IM-EN-PR23AC-VACC-A

Appendix

to PR-23 Instruction Manual for Vaisala K-PATENTS® Products Intended for Use in Vaccine Production

Vaisala K-PATENTS® Pharma Refractometer PR-23-AC

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

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

This instruction manual appendix covers Vaisala K-PATENTS® Pharma Refractometer PR-23-AC 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 internal subviral core of the virus is separated and fractionated on the basis of its' sedimentation rate, and the buoyant sucrose density. Pharma Refractometer PR-23-AC is used for accurate measurement of these sucrose densities. The measurement signal is used for reliable and 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-23-AC 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.

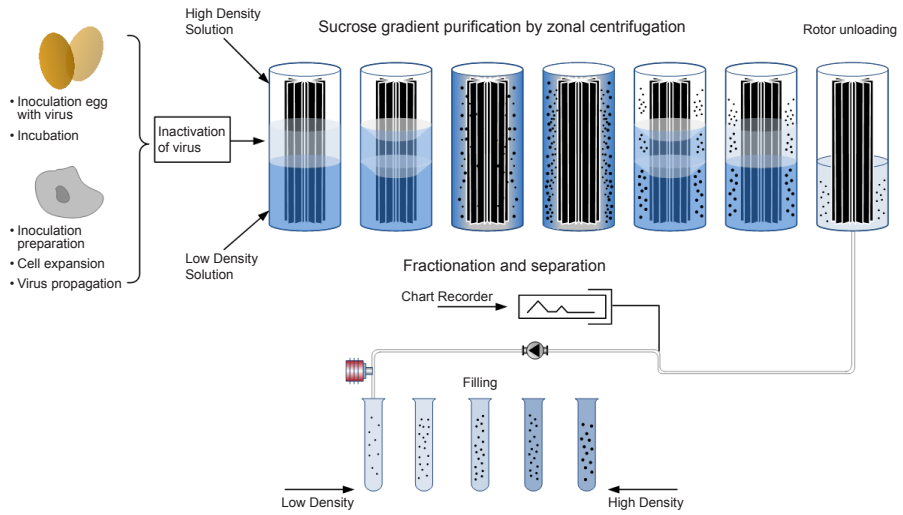

Figure 1.1 Ultracentrifugation density gradient purification process steps.

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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-23-AC 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-23-AC 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 PR-23-AC also meets the 3-A Sanitary Standard and is tested for in-place-cleanability according to the Euopean Hygienic Engineering Design Group (EHEDG) test.

The refractometer has an Ethernet communications solution. The transmitter 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 and padlock protection.

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 sensor is provided with a calibration certificate comparing a set of standard liquids to the actual sensor output. Vaisala verifies the calibration of all delivered instruments according to the procedure similar to the one described in the PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL, **Section 13**.

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 a branch in the U.S.

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-23-AC

2.1 System description

The recommended system for the vaccines production process comprises of a Pharma Refractometer PR-23-AC unit and a Pharma Mini Flow Cell PMFC-HSS that allows the sensor connection to the zonal ultracentrifuge rotor unloading and fractionation phase.

The standard Ethernet communication solution allows for simultaneous data logging and continuous monitoring of the measurement values and diagnostic data from the Indicating Transmitter DTR to a computer via an Ethernet connection.

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2.2 System components

2.2.1 Checklist of components

☐ 1	Pharma Refractometer Sensor PR-23-AC-62-HSS-SC-EP calibrated with raw measurement data refractive index (n_D) and temperature (T)
☐ 2 ☐ 2a	Indicating Transmitter DTR-M/U-GP-SC that calculates and displays the process liquid concentration based on the refractive index and temperature, installed in a stainless steel enclosure that contains a key
☐ 3 ☐ 3a	Table top stand PR-7603-SS for Indicating Transmitter, contains a set of two M5x10 A2 DIN 912 screws
☐ 4	Wall mounting screws kit for mounting the Indicating Transmitter DTR on the wall
☐ 5	Interconnecting cable between transmitter and sensor PR-8230
☐ 6	PR-8820 Crossover cable for Ethernet connection between Indicating Transmitter and computer, length 5 m (16 inch), contains cable gland for enclosure connection
☐ 7 ☐ 7a ☐ 7b	Table top stand PR-7605-SS with an integral support rod and 2.5” Sanitary Clamp for the Pharma Refractometer Sensor PR-23-AC-62-HSS contains a M5x16 A4 DIN 912 screw
☐ 8	Pharma Mini Flow Cell PMFC-HSS
☐ 9	PR-9244-USP O-ring for the Pharma Mini Flow Cell, 22.2x3.0 EPDM
☐ 10	Two sets of PR-9235 0.5” Sanitary Clamp for the Pharma Mini Flow Cell connection
☐ 11	Two sets of PR-9236-USP Sanitary gasket EPDM for the 0.5” Sanitary Clamps
☐ 12	Two sets of PR-9237 0.5” Sanitary ferrule (lenght 1.5 cm) for the inlet and outlet hose connections and Pharma Mini Flow Cell
☐ 13	Universal sample holder PR-1012
☐ 14	R.I. Liquid set PR-2300, consists of Cargille Certificate for the liquids

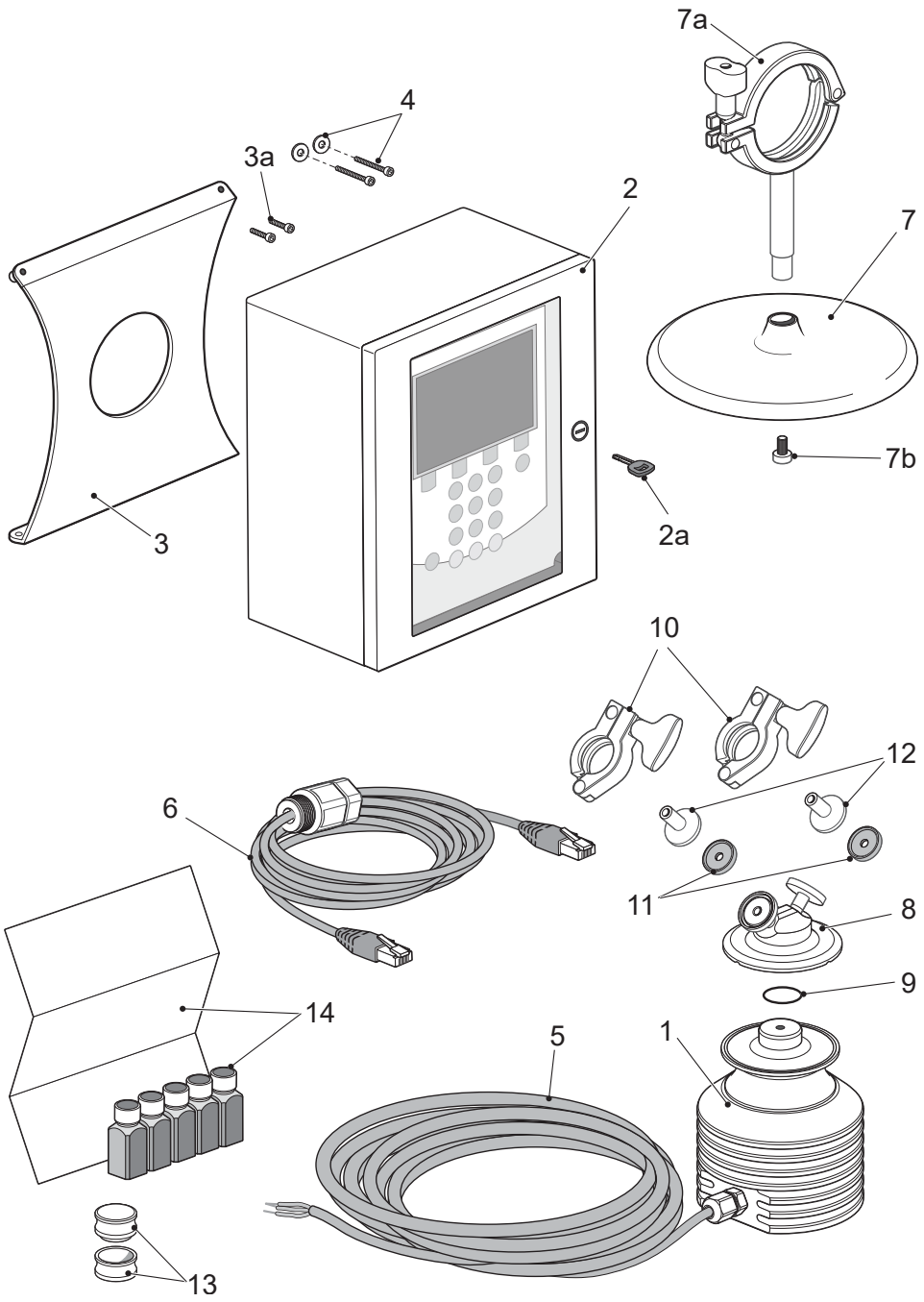

Figure 2.1 System components provided by Vaisala.

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2.3 Pharma Refractometer Sensor PR-23-AC-62-HSS-SC

2.3.1 Sensor model code

Model and Description	Model
PR-23 = Sensor	PR-23
Sensor model	
-A = 3A approved	-A
Sensor type	
C = Compact type for pipe line installation	C
Refractive Index range limits	
-62 = R.I. 1.320....1.530 (0-100 Brix)	-62
Process connection	-SC
-H = Sanitary 3A-clamp, 2 ½ inch	-H
Sensor wetted parts material	
SS = AISI 316 L	SS
Electrical classification	
-GP = General purpose	-GP
-AX = ATEX certified EX II 3 G Eex nA II T4 (up to Zone 2)	-AX
-IA = ATEX and IECEx certified EX II 1 G Ex ia II C T4 Ga (up to Zone 0) (A)	-IA
Sensor housing	
-SC = Stainless steel	-SC
Sensor wetted parts surface treatment option	
-EP = Electropolished process wetted parts (Ra 0.4µm, 15 µ inch)	-EP

(A) Available with STR- Indicating Transmitter and IS Isolator only

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 0.4µm, 15 µ inch and EPDM (ethylene propylene diene monomer) for the O-ring sealing.

Model and Description	Model
PMFC = Pharma Mini Flow Cell	PMFC
Sensor 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 0.4µm, 15 µ inch)	-EP

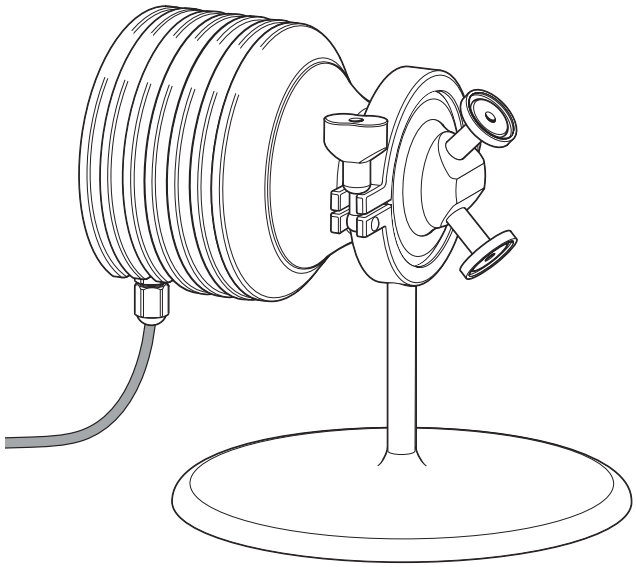

Figure 2.2 Pharma Refractometer PR-23-AC-62-HSS-EP sensor and Pharma Mini Flow Cell PMFC-HSS-EP with PR-7605-SS table top stand.

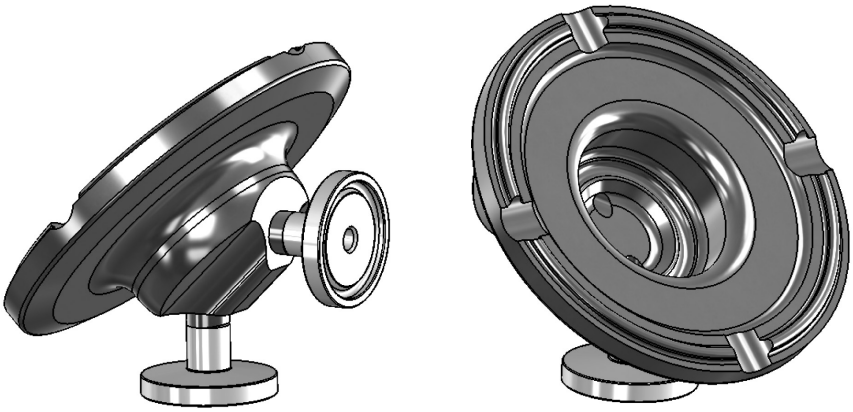

Figure 2.3 Pharma Mini Flow Cell PMFC-HSS-EP.

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2.4 Indicating Transmitter DTR-GP-SC

Indicating Transmitter DTR is a specialized computer designed to process data received from the refractometer sensor. Indicating Transmitter (Figure 2.4) contains a front panel with a backlit Liquid Crystal Display (LCD) and a keyboard. A lock and a key are included in the enclosure's door to prevent unauthorized access. Please note that neither any power cables nor any external power switches are included in the standard delivery.

Materials for the Pharma Indicating Transmitter Enclosure DTR-M/U-GP-SC are: Stainless steel enclosure and polycarbonate window.

2.4.1 Indicating Transmitter model code

Model and Description	Model
DTR = Indicating Transmitter (connectivity for two sensors) STR = Indicating Transmitter (connectivity for one –IA/-IE sensor)	DTR STR
Cable connection	
-U = ½ inch NPT-type conduit hubs	-U
-M = M20x1,5 metric cable glands	-M
Electrical classification	
-GP = General purpose	-GP
Enclosure	
-SC = Stainless Steel enclosure with window	-SC
Transmitter options (A) (leave this section blank, if AC supply is specified)	
-AC = Power supply 100-240 VAC 50/60 Hz	-AC
-DC = Power supply 24 V DC	-DC
(A) Note standard power supply is 100-240 VAC 50/60 Hz	

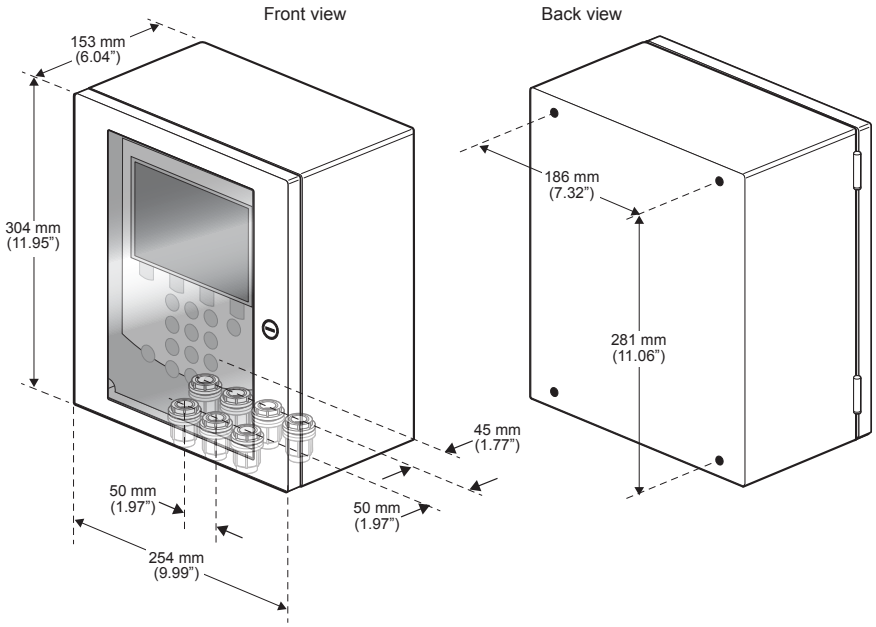

Figure 2.4 Indicating Transmitter DTR-GP-SC with Stainless steel enclosure; dimensions (mm/in).

2.5 Pharma vaccines accessories

Vaisala recommended accessories for the vaccines production application contain Ethernet crossover cable, IQ and OQ documentation (this document) and parts for verification and usage of Pharma Refractometer sensor and Indicating Transmitter mounted on a table top or a trolley via metal support stands. **The recommended accessories and corresponding part numbers are**:

- **PR-7603-SS Table top stand** for Indicating Transmitter (contains a set of two M5x10 A2 DIN screws)
- **PR-7605-SS Table top stand** with the intregral support rod and 2.5" Sanitary Clamp for the Pharma Refractometer Sensor PR-23-AC (contains a screw)
- **PR-8820 Crossover cable** for Ethernet connection between Indicating Transmitter and computer, length 5 m (16 feet)
- **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-PR23AC-VACC** IQ and OQ Documentation for Equipment qualification

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3 Installation of PR-23 Pharma Refractometer

3.1 Hardware and software requirements

PR-23 software is included in the Indicating Transmitter DTR and it comprises the following functions:

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

3.2 Mechanical and electrical requirements

Power supply for the refractometer is AC input 100-240 VAC/50-60 Hz, optional 24 VDC, 30 VA.

3.3 Sensor 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: 100-240 VAC/50-60 Hz (optional 24 VDC, 30 VA) electrical power supply and computer network connection.

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Attaching table top stand PR-7605-SS for Sensor 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 sensor 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 connectios using the two PR-9235 0.5” Sanitary Clamps.

Sensor can now be connected to flexible hoses and used as a free standing tabletop unit, see Figure 3.3.

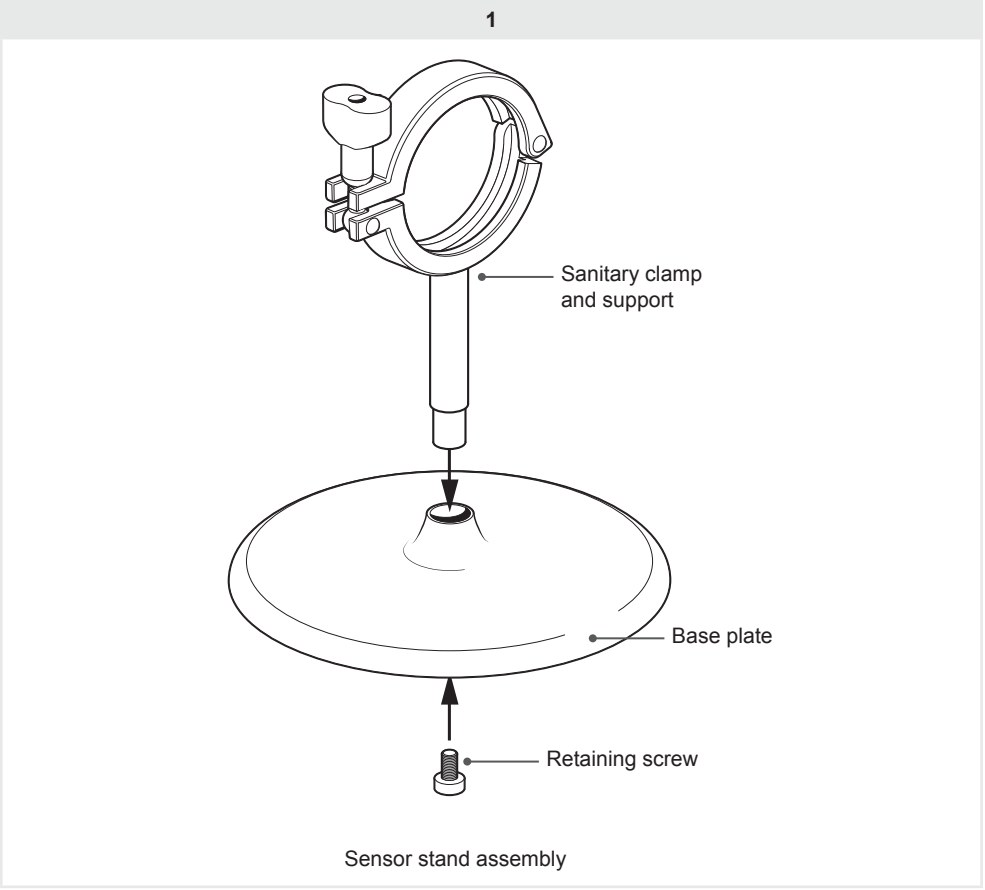

Figure 3.1 Sensor stand assembly: Attaching the clamp and support rod to the base plate.

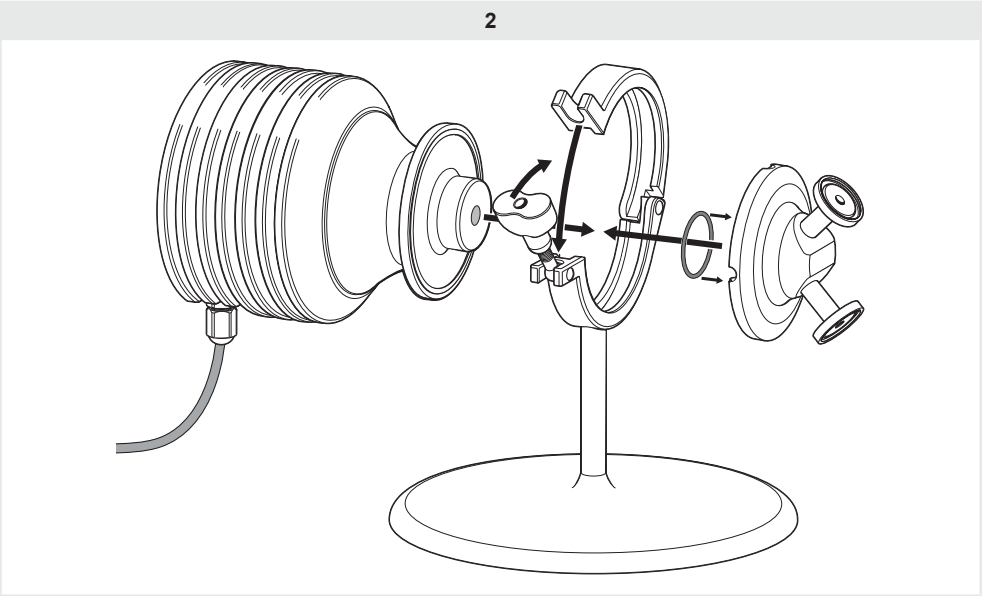

Figure 3.2 Sensor stand assembly: Installing the sensor and Mini Flow Cell to the stand.

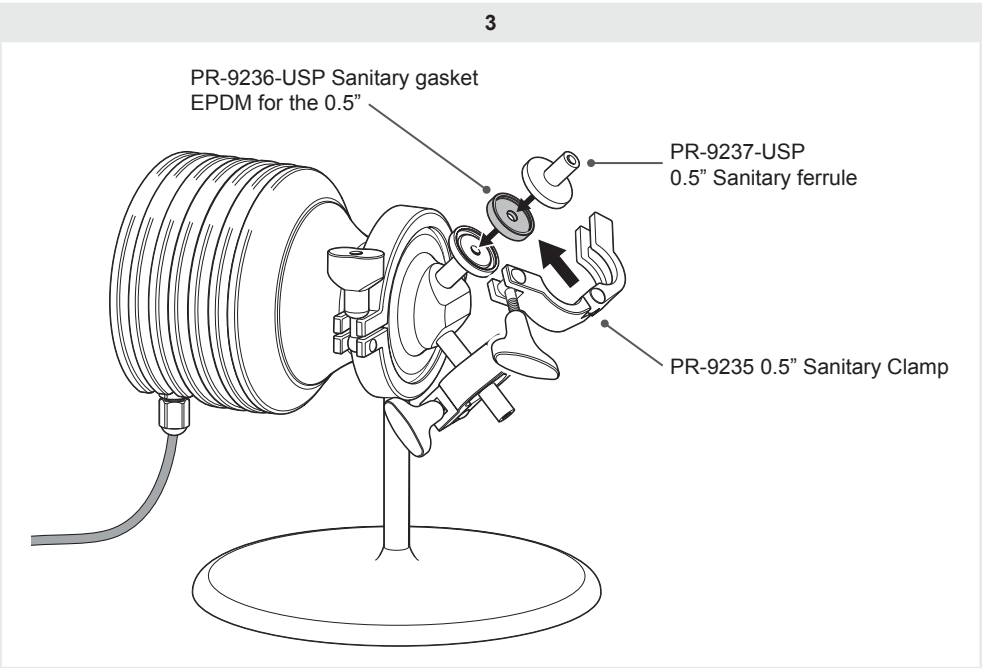

Figure 3.3 Sensor assembly: Attaching the ferrules for the feed pipes.

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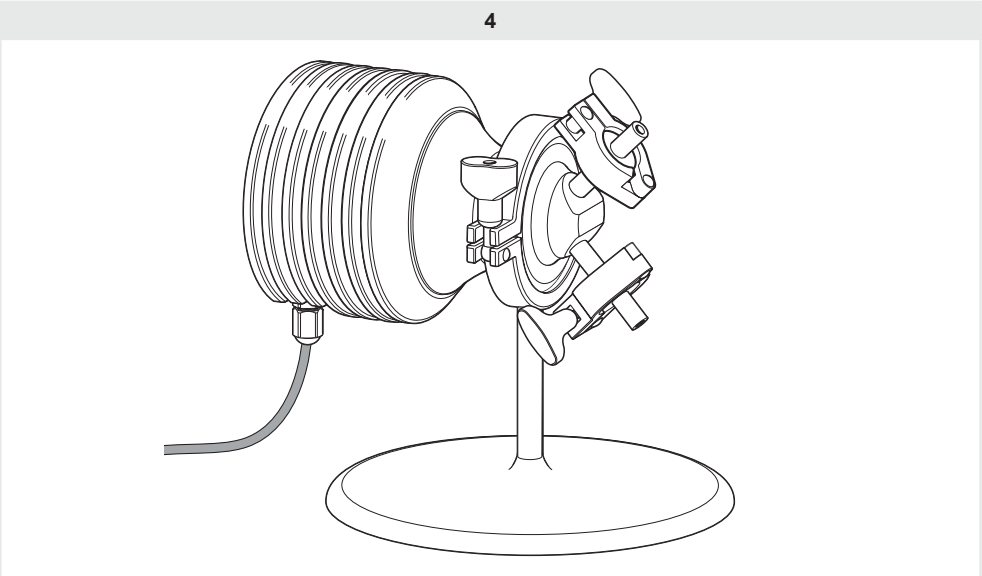

Figure 3.4 Sensor stand assembled.

3.4 Indicating Transmitter installation for use in table top

Attaching table top stand PR-7603-SS for Indicating Transmitter

Unlock and open the transmitter cabinet door, then unscrew the retaining screw for the keypad panel and open the panel. The supplied screws (M5x10 A2 DIN 912) for attaching the stand are inserted from the inside through the top two holes located at the back of the cabinet. These are aligned and screwed into the threaded attachment points located at the top of the stand. The enclosure can now be used as a free standing tabletop unit, see Figure 3.2.

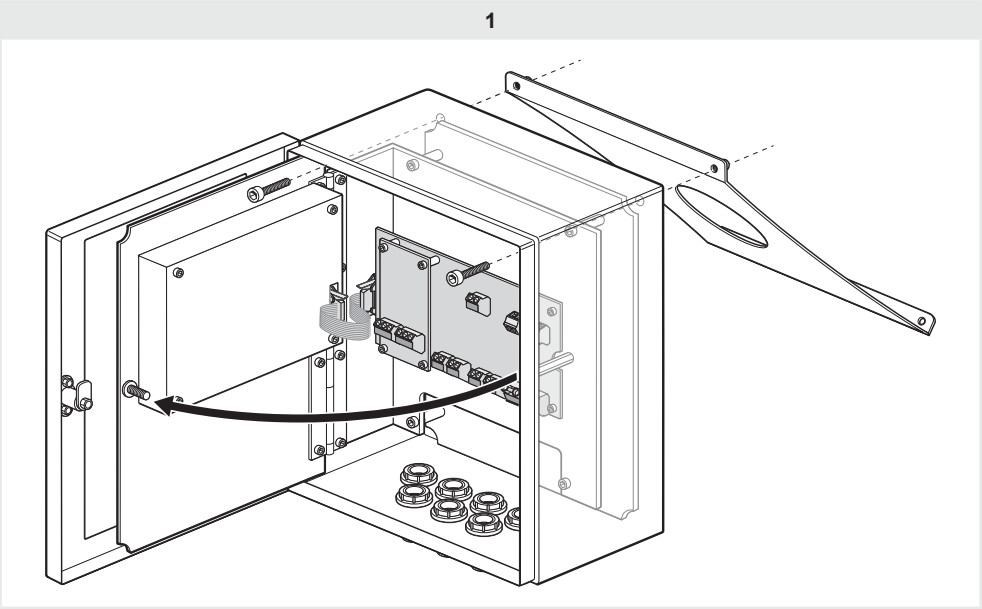

Figure 3.5 Attaching the laboratory table top stand to the Transmitter for use in the laboratory.

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3.5 Wiring transmitter connections to sensor, power cable and computer

For Indicating Transmitter DTR wiring and Ethernet connections instructions see PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL, **Section 3** and **Section 12**. When the wiring connections have been made sensor calibration and verification can commence.

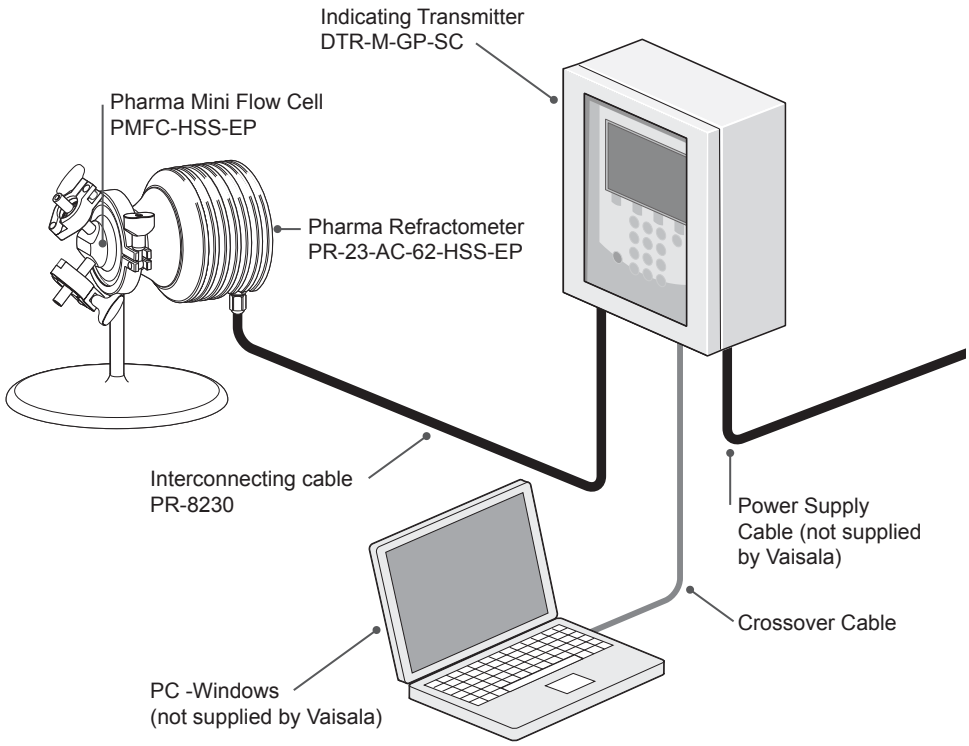

Figure 3.6 Connection diagram

3.6 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 sensor wetted surfaces and the sample holder.

For full Sensor verification instructions see PROCESS REFRACTOMETER PR-23, INSTRUCTION MANUAL **Section 13**.

After verification of the PR-23 sensor, further verification of the Laboratory Test Cuvette and Sensor combination can be carried out.

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4 Electronic data capture and storage

4.1 Ethernet connection

In addition to software operation via the hardware, the DTR 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 an Indicating Transmitter DTR to a computer and replaces the traditional paper-based data collection methods and streamlines data collection. The connection works both directly between the DTR and a computer, or via a hub or a switch, local area network (LAN), wireless network (WLAN) or fiber Ethernet. Any type of computer (PC, Mac, PDA, mainframe…) with a compatible network connection can be configured to download data from the DTR.

For connecting and operating instructions of the Ethernet connection see PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL **Section 12**.

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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.

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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 using the lock on the Indicating Transmitter door and password protected access to the transmitter and to the computer. There are also four input switches behind the front panel of Indicating Transmitter. An input switch can be configured to seal the calibration and to prevent access to the calibration and to configuration, see PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL, Section 6.4.

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.

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6 Onsite qualification protocols and records: Installation Qualification

This Installation Qualification (IQ) involves documented verification of the complete system: Pharma Refractometer PR-23-AC and Pharma Mini Flow Cell PMFC-HSS with 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.

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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 Sensor and Pharma Mini Flow Cell:

_____

Location of the Indicating Transmitter: _____

Device	Serial Number	Supplier	Manufacturer
Pharma Refractometer: Sensor PR-23-AC-62-HSS			Vaisala Oyj
Pharma Refractometer: Indicating Transmitter DTR-M/U-GP-SC			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:				

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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 Inline Refractometer PR-23(-...-AX/FM/CS/IA/IF)	IM-EN-PR23	☐	☐	☐
Appendix to Instruction Manual	IM-EN-PR23AC-VACC-A	☐	☐	☐
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 100-230 VAC/50-60 Hz (Optional 24 VDC). 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:

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6.7 Setting up the system components and devices

Description of requirements

The Pharma Refractometer system with Refractometer sensor, Pharma Mini Flow Cell and Indicating Transmitter, are 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 PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL **Section 12**.

Requirement acceptance values

All electrical wiring connections have been connected in compliance with the instructions laid down in the PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL **Section 12**.

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

Description of requirements

Ethernet connections and wiring have been connected and set up in accordance with the PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL **Section 12**.

Requirement acceptance values

The Ethernet connections comply with the PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL **Section 12**.

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

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6.9 Ethernet connection

Description of requirements
Ethernet connections and wiring have been connected and set up in accordance with the PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL **Section 12**.

Requirement acceptance values
The Ethernet connections comply with the PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL **Section 12**.

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 PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL **Section 5.1.1**.

Requirement values
The corresponding screen displays occur in accordance with the PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL **Section 5.1.1**.

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: _____

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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.

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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 sensor, Pharma Mini Flow Cell and Indicating Transmitter, 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-23 INSTRUCTION MANUAL, **Section 5**. 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:				

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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-23 INSTRUCTION MANUAL, **Section 13**.

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:				

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: _____

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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.

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9 Preventive maintenance

The need for Pharma Refractometer regular maintenance is minimal, due to the construction with no moving parts, no mechanical adjustments, no trimpots and with a solid-state light source, see **Section 7,** PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL.

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

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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

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Notes

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