that the correct refractometer model and parts have been ordered, delivered and installed according to Vaisala's recommendations, and also to check that the refractometer meets its performance specification and is able to reliably measure typical samples using the selected measurement method. Users are able to create their own protocols using the relevant information from this manual appendix and the product manual, and/or using their own templates. The complete qualification process must be fully documented.

5.3 Protocol acceptance by customer and list of tests performed

A qualification protocol which provides details about the system, the scope and constraints of the qualification, the qualification tests, test procedures and acceptance criteria should be available for review and approval before the qualification begins. The protocol should also contain an exception log to record any out of the specification results, investigation and problem resolution. After the qualification, the test results must be reviewed and approved before the instrument can be put into routine use.

5.4 Electronic data management and data storage

The Code of Federal Regulations (CFR) FDA 21, Part 11 requires that pharmaceutical companies use electronic (i.e. software-maintained) data recording and storage, rather than paperwork. In case of instrument measurements, the code requires that every reading taken with the instrument must be logged and permanently stored electronically, and the data is password-protected ensuring alteration accountability (i.e. which operator makes an alteration) and tracking.

Part 11 describes four basic system elements that must be addressed. They are:

- Electronic signatures and tracking
- Data storage and logs
- Security
- System validation.

5.5 Electronic signatures/audit trail

Data records must be linked to the relevant electronic signatures so that when accessed, either electronically or through printout, the signatures will be openly displayed along with the date and time of execution.

5.6 Record keeping

Data records must be stored in a format that the FDA can reasonably expect to be able to read. These records must be retained for the length of time required by the predicate rule.

5.7 Security

System access can be restricted to authorized individuals by using password protected access. Multichannel user interface door can be locked with a padlock to prevent access to the screen.

The actions of these authorized individuals in relation to the data must be openly accounted for throughout the audit trail.

5.8 System validation

The system must be validated to prove that it complies with the technical requirements of Part 11. The Installation Qualification, Operation Qualification, and Performance Qualification (IQ/OQ/PQ) should also be performed.

5.9 Vaisala K-PATENTS refractometer system adherence to Part 11

It is not possible to supply a system readily in compliance with Part 11. This is because the requirements of Part 11 fall into two categories: those that are handled technically (through software features), and those that are handled procedurally (such as through system validation, SOPs, policies, etc.).

Part 11 applies to all computerized systems that create, modify, maintain, archive, or retrieve records required by the FDA. Pharma Refractometer generates electronic records via Ethernet connection. These records can be stored as digital files and printed out for signature or filed and maintained as hard copies. The computer files are subject to Part 11 regulation. The instrument parameter and configuration changes also fall into this category.

These computer files may be used in either of the two ways:

1. as a non-subject system by printing results, signing by hand, and maintaining hard copies
2. as an electronic record-keeping system subject to Part 11 regulation.

Systems described by number 1 would be subject only to predicate rules, not Part 11. Systems described by number 2 must comply with Part 11.

Please note: While Vaisala has taken account of the FDA Part 11 rules during development of the Pharma Refractometer package and in the compilation of the instructions and guidelines contained in this Instruction manual appendix, the system described has not been approved or mandated by the FDA or any other government agencies. So all compliance responsibility lies with the end user and Vaisala makes no claims that the completion of all the procedures described here will exempt these companies or individuals from FDA sanctions.

6 Onsite qualification protocols and records: Installation Qualification

This Installation Qualification (IQ) involves documented verification of the complete system: Pharma Refractometer PR-43-PC and Pharma Mini Flow Cell PMFC-HSS with Compact User Interface CI or Multichannel User Interface MI and Ethernet connection, as installed and connected to a fractionation unit and a computer, and in compliance with the approved design, the manufacturer's recommendations and user requirements.

6.1 Authorization and responsibilities

6.1.1 Documents and procedures

The following documents and procedures are inspected:

- Scope and Procedure for Qualification
- Report on Installation Qualification
- Protocol for Installation Qualification

The authorized official (client) hereby declares that the execution of the Installation Qualification (IQ) for the Pharma Refractometer and Pharma Mini Flow Cell have been approved in accordance with this document/log. The authorized official is responsible for all relevant matters in regard to the installation qualification.

Release by superior department:

_____

Name: _____

Function: _____

Date: _____

Signature: _____

Initials: _____

Authorization by a higher-level authority is a prerequisite for carrying out the qualification procedure. If no valid written authorization is available, terminate the Installation Qualification.

6.1.2 Authorized officiator

Selection of the individual authorized to carry out the Installation Qualification of the Pharma Refractometer system should be in accordance to their relevant ability to undertake the procedure. The authorized officiator's signature is required for the next stage to validate Date/Initials in the Installation Qualification log and reports.

Name: _____

Function: _____

Date: _____

Signature: _____

Initials: _____

6.1.3 Execution

As it is executed, each described step of the Installation Qualification requires initialing and dating. If any deviations occur, the qualification must either be aborted or a detailed explanation of the deviations must be entered in the subsequent "Deviation, evaluation, corrective actions" logs and must be documented appropriately.

6.2 System

6.2.1 Qualifying the system

Location of the Pharma Refractometer and Pharma Mini Flow Cell:

_____

Location of the user interface (if used): _____

Device	Serial Number	Supplier	Manufacturer
Pharma Refractometer PR-43-PC			Vaisala Oyj
Compact user interface CI			Vaisala Oyj
Multichannel user interface MI			Vaisala Oyj
Computer _____			

6.2.2 Manufacturers and suppliers

Full address of the manufacturers and suppliers:

Manufacturer:	Supplier:
Vaisala Oyj Postal address: P.O. Box 26, FI-00421 Helsinki, Finland Street address: Vanha Nurmijärventie 21, FI-01670 Vantaa, Finland Tel. Int.+358 9 89491 Fax Int.+358 9 8949 2227 www.vaisala.com	

6.3 IQ protocol

6.3.1 Scope of delivery

Description of requirements

Check that the delivery is complete and that all the listed instrument components and accessories are included in the delivery.

Requirement acceptance values

Compliance with the component checklist “System components provided by Vaisala”, included in the Manual Appendix (this document) **Section 2.2**.

Failure to meet delivery values

If any essential component is missing terminate the installation qualification and call your support, otherwise check conditional pass and move with the IQ, inform your support. Terminate the IQ.

Date	Signature	☐ Pass	☐* Conditional Pass	☐ Fail
*Conditional pass:				

6.3.2 Damage

Description of requirements
Inspection of all components and devices to check they are undamaged and functional.

Damage or malfunction detected
Terminate the IQ.

Report to: _____

Date	Signature	☐ Pass	☐* Conditional Pass	☐ Fail

*Conditional pass: _____

6.4 Documentation

Description of requirements
Make sure that the Operating Instructions and all other required documentation are complete and accessible.

Type of document	Document/Revision No.	Requested		
		Present	Missing	Not requested
Instruction manual for PR-43 series	IM-EN-PR43GEN	☐	☐	☐
Instruction Manual for Refractometer PR-43-PC	IM-EN-PR43PC	☐	☐	☐
Appendix to Instruction Manual	IM-EN-PR43VAC	☐	☐	☐
Operating Manual for: _____		☐	☐	☐
Material Safety Data Sheet for Cargille Refractive Index Liquids		☐	☐	☐

Date	Signature	☐ Pass	☐* Conditional Pass	☐ Fail

*Conditional pass: _____

6.5 Operating environment

Description of requirements

Ensuring that the appropriate power supply and power switch are available.

Requirement acceptance values

An electrical power supply with a voltage and frequency of 24 VDC (or 100-240 V AC if required by MI). A computer (PC, Mac, PDA or mainframe).

Failure to meet any of the acceptance values

A new environment must be established and the qualification performed again from **Section 6.3.1** (of this document) onwards.

Date	Signature	☐ Pass	☐* Conditional Pass	☐ Fail

*Conditional pass:

6.6 Installation

Requirement description

The authorized operator who in accordance with **Section 6.2** (of this document), must read the installation instructions in **Section 3** (of this document).

Requirement acceptance values

The relevant sections have been read.

Date	Signature	☐ Pass	☐* Conditional Pass	☐ Fail

*Conditional pass:

6.7 Setting up the system components and devices

Description of requirements

The Pharma Refractometer system with refractometer and Pharma Mini Flow Cell is assembled and mounted correctly as described in the **Section 3** (this document). Also the ancillary sample system is connected in accordance with the **Section 3** (this document). The ancillary equipment is switched on in accordance with the corresponding operating manuals.

Requirement acceptance values

The system and devices are complete and have been set up in compliance with the instructions.

Failure to meet the acceptance values

Terminate the IQ.

Date	Signature	☐ Pass	☐ * Conditional Pass	☐ Fail

*Conditional pass:

6.8 Electrical connections and wiring

Description of requirements

The frequency of the power supply must match the frequency indicated on the instrument's rating plate. The electrical wiring connections have been connected in accordance with the instructions laid down in the Compact User Interface CI instruction manual or Multichannel User Interface MI instruction manual.

Requirement acceptance values

All electrical wiring connections have been connected in compliance with the instructions laid down in the CI/MI instruction manual.

Date	Signature	☐ Pass	☐* Conditional Pass	☐ Fail
*Conditional pass:				

Description of requirements

Ethernet connections have been connected and set up in accordance with the CI/MI instruction manual.

Requirement acceptance values

The Ethernet connections comply with the CI/MI instruction manual.

Date	Signature	☐ Pass	☐* Conditional Pass	☐ Fail
*Conditional pass:				

6.9 Ethernet connection

Description of requirements

Ethernet connections and wiring have been connected and set up in accordance with the CI/MI instruction manual

Requirement acceptance values

The Ethernet connections comply with the CI/MI instruction manual.

Date	Signature	☐ Pass	☐* Conditional Pass	☐ Fail

*Conditional pass:

6.10 Initial check and switching the device on

Description of requirements

The initial check has been performed and the electrical power has been connected in accordance with the CI/MI instruction manual.

Requirement values

The corresponding screen displays occur in accordance with the CI instruction manual Section 3 or MI instruction manual Section 4.

Failure to meet acceptance values

Terminate the IQ.

Date	Signature	☐ Pass	☐* Conditional Pass	☐ Fail

*Conditional pass:

6.11 Installation Qualification summary report

Successful completion of the preceding activities and checks indicates that this instrument has been satisfactorily delivered and installed. This instrument has passed the Installation Qualification and may now be submitted for Operational Qualification.

IQ completed by

Name: _____

Function: _____

Date: _____

Signature: _____

Signature: _____

IQ deviations approved by

Name: _____

Function: _____

Date: _____

Signature: _____

Signature: _____

IQ approved by

Name: _____

Function: _____

Date: _____

Signature: _____

Signature: _____

Comments (including discrepancies)

7 Onsite qualification protocols and records: Operational Qualification

Operational Qualification (OQ) is documented verification stating that the equipment and systems, as installed for the first time or after repairs and major incidents, perform as intended throughout the required operating ranges. The OQ is to ensure that the Pharma Refractometer meets predefined specifications, and all system components function correctly and according to specifications within a specific environment.

7.1 Individual module and system components check

Checking the operation of the refractometer as an individual module, and as a system that comprises also of the Pharma Mini Flow Cell, the computer, the Ethernet connection and Ancillary equipment such as fractionation unit.

- Operational check on the refractometer consists of refractive index n_D accuracy, linearity and short-term repeatability and reproducibility verification tests with Cargille standard refractive index n_D liquids.
- In addition to the system components, testing functional challenge, testing the system software operation, should be conducted.
- Stage by stage operational procedure checking. A pre-determined set of instructions can be input stage by stage into the system. The system responses are then compared to the expected outcome of the instructions to determine any problems in their fulfillment.
- Sign off when successfully completed.

7.2 Installation Qualification has been performed successfully

Description of requirement
An Installation Qualification has been performed for the system.

Requirement acceptance values
The Installation Qualification has been carried out successfully with the required approval.

Date of Installation Qualification: _____

Performed by: _____

Do not proceed with the Operational Qualification until a valid Installation Qualification has been successfully completed and signed off.

7.3 Test procedure

The Operational Qualification of the system is performed in accordance with a set plan in which the following points are tested and documented sequentially:

- The required documents, measuring instruments, refractive index liquids, and required cleaning materials are available
- Functional checks and verification of the refractometer performance
- Functional checks have been made for the ancillary equipment.

The authorized official (client) hereby declares that the performance of the Operational Qualification (OQ) for the Pharma Refractometer and Pharma Mini Flow Cell has been approved in accordance with this document/protocol. The authorized official is responsible for all relevant matters in regard to the operational qualification.

Release by superior department:

_____

Name: _____

Function: _____

Date: _____

Signature: _____

Initials: _____

Authorization by a higher-level authority is a prerequisite for carrying out the qualification procedure. If no valid written authorization is available, terminate the Operational Qualification.

7.4 Authorized officiator

Selection of the individuals authorized to carry out the Operational Qualification of the Pharma Refractometer system should be in accordance with their relevant ability to undertake the procedure. The authorized officiator's signature is required for the next stage to validate Date/Initials in the Operational Qualification log and reports.

Name: _____

Function: _____

Date: _____

Signature: _____

Initials: _____

7.5 System qualification

Check that the system is the same as defined in the IQ, with no changes.

Definition of requirements

All system equipment remains the same as for the IQ and the ancillary equipment IQ is valid.

Date	Signature	☐ Pass	☐ Conditional Pass	☐ Fail
Conditional pass:				

7.6 Setting up the system components and devices

Description of requirements

The Pharma Refractometer system comprised of refractometer, Pharma Mini Flow Cell and Compact User Interface CI or Multichannel User Interface MI, is assembled and mounted correctly as described in the **Section 3** (this document). Initial startup checks for the Refractometer have been made according to PROCESS REFRACTOMETER PR-43 SERIES MANUAL, **Section 4**. Also the ancillary fractionation unit and the sample delivery system (if required) are connected and the ancillary equipment is switched on and functional checks are made in accordance with the corresponding operating manuals.

Requirement acceptance values

The system and devices are complete and have been set up in compliance with the instructions.

Failure to meet any of the acceptance values

Terminate the OQ.

Date	Signature	☐ Pass	☐ Conditional Pass	☐ Fail
Conditional pass:				

7.7 Instrument verification with sample holder and refractive index liquids

Description of requirements
Refractometer, Sample Holder PR-1012 and a set of five standard refractive index liquids PR-2300 with Cargille Certification are allowed to be settled to laboratory ambient temperature (between 20-30 °C, 77-86°F) 24 hours prior to commencement of the qualification.

Requirement acceptance values
Refractometer, sample holder and Refractive index liquids positioned in the laboratory 24 hours prior to verification with the ambient temperature at between 20-30 °C (77-86°F).

Date	Signature	☐ Pass	☐ Conditional Pass	☐ Fail
Conditional pass:				

Description of requirements
The procedure is done with all five liquids using a sample holder and verification instructions at PROCESS REFRACTOMETER PR-43 SERIES MANUAL, **Section 9** (for verification with MI, see also MI manual Section 5).

Nominal R.I. values:
- 1.330
- 1.370
- 1.420
- 1.470
- 1.520

Requirement values
The verification results are OK for all samples and acceptance / deviation values (not more than + 0.0004 of the nominal values) are received for each sample. The Instrument Verification page in the browser for the complete verification test procedure shows **Verification result: pass**.

Failure to meet acceptance values
Terminate the OQ.

Date	Signature	☐ Pass	☐ Conditional Pass	☐ Fail
Conditional pass:				

Date	Signature	☐ Pass	☐ Conditional Pass	☐ Fail

7.8 Operational Qualification summary report

Successful completion of the preceding activities and checks indicates that this instrument performs satisfactorily. The Operational Qualification has been accepted.

OQ completed by

Name: _____

Function: _____

Date: _____

Signature: _____

Signature: _____

OQ deviations approved by

Name: _____

Function: _____

Date: _____

Signature: _____

Signature: _____

OQ approved by

Name: _____

Function: _____

Date: _____

Signature: _____

Signature: _____

Comments (including discrepancies)

8 Routine operation phase

After the instrument is qualified, it can be used to measure analytical data. A Standard Operating Procedure (SOP) has to be written for the new instrument. Operational instructions, maintenance and calibration should be included in the SOP. It is unnecessary to copy the complete operation manual into the SOP. Writing down simple instructions referencing the related manual sections is more effective. The particular tasks and the frequency they should be performed during maintenance should be clearly stated in the maintenance section. Tests required to verify the instrument, the acceptance criteria and the frequency for each test should be covered in the calibration section of the SOP.

Definitions of major and minor repairs, which necessitate partial or full system re-qualification, should be included as well. For example, the replacement of a Teflon pad in the sample mixer does not require a full re-qualification. Replacement of optical parts (prism) will warrant full re-qualification.

Good system maintenance starts with the users. Proper care, which can be as simple as a good system rinsing and clean up after use, will reduce the possibility of system failure during runs and will extend the useful life of the instrument.

Maintain good usage and service records for the instrument for Good Manufacturing Practice (GMP) purposes. Records of usage allow the users to be alerted to any system or instrument calibration failure. The user may have to do an impact assessment to determine whether the failure would have affected the reliability of the results generated by the system. The service records will also provide useful information about the system, which may simplify trouble shooting in some cases.

The GMP requirements dictate that the refractometer calibration verification (see **Section 3.1**) should be performed at suitable intervals in accordance with an established schedule. Any instrument failing to meet established specifications shall not be used. Each Pharma Refractometer is recommended to have a calibration verification label applied with the relevant status information on the system, date of the last calibration verification, who carried out the verification and the scheduled date for the next verification.

9 Preventive maintenance

The need for Pharma Refractometer regular maintenance is minimal, due to the construction with no moving parts, no mechanical adjustments and with a solid-state light source.

The following checks should be performed for Mini Flow Cell at suitable intervals in accordance with an established schedule:

- Check the condition of the O-ring (PR-9244-USP O-ring 22.2x3.0 EPDM) of the Pharma Mini Flow Cell
- Check the condition of the two sanitary gaskets (PR-9236-USP EPDM) of the 0.5” sanitary clamps

10 Other documentation

You may want to include the following documents in your files concerning this Vaisala K-PATENTS instrument:

- Delivery Data Sheet (supplied with the instrument)
- Certificate of Traceability for Standard Refractive Index liquids (supplied with the liquids PR-2300)
- Material Traceability Certificate of Compliance in accordance with EN 1024-3.1b. Note: This document is delivered on request and it must be specified when ordering.
- Vaisala ISO 9001 certificate

Notes

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