

## Appendix to the Instructions Manual PR-23 for K-Patents Products Intended for use in the Pharmaceuticals Industry

K-Patents Pharma Refractometer PR-23-AC  
and Laboratory Test Cuvette LTC



## 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



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# 1

## K-Patents Products for the Pharmaceutical Industry

This Instruction Manual Appendix covers K-Patents Pharma Refractometer PR-23-AC, and the Laboratory test cuvette LTC. Using these allows accurate measurements of liquid concentration to be obtained in compliance with pharmaceutical industry requirements. Validation of an analytical method is the process, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications. The Laboratory test cuvette LTC is designed as an additional off-line testing and validation tool for use with the Pharma Refractometer PR-23-AC.

Qualification is a subset of the validation process that verifies the Pharma Refractometer instrument performance before it is placed in-line in a regulated environment (Figure 1.1). System suitability tests are used to verify that the accuracy, repeatability and reproducibility of the refractometer are adequate for the analysis to be performed. After all qualification checks have been performed and the required validation standards have been met, the Pharma Refractometer can then be installed in the production process for in-process control.

DESIGN QUALIFICATION	INSTALLATION QUALIFICATION	OPERATIONAL QUALIFICATION	PERFORMANCE QUALIFICATION
<b>TIMING AND APPLICABILITY</b>			
Prior to purchase of a new model of instrument	At installation of each instrument (new, old or existing unqualified)	After installation or major repair of each instrument	Periodically at specified intervals for each instrument
<b>EXAMPLE ACTIVITIES</b>			
Assurance of manufacturer's DQ	Description	↔ Fixed parameters	Preventive maintenance and repairs
Assurance of adequate support availability from manufacturer	Instrument delivery (Instrument, manuals etc.)	Verify calibration and accuracy Validation	Establish practices to address operation, calibration, maintenance and change control
Preliminary instrument performance valuation (fitness for purpose)	Utilities/Facility (are prerequisites met?)	↔ Environment	
	Assembly and installation Network and data storage	← Secure data storage, → back-up and archive	
	Installation verification (initial testing after installation before operational qualification)	↔ Instrument function test ↔ Performance checks	

**Figure 1.1** Qualification process steps.

## 1.1 Design Qualification

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

K-Patents 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. K-Patents Pharma Refractometer PR-23-AC fulfills the pharmaceutical drug production regulations for process wetted part materials, sealing, and surface roughness. No animal originated media are used in the machining and polishing processes. The model PR-23-AC meets the 3-A Sanitary Standard requirements and is EHEDG (European Hygienic Equipment Design Group) tested.

The K-Patents 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 refractometer generated measurement and diagnostic data for storage, analysis and reporting. K-Patents provides a software package for data downloading. Full software specifications are freely available to users who wish to develop their own communications program. Access to the refractometer and the generated data can be restricted to authorized personnel using password and padlock protection.

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. K-Patents verifies the calibration of all delivered instruments according to a procedure similar to the one described in the PROCESS REFRACTOMETER P2-23 INSTRUCTION MANUAL, **Section 13**.

K-Patents 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.

K-Patents has an ISO 9001 certified quality system, which covers all its functions. 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 K-Patents 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.

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 also by the headquarters in Finland and the branch in the U.S.

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



# The Pharma Refractometer PR-23-AC with Laboratory Test Cuvette LTC

## 2.1 System description

The system comprises of a Pharma Refractometer PR-23-AC unit, a Laboratory Test Cuvette LTC, a computer for data logging and a microprocessor controlled thermostat. A thermostatic water bath is used to accurate and reliable temperature regulation of the liquid sample concentration in the Laboratory Test Cuvette during the off-line laboratory measurements. With this temperature control system the temperature of the Lab Test Cuvette test sample can be accurately adjusted and maintained.

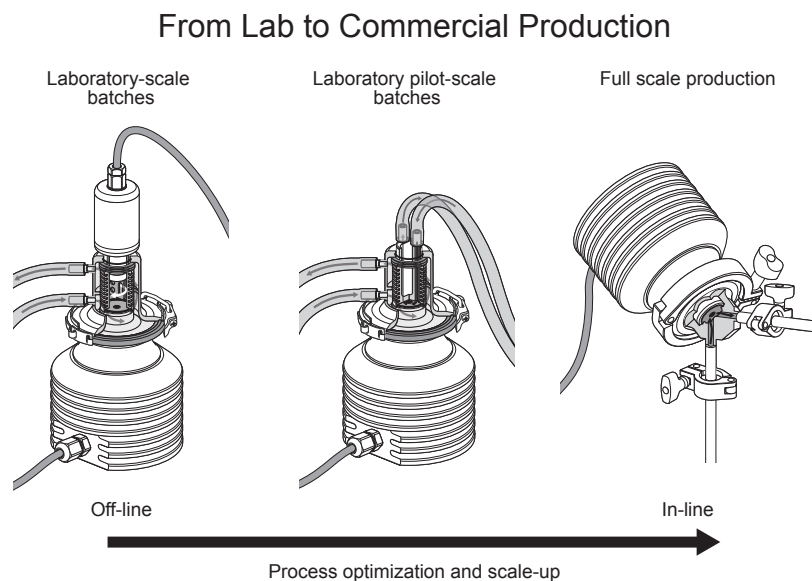
## 2.2 Use of Laboratory Test Cuvette for validation and sample testing

Any significant change in a process of making a pharmaceutical product is a regulatory concern. Postapproval changes in the size of a batch from the pilot scale to larger or smaller production scales call for submission of additional information in the application to the Food and Drug Administration (FDA), with a specific requirement that the new batches are to be produced using similar test equipment and in full compliance with GMPs and the existing SOPs.

Manufacturing changes may also require new stability and dissolution testing. This is especially true for equipment changes (change to equipment of a different design and different operating principles) and the process changes (e.g. in mixing times and operating speeds). The Laboratory Test Cuvette LTC with static sample feature can be used to further study the sample characteristics. For instance the concentrations of the samples can be tested in varied conditions, e.g. in accelerated, elevated temperature tests.

Also, the preparation of the laboratory pilot batch is required many times as an intermediate step in a scale-up process. The Laboratory Test Cuvette LTC with the continuous sampling feature is designed for testing samples in a laboratory pilot batch.

The benefit of K-Patents Pharma Refractometer with the Laboratory Test Cuvette is that it allows the use of the same equipment in all test faces as well as in the full scale on-process stage (see Figure 2.1).



**Figure 2.1** Test and validation equipment from laboratory to commercial production.

## 2.3 System components provided by K-Patents

### 2.3.1 Checklist of components

- |                              |  |
|------------------------------|--|
| <input type="checkbox"/> 1   | Pharma Refractometer PR-23-AC-62-HSS calibrated with raw measurement data refractive index (nD) and temperature (T)  |
| <input type="checkbox"/> 2   | 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 |
| <input type="checkbox"/> 2a  |  |
| <input type="checkbox"/> 3   | Table top stand PR-7603-SS for Indicating transmitter, contains a set of two M5x10 A2 DIN 912 screws   |
| <input type="checkbox"/> 3a  |  |
| <input type="checkbox"/> 4   | Wall mounting screws kit for mounting the Indicating transmitter DTR on the wall   |
| <input type="checkbox"/> 5   | Interconnecting cable between transmitter and sensor PR-8230   |
| <input type="checkbox"/> 6   | PR-8820 Crossover cable for Ethernet connection between Indicating transmitter and computer, length 5 m (16 inch), contains cable gland for enclosure connection   |
| <input type="checkbox"/> 7   | Outer casing of Laboratory Test Cuvette LTC-HSS  |
| <input type="checkbox"/> 8   | PR-9254 O-ring, 21x2 EPDM  |
| <input type="checkbox"/> 9   | Compression spring   |
| <input type="checkbox"/> 10  | Sample chamber, static sampling  |
| <input type="checkbox"/> 11  | PR-9253 O-ring, 20.2x3 EPDM  |
| <input type="checkbox"/> 12  | Sample chamber, continuous sampling  |
| <input type="checkbox"/> 13  | 2.5" EPDM sanitary gasket  |
| <input type="checkbox"/> 14a | 2.5" Sanitary Clamp for the Laboratory Test Cuvette  |
| <input type="checkbox"/> 14b |  |
| <input type="checkbox"/> 15  | PR-12151 Sample mixer  |
| <input type="checkbox"/> 16  | PR-12152 Mixer paddles, set includes 2 paddles   |
| <input type="checkbox"/> 17  | PR-10956 Universal power adapter for Sample mixer  |
| <input type="checkbox"/> 18  | Sample holder PR-1012  |
| <input type="checkbox"/> 19  | R.I. Liquid set PR-2300, consists of Cargille Certificate for the liquids  |
| <input type="checkbox"/> 20  | Memory stick with PR-23 Toolkit program PR-8890 (a standalone software that allows data logging via a cross-over Ethernet cable)   |

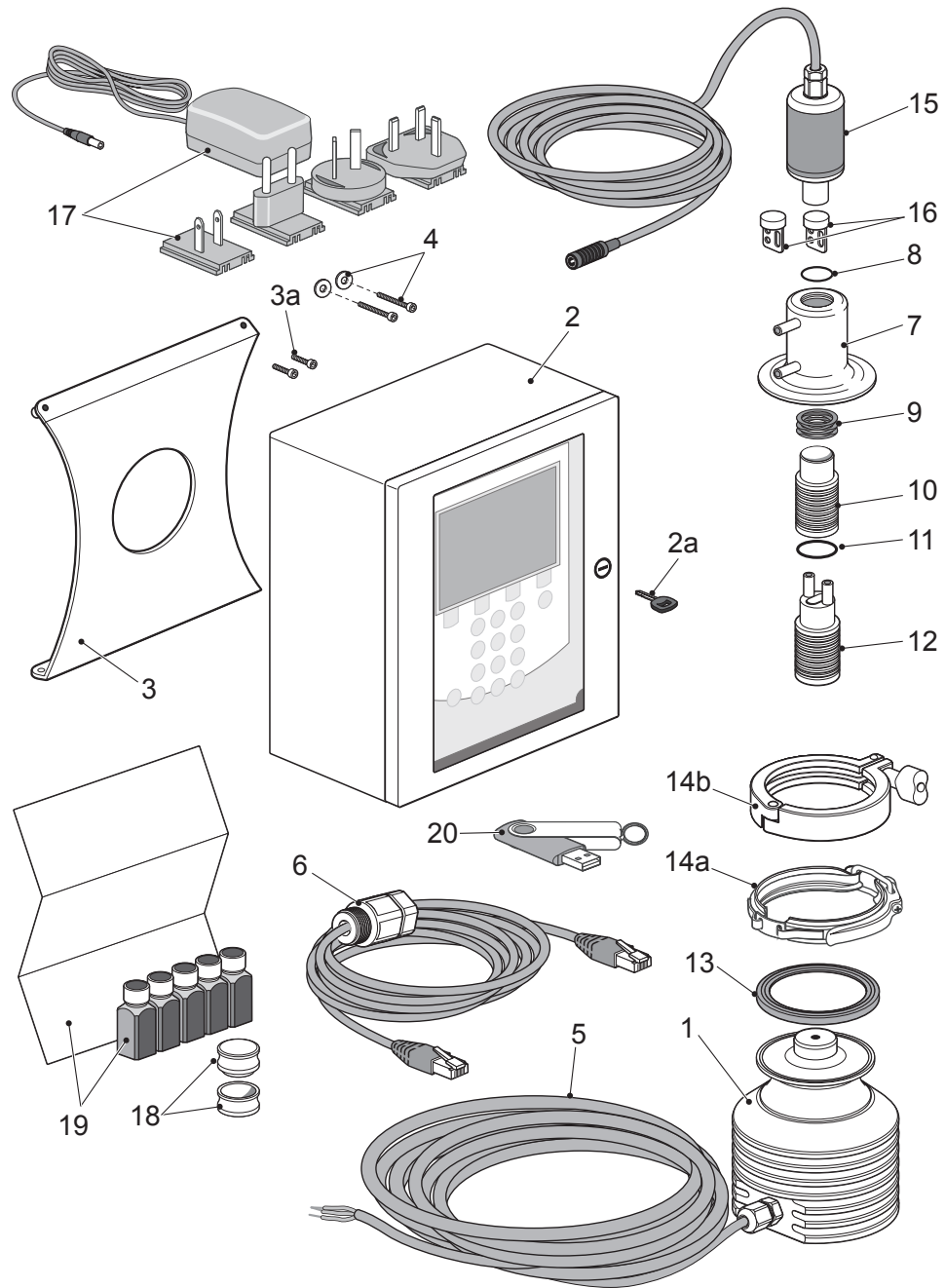


Figure 2.2 System hardware and software components provided by K-Patents.

## 2.4 Pharma validation package

Pharma validation package PR-12150 contains parts for usage of K-Patents Pharma Refractometer for off-line testing and validation in a laboratory.

### 2.4.1 Model code

**PR-12150 Pharma validation package**, consisting of:

- **R-7603-SS Table top stand** for Indicating transmitter (contains a set of two M5x10 A2 DIN screws)
- **PR-8820 Crossover cable** for Ethernet connection between Indicating transmitter and computer, length 5 m (16 inch)
- **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
- **USB Memory stick** with PR-23 Toolkit program PR-8890 (a standalone software that allows data logging via a cross-over Ethernet cable)
- **IM-GB-PR23-ACP** IQ and OQ Documentation for Equipment qualification

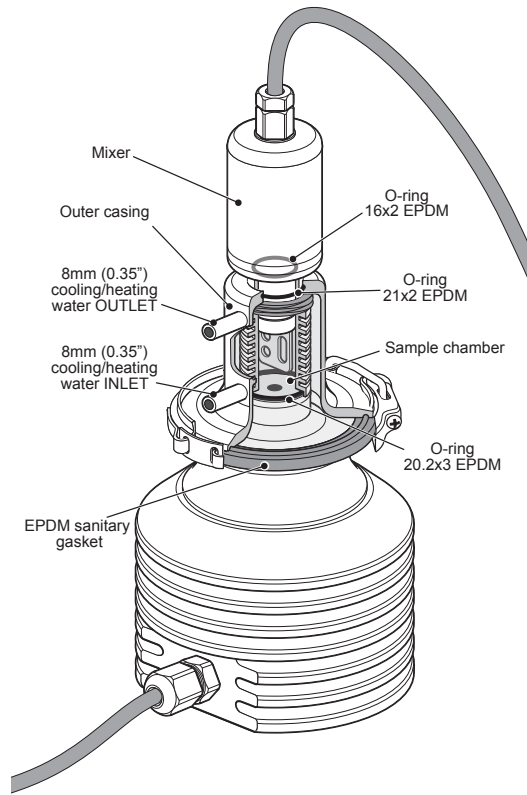
## 2.5 Laboratory Test Cuvette LTC

K-Patents Laboratory Test Cuvette LTC is designed for off-line testing of Pharma Refractometer PR-23-AC in a laboratory in making small quantities of the drug. The Laboratory Test Cuvette contains parts for static sampling (Figure 2.3) and continuous sampling (Figure 2.4).

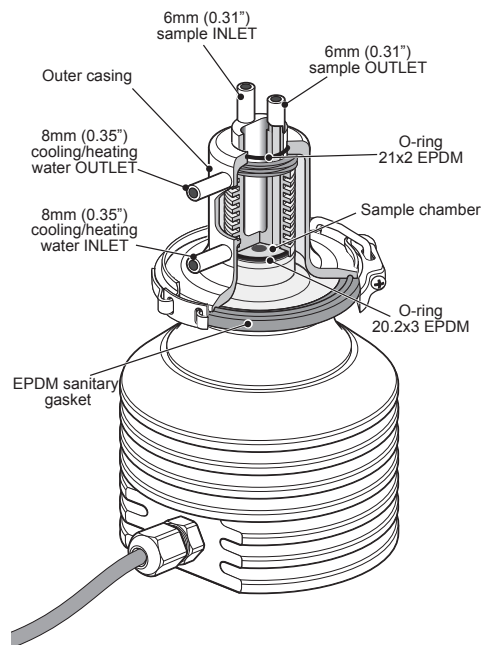
Materials for wetted parts on the Laboratory Test Cuvette LTC are: PVDF, 316L Stainless steel, Viton, and EPDM. Materials for wetted parts of the PR-23-AC-62-HSS sensor are: 316L Stainless steel, PTFE Teflon and Sapphire.

### 2.5.1 Model code

Model and Description	Part No.
LTC = Laboratory Test Cuvette	LTC
<b>Sensor connection</b>	
-H = Sanitary 3A-clamp, 2 ½ inch	-H
<b>Material of Construction</b>	
SS = AISI 316	SS



**Figure 2.3** Pharma Refractometer PR-23-AC-62-HSS sensor with Laboratory Cuvette LTC for static sampling; dimensions (mm/in).



**Figure 2.4** Pharma Refractometer PR-23-AC-62-HSS sensor with Laboratory Cuvette LTC for continuous sampling; dimensions (mm/in).

## 2.6 Indicating Transmitter DTR-GP-SC

The Indicating transmitter DTR is a specialized computer designed to process data received from one or two refractometer sensors. The Indicating transmitter (Figure 2.5) 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.

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

### 2.6.1 Model code

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

(A) Note standard power supply is 100-240 VAC 50/60 Hz

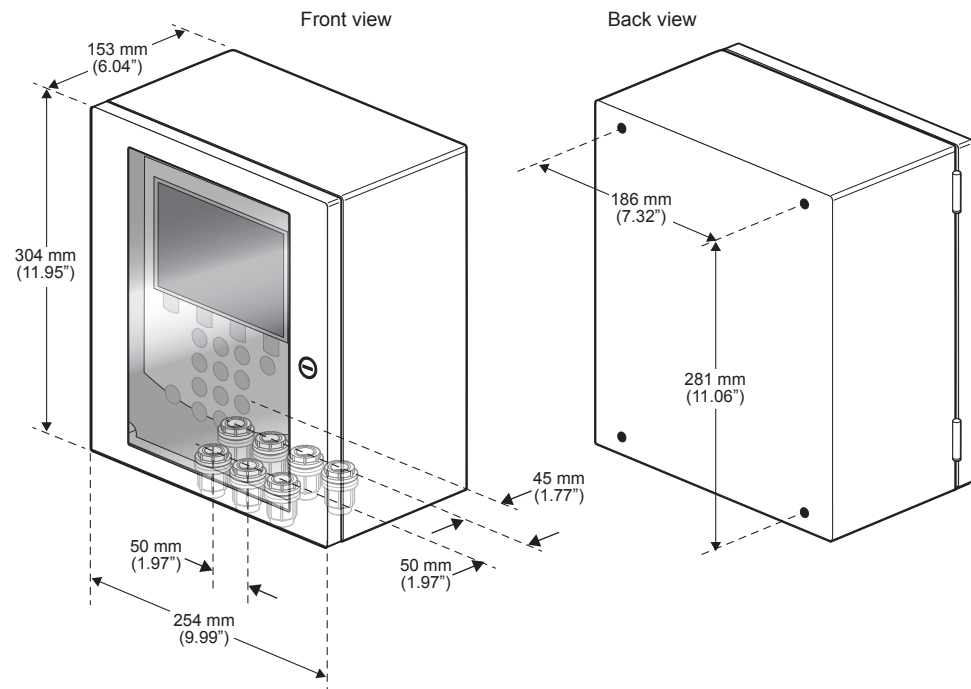
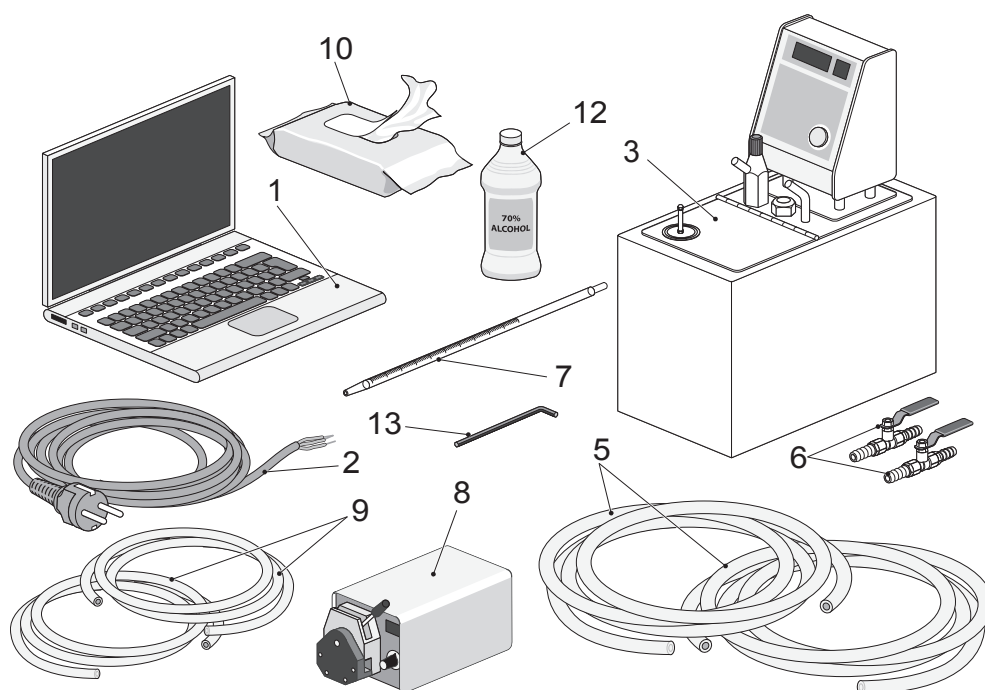


Figure 2.5 Indicating transmitter DTR-GP-SC with Stainless steel enclosure; dimensions (mm/in).

## 2.7 Ancillary equipment and materials required, but not supplied by K-Patents

- |                             |   |
|-----------------------------|---|
| <input type="checkbox"/> 1  | Any type of computer (PC, Mac, PDA, or mainframe)   |
| <input type="checkbox"/> 2  | Power cables, Optional: External power switches   |
| <input type="checkbox"/> 3  | Thermostatic bath and closed-looped circulator for precise temperature control of samples   |
| <input type="checkbox"/> 4  | Cooling water or non-aqueous cooling/heating fluid (silicon and other oil, glycol mixture, etc.).   |
| <input type="checkbox"/> 5  | Water hoses (inner dia. 8 mm/0.3 inch) to connect LTC to thermostatic bath.<br>Optional: Ball valves with hose fittings at both ends for opening and closing the water supplies to the laboratory cuvette between the cleansing and test sessions |
| <input type="checkbox"/> 6  | Optional: 2 Ball valves for shutting off thermostatic fluid flow  |
| <input type="checkbox"/> 7  | Pipettes for static sampling  |
| <input type="checkbox"/> 8  | Continuous sample delivery system with sample delivery pump or peristaltic pump for sucking the sample  |
| <input type="checkbox"/> 9  | ID 6 mm (0.23 inch) sampling hose between continuous sampling LTC and test supply system  |
| <input type="checkbox"/> 10 | Cleaning tissue   |
| <input type="checkbox"/> 11 | Optional: Distilled water   |
| <input type="checkbox"/> 12 | Cleaning agent, e.g. Isopropyl Alcohol (IPA)  |
| <input type="checkbox"/> 13 | DIN 911 Long arm hexagon key (N:o 4) for opening and closing the socket screws of DTR support   |



**Figure 2.6** Ancillary equipment and materials required, but not supplied by K-Patents.

## 2.8 Hardware and Software Requirements

PR-23 software is included in the Indicating Transmitter DTR and it includes:

- Automatic temperature compensation
- Sensor diagnostics and verification

In addition to software operation via the hardware, the DTR can be considered a web server and is accessible via web-browser (e.g. Internet Explorer, Mozilla, Firefox etc.). The Ethernet connection enables data download from an Indicating transmitter DTR to a computer. The connection works both directly between DTR and computer, or via a hub or 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. See PROCESS REFRACTOMETER INSTRUCTION MANUAL, **Section 12** for detailed instructions.

## 2.9 Mechanical and Electrical Requirements

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

## 2.10 Sensor installation and system connections

### Laboratory installation and key considerations for the site preparation

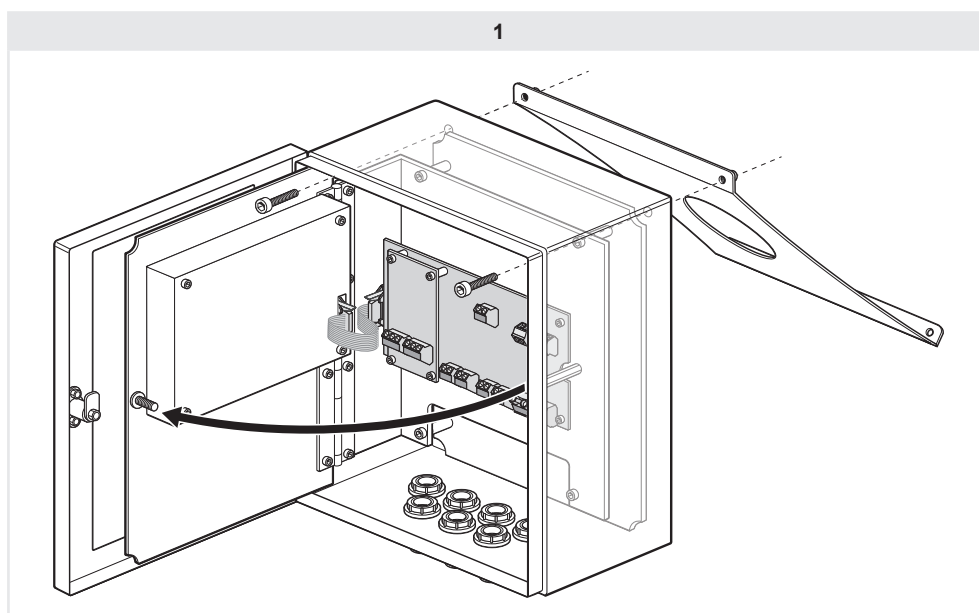
1. Physical dimensions of the instrument and accessories: Make sure there is enough space to accommodate them.
2. Suitable recommended operational environment for the instrument and for the Cargille Refractive Index Liquids should be maintained between 20 – 30 °C (68 – 86°F).
3. Utilities: 100-240 VAC/50-60 Hz (optional 24 VDC, 30 VA) electrical power supply, computer network connection, fume hood if required and water supply.



## 2.11 Indicating Transmitter DTR assembly for use in Laboratory

### Attaching laboratory stand to DTR

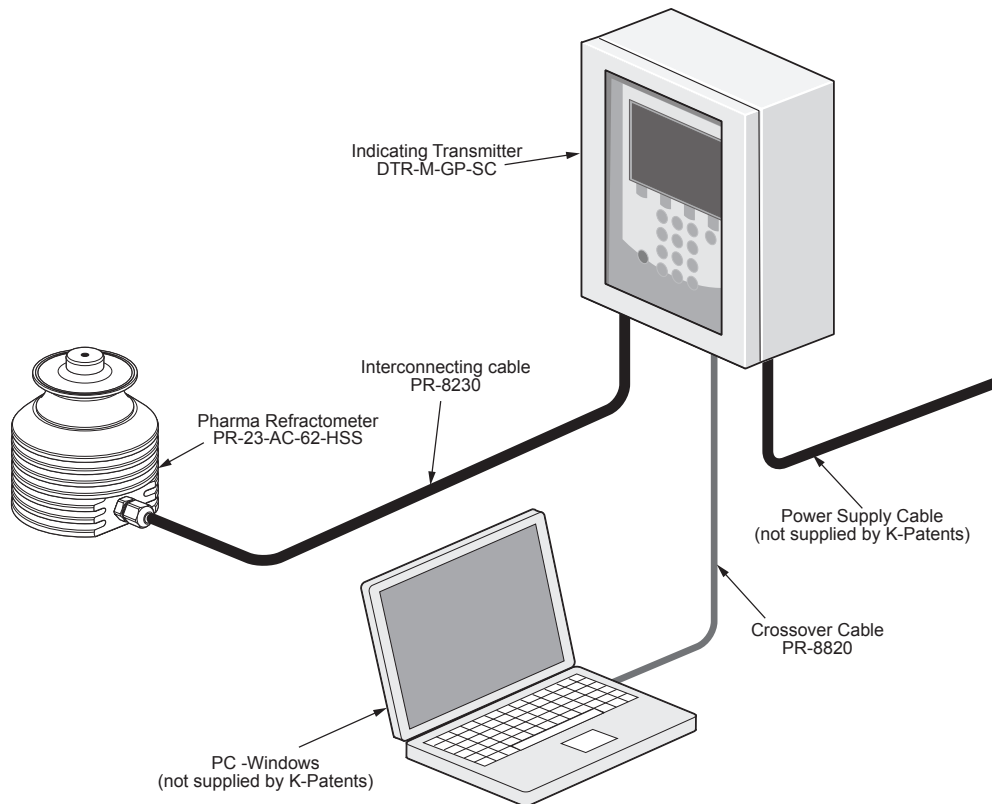
Unlock and open the DTR cabinet door, then unscrew the retaining screw for the keypad panel and open the panel. The supplied screws (M5x10 A2 DIN 912) for attaching the stand are inserted from the inside through the top two holes located at the back of the cabinet. These are aligned and screwed into 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 2.7.



**Figure 2.7** Attaching the laboratory table top stand to the Transmitter for use in the laboratory.

## 2.12 Wiring connections of transmitter 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 2.8** Connection diagram for sensor calibration verification.

# 3

## Use of PR-23 Pharma Refractometer with Laboratory Test Cuvette LTC: Static Sampling

### 3.1 Refractometer Instrument verification

The operational procedure checking the refractometer calibration's 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 K-Patents 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 should be performed once every 6 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 K-Patents. 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 in 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.

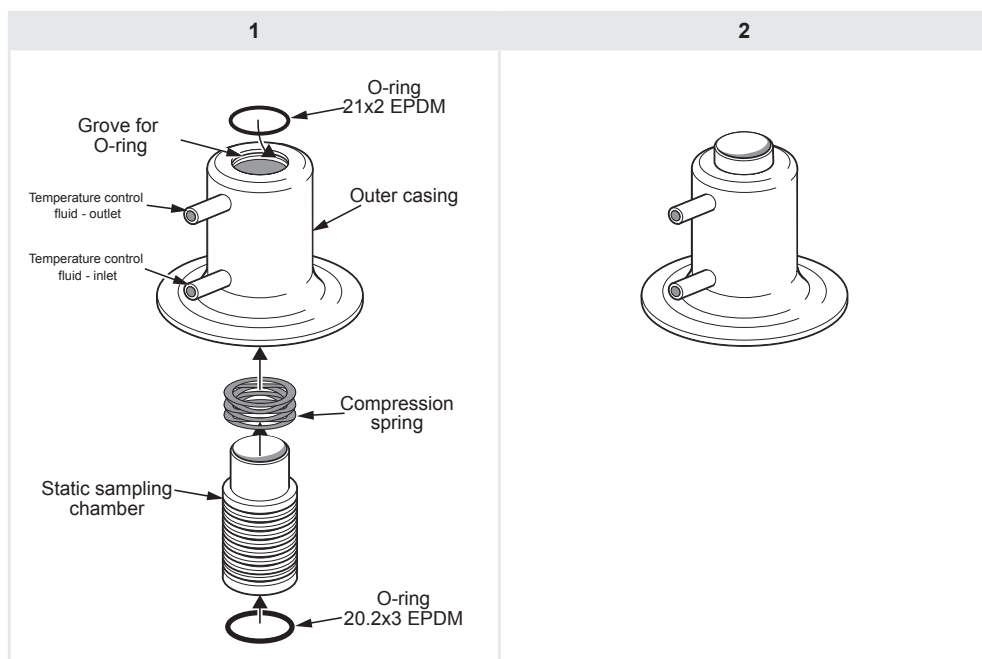
## 3.2 Laboratory Test Cuvette: Static sampling

The Laboratory Test Cuvette (LTC) for static sampling has a sample chamber accommodating a mixer. The LTC mixer has a 12 VDC geared electrical motor that rotates the PVDF mixer paddle via a magnetic link. Magnetic drive is used for ease of cleaning and reliability. The LTC mixer is supplied with a 100-240 VAC universal power supply equipped with a plug which has interchangeable connecting prongs.

The LTC sample chamber consists of two main components, an inner sample chamber and a cooling/heating jacket. Temperature regulated fluid flows through the water jacket to circulate around the sample chamber and refractometer sensor head. This system avoids any contamination of the sample by the temperature regulating fluid. There are machined fins around the outside of the Sample chamber to facilitate effective thermal transfer between the fluid in the water jacket and the liquid sample. There is also a compression spring to keep the sample chamber tight to the sensor head.

## 3.3 Assembly of Laboratory Test Cuvette: Static sampling

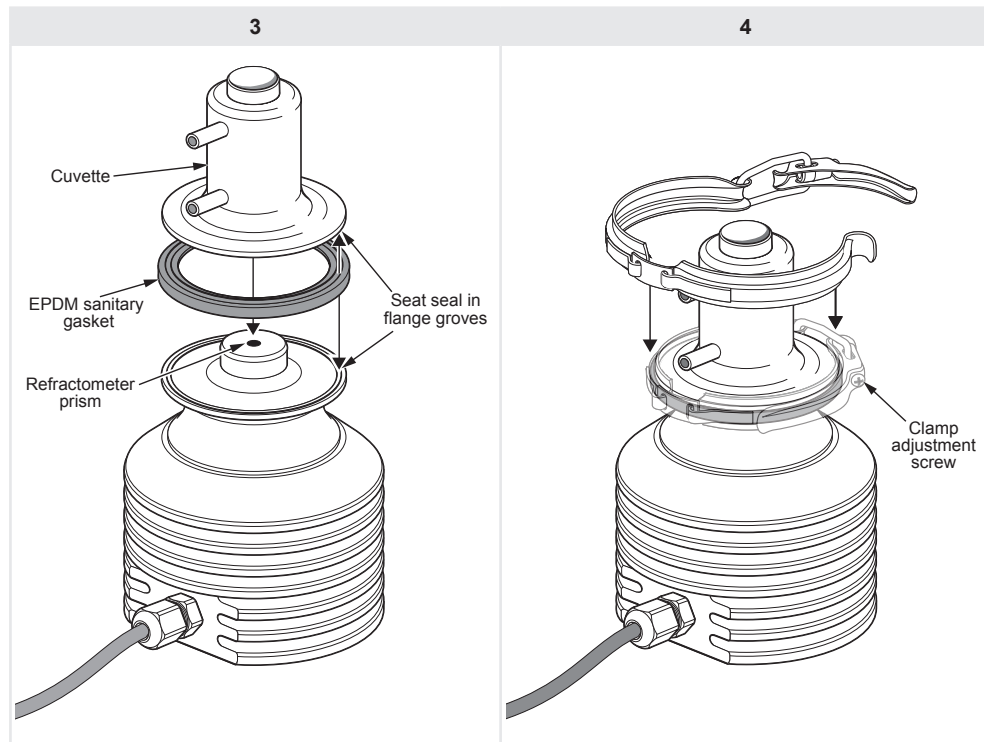
To assemble the test cuvette first locate the 2x2 EPDM O-ring into the groove in the top aperture of the outer casing (Figure 3.1). Then insert the narrow top of the static sampling chamber through the compression spring. Then insert the sample chamber and spring into the outer casing from the bottom, inserting the top end of the sample chamber through the top aperture of the outer casing. Finally place the 20.2x3 EPDM O-ring into the bottom of the sample chamber ready for mounting on the Refractometer PR-23-AC Sensor.



**Figure 3.1** K-Patents Laboratory Cuvette LTC for Static sampling: Components and assembly of sample chamber.

### 3.4 Mounting Laboratory Test Cuvette to Sensor

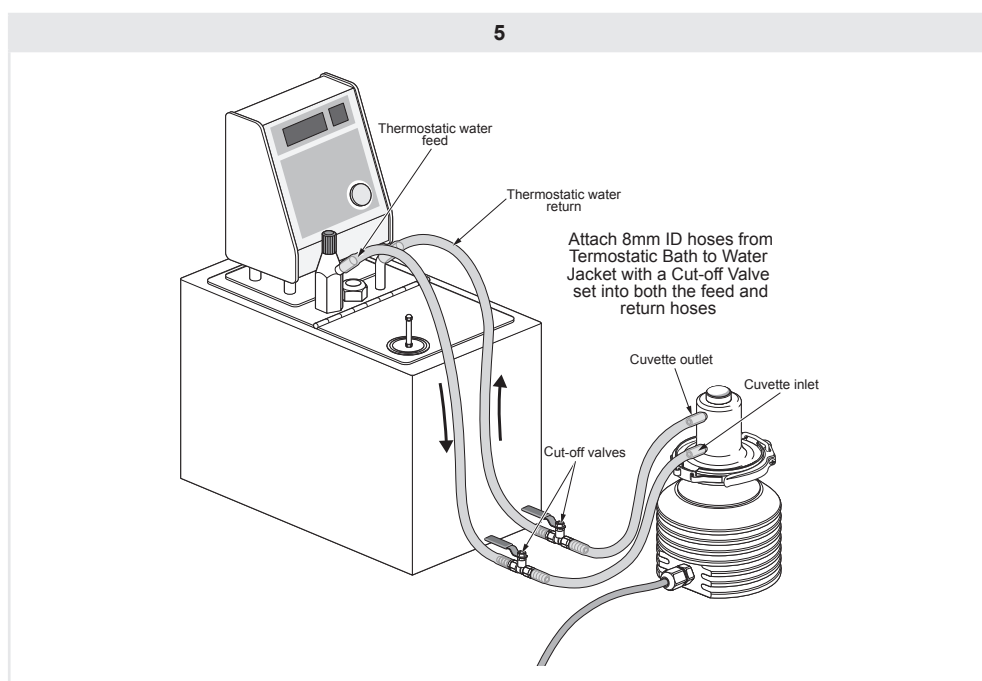
The test cuvette is mounted on the refractometer sensor using a 2.5" EPDM sanitary gasket and clamp. Position the gasket in its seating groove with the lip downward. Now position the assembled test cuvette with the gasket groove correctly seated on to the gasket (Figure 3.2). Attach clamp and lock. Check that the clamp is tight, and if not, adjust the tension using the clamp adjustment screw.



**Figure 3.2** Attaching Laboratory Test Cuvette LTC to Refractometer.

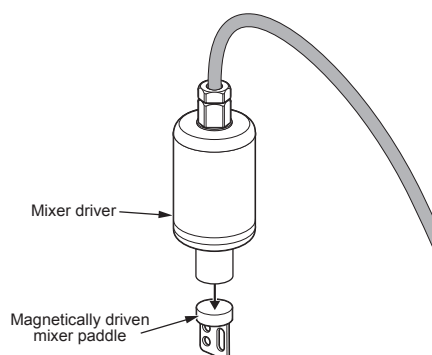
### 3.5 Connecting hoses from thermostatic bath

The temperature control Water Jacket is connected to the Thermostatic bath using the 8 mm (0.3 inch) hoses. These hoses should each have a ball valve inserted between the thermostatic bath and the water jacket (see Figure 3.3). These valves are to enable the shutting off of the water flow to the water jacket to allow disassembly for cleaning. The water jacket inlet pipe is the one positioned nearest the base and the outlet is positioned at the top. Thus the water circulates through the water jacket from bottom to top, therefore avoiding air pocket formation within the water jacket.



**Figure 3.3** Attaching hoses to connect LaboratoryTest Cuvette LTC to Thermostatic bath.

Operational procedure checking the operation of Laboratory Cuvette sample mixer: Check that the magnetically driven mixer paddle starts to rotate when the mixer driver's power is switched on (Figure 3.4).

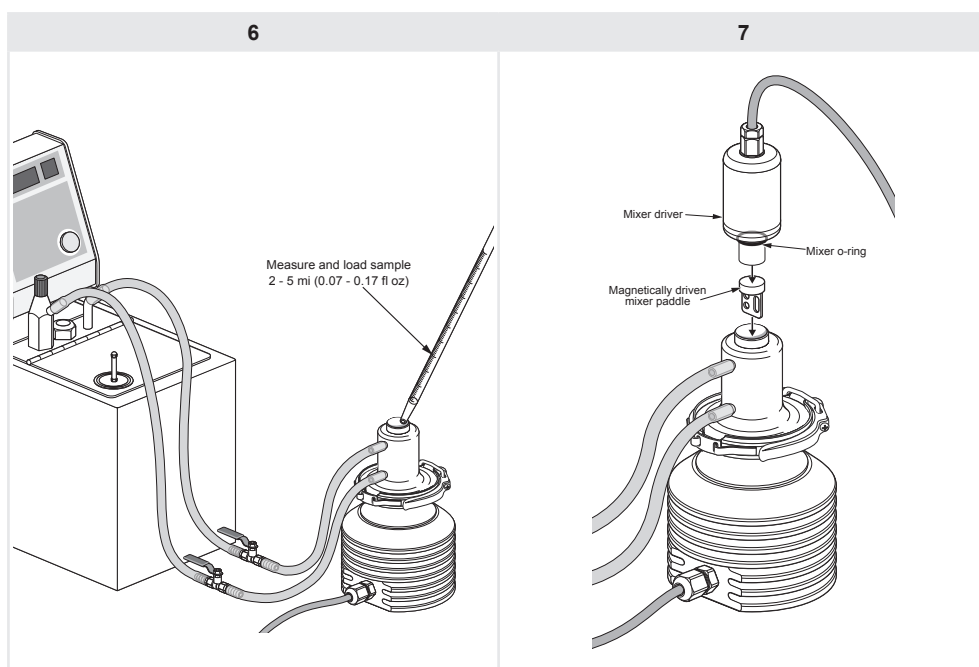


**Figure 3.4** Mixer components.

### 3.6 Sample loading and mixer insertion

The correct liquid sample volume is 2-5 ml (0.07 - 0.17 fl oz). Any larger volume will overflow from the sample chamber. The sample is measured and inserted using a laboratory pipette (Figure 3.5). The ball valves on the hoses from the Thermostatic bath are opened and the temperature is set at the required level.

The mixer paddle is placed into the sample chamber after the sample. Then the mixer is inserted into the top of the sample chamber. It has to be pushed down far enough, so the O-ring mounted on the mixer is positioned inside the sample chamber, thus avoiding any sample evaporation. The mixer is now ready to be plugged in for operation.



**Figure 3.5** Loading liquid sample into the sample chamber and then inserting the LTC mixer into the top of the sample chamber.

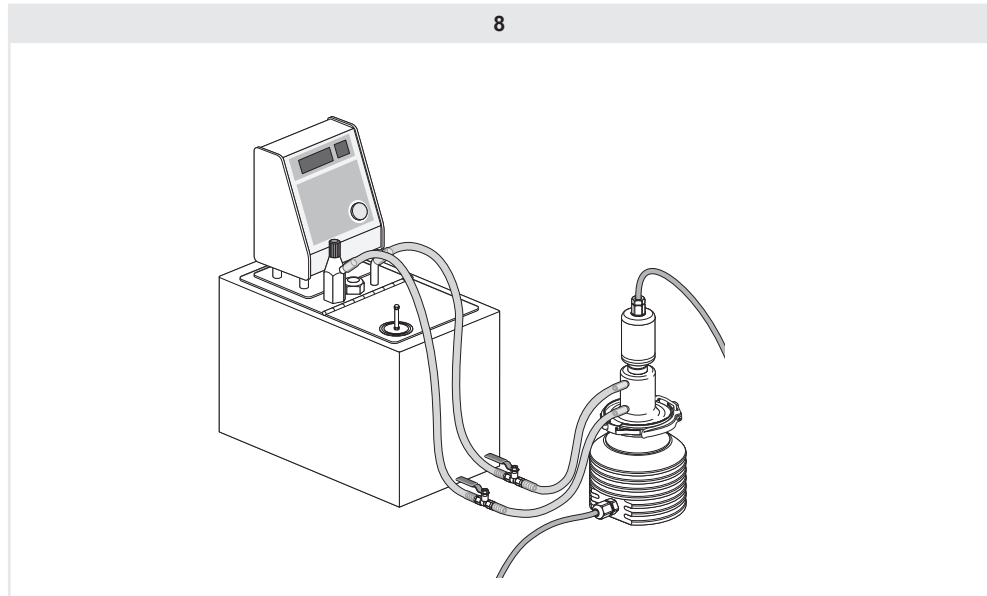


Figure 3.6 LaboratoryTest Cuvette LTC is ready for liquid sample analysis.

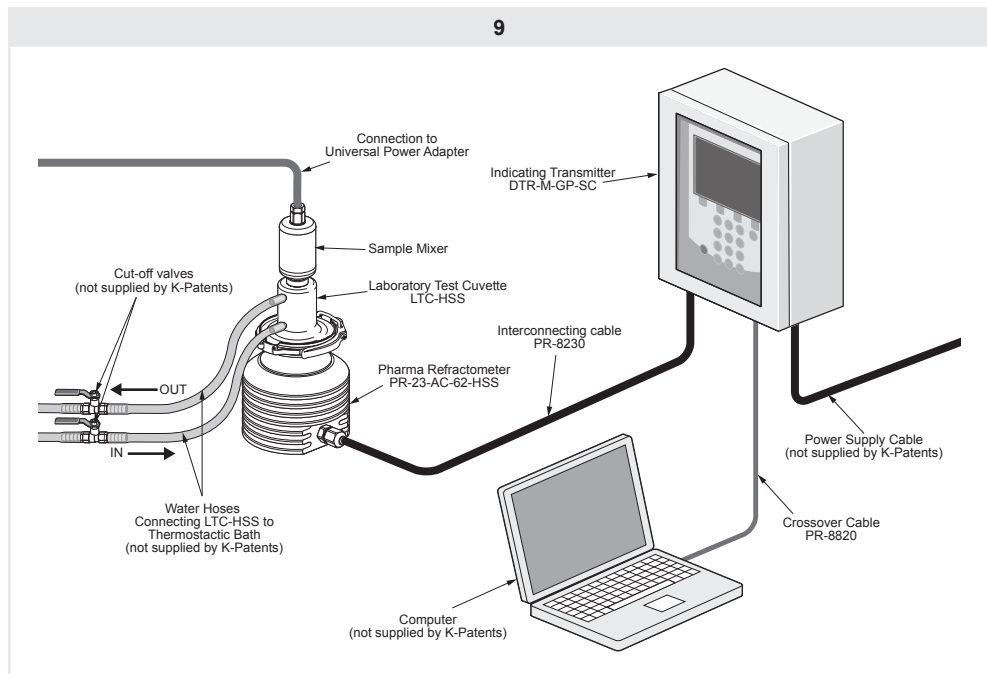


Figure 3.7 System diagram showing interconnection of component parts in laboratory.



# 4

## Verification of Laboratory Test Cuvette LTC: Static sampling

### 4.1 Refractometer and Laboratory Test Cuvette Verification

The verification of the Pharma Refractometer PR-23-AC sensor and static sampling Laboratory Test Cuvette LTC combination can be made using a set of standard refractive index (R.I.) liquids following the same procedure laid down in the PROCESS REFRACTOMETER PR-23 INSTRUCTION MANUAL, Sensor Verification **Section 3.2**.

Thorough cleaning of the Laboratory Test Cuvette should be undertaken between each step of the verification process. This is best achieved by disassembly of the cuvette. This first requires removal of the Mixer and Paddle. Extraction of the R.I. liquid using a pipette. Then close both Ball Valves fitted to the inlet and outlet hoses to the Water Jacket. Unclamp the cuvette assembly from the sensor. Remove the Sample Chamber from the Water Jacket for cleaning. Clean thoroughly all the wetted surfaces of the Sensor and Cuvette assembly between each sample change using the specified cleaning solution (e.g. Isopropyl alcohol) and cleaning tissues.

Operational verification of the Laboratory Test Cuvette using the standard refractive index liquids is carried out at an operating (liquid sample) temperature of 25 °C (77 °F) with max. temperature deviation of 1°C.

The deviation of repeated readings should be no more than  $\pm 0.0004$  R.I. for valid verification.

For operating instructions of the static sampling Laboratory Test Cuvette LTC see **Section 3.2 – Section 3.6** (this document) and for full Sensor verification instructions see PROCESS REFRACTOMETER PR-23, INSTRUCTION MANUAL **Section 13**.



# 5

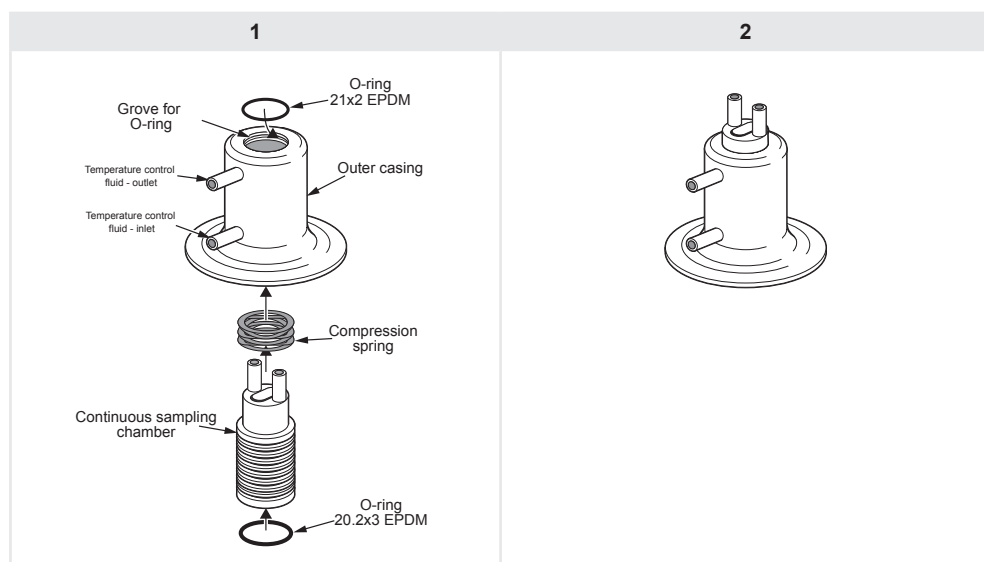
## Use of Laboratory Test Cuvette LTC: Continuous sampling

The Laboratory Test Cuvette LTC for continuous sampling can be used for further testing of samples in pilot scale-up trials for instance in drug formulation or process scale-up. The typical size of such laboratory batch is 3-10 liters (100 - 300 fl oz).of a liquid.

With continuous sampling the liquid sample is circulated by an external sample pump so the LTC mixer is not required. Liquid line hoses are used to connect the external sample pump to the continuous sampling chamber inlet and outlet.

### 5.1 Assembly of continuous sampling Laboratory Test Cuvette

The Laboratory Test Cuvette LTC for continuous sampling is assembled using the same components as the LTC for static sampling, except for the replacement of the static sampling chamber with the continuous sampling chamber (Figure 5.1). The continuous sampling chamber has two pipes at the top for inlet and outlet hose connections to an external sample pump.



**Figure 5.1** K-Patents Laboratory Cuvette LTC for continuous sampling: Components and assembly of sample chamber.

## 5.2 Mounting Laboratory Test Cuvette to Sensor

LTC is mounted on the PR-23-AC sensor using a 2.5" EPDM sanitary gasket and clamp (Figure 5.2). Position the gasket in its seating groove with the lip downward. Now position the assembled LTC with the gasket groove correctly seated on to the gasket. Attach clamp and lock. Check that the clamp is tight, if it is not adjust the tension using the clamp adjustment screw.

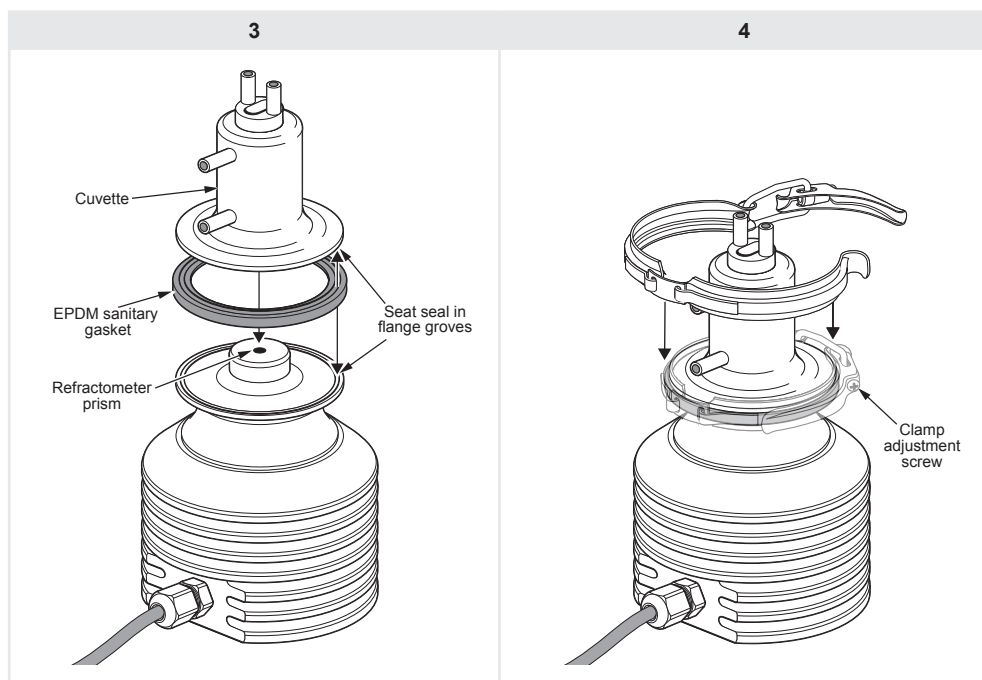


Figure 5.2 Attaching Laboratory Test Cuvette LTC to Refractometer

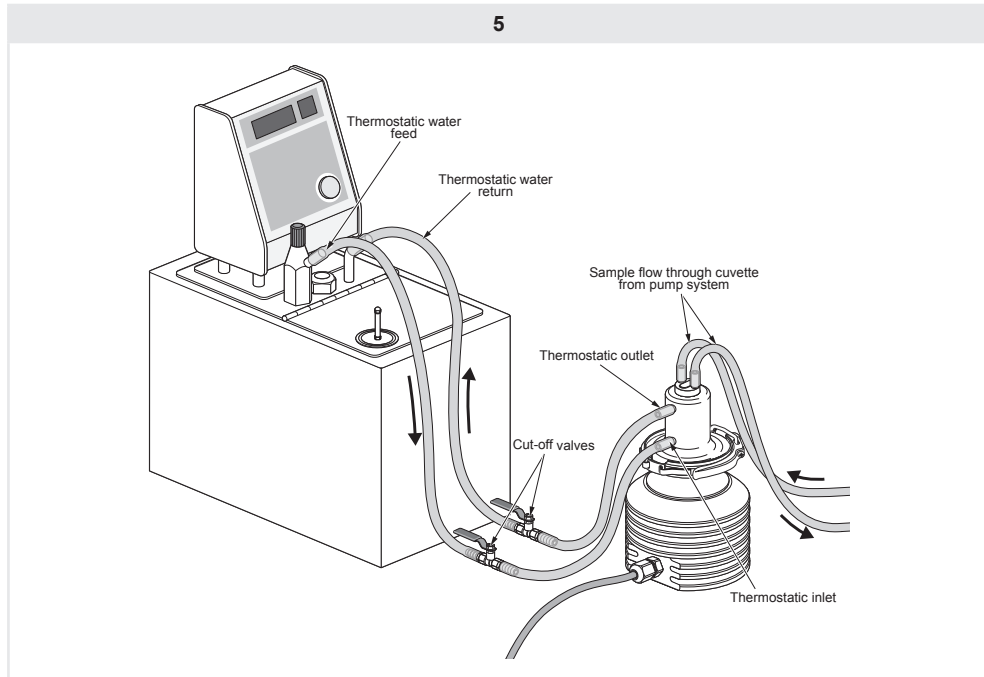
## 5.3 Connecting hoses

The temperature control Water Jacket is connected to the Thermostatic bath and to an external sample delivery system using the 8 mm (0.3 inch) hoses (Figure 5.3). The hoses to the Thermostatic bath should each have a ball valve inserted between the thermostatic bath and the water jacket. The valves are to enable the shutting off of the water flow to the water jacket to allow disassembly for cleaning. The water jacket inlet pipe is the one positioned nearest the base and the outlet is positioned at the top. Thus the circulation through the water jacket is from bottom to top, therefore avoiding air pocket formation within the water jacket.

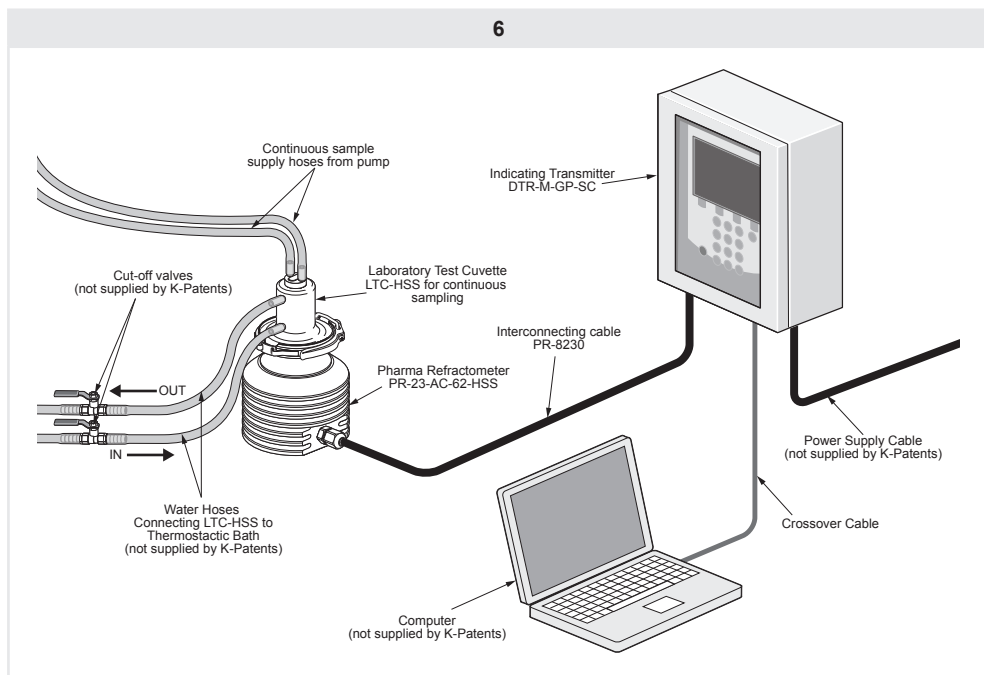
The continuous sample supply hoses allow liquid flow through the cuvette via two pipes at the top. The hoses are connected for the inlet and outlet hose connections and to an external sample delivery system with a pump. With the sample delivery pump the sample can be further directed to an external laboratory pilot process, e.g. kilolab filtration.

## 5.4 Interconnection of all system parts

Figure 5.4. shows the interconnection of all components in a laboratory.



**Figure 5.3** Attaching hoses to connect LaboratoryTest Cuvette LTC to Thermostatic bath and to laboratory pilot process (via sample delivery system).



**Figure 5.4** System diagram showing interconnection of all parts in laboratory.



# 6

## Complying with Documentation and Validation Regulations

### 6.1 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). These require that all processes and computerized systems directly related to product manufacture must be subject to validation.

These requirements vary from company to company, as each pharmaceutical company is responsible for defining and maintaining its own documentation requirements list. Some areas to consider and their K-Patents solutions are presented in the sections below.

### 6.2 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 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 K-Patents 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.

## 6.3 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 specification results, investigation and problem resolution. After the qualification, the test results must be reviewed and approved before the instrument can be put to routine use.

## 6.4 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 the 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.

## 6.5 Electronic Signatures/Audit Trail

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

## 6.6 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 predicate rule.

## 6.7 Security

System access can be restricted to authorized individuals using the lock on the Indicating transmitter door and password-protected access to the indicating transmitter and to the computer. The actions of these authorized individuals in relation to the data must be openly accounted for throughout the audit trail.



## 6.8 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.

## 6.9 K-Patents Refractometer System Adherence to Part 11

It is not possible to supply a system “ready” compliant 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. K-Patents Pharma Refractometer generates electronic records via Ethernet connection. These records can be stored as digital files and be 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 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 K-Patents 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 K-Patents makes no claims that the completion of all the procedures described here will exempt these companies or individuals from FDA sanctions.



# 7

## Onsite Qualification Protocols and Records: Installation Qualification

This Installation Qualification (IQ) involves documented verification of the complete system: K-Patents Pharma Refractometer PR-23-AC with Ethernet connection and Laboratory Test Cuvette LTC, as installed and connected to a thermostatic bath and a computer in laboratory, and in compliance with the approved design, the manufacturer's recommendations and user requirements.

### 7.1 Authorization and responsibilities

#### 7.1.1 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 Laboratory Cuvette LTC 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.

### 7.1.2 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: \_\_\_\_\_

### 7.1.3 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.

## 7.2 System

### 7.2.1 Qualifying the system

Location of the Pharma Refractometer Sensor and Laboratory Test Cuvette LTC:

\_\_\_\_\_

Location of the Indicating Transmitter: \_\_\_\_\_

Device	Serial Number	Supplier	Manufacturer
Pharma Refractometer: Sensor PR-23-AC-62-HSS			K-Patents Oy
Pharma Refractometer: Indicating transmitter DTR-M/U-GP-SC			K-Patents Oy
Computer:  _____			
Temperature bath:  _____			
For continuous sampling: Sample delivery system  _____			
For continuous sampling: Sample delivery pump:  _____			

## 7.2.2 Manufacturers and suppliers

Full address of the manufacturers and suppliers:

Manufacturer:	Supplier:
K-Patents Oy  Postal address: PO Box 77 FI-01511 Vantaa, Finland  Street address: Elannontie 5 FI-01510 Vantaa, Finland  Tel. Int.+358 207 291 570 Fax Int.+358 207 291 577  E-mail: info@kpatents.com www.kpatents.com	

## 7.3 IQ Protocol

### 7.3.1 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 hardware and software components provided by K-Patents, included in the Manual Appendix (this document) **Section 2.3**.

#### 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	<input type="checkbox"/> Pass	<input type="checkbox"/> * Conditional Pass	<input type="checkbox"/> Fail
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\*Conditional pass:

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### 7.3.2 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: \_\_\_\_\_

		<input type="checkbox"/>	<input type="checkbox"/> *	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

\*Conditional pass:

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## 7.4 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-GB-PR23	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Appendix to Instruction Manual	IM-GB-PR23-ACP: Rev. 1.0	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Operating Manual for Tempered bath		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Operating Manual for: _____		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Material Safety Data Sheet for Cargille Refractive Index Liquids		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

		<input type="checkbox"/>	<input type="checkbox"/> *	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

\*Conditional pass:

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## 7.5 Operating environment

### Description of requirements

Ensuring that the environmental requirements for the system regarding temperature are within specification. Ensuring that the appropriate power supply and power switch are available.

### Requirement acceptance values

Ambient temperature is between 20 and 30 °C (68 - 86°F). 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). An available water supply. Optional: Fume hood if required.

### Failure to meet any off the acceptance values

A new environment must be established and the qualification performed again from **Section 7.3.1** (of this document) onwards.

		<input type="checkbox"/>	<input type="checkbox"/> *	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

\*Conditional pass:

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## 7.6 Installation

### Requirement description

The authorized operator who in accordance with **Section 7.2** (of this document), must read the start-up and operation instructions in **Section 3** (of this document).

### Requirement acceptance values

The relevant sections have been read.

		<input type="checkbox"/>	<input type="checkbox"/> *	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

\*Conditional pass:

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## 7.7 Setting up the system components and devices

### Description of requirements

The Pharma Refractometer system with Refractometer sensor, Laboratory Test Cuvette LTC and Indicating transmitter, are assembled and mounted correctly as described in the **Section 3** (this document). Also that the ancillary thermostatic bath and the sample delivery system (if required) are 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 any of the acceptance values

Terminate the IQ.

		<input type="checkbox"/>	<input type="checkbox"/> *	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

\*Conditional pass:

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## 7.8 Electrical connections and wiring

### Description of requirements

The frequency of the power supply must match 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

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

		<input type="checkbox"/>	<input type="checkbox"/> *	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

\*Conditional pass:

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### Description of requirements

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

### Requirement acceptance values

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

		<input type="checkbox"/>	<input type="checkbox"/> *	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

\*Conditional pass:

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## 7.9 Ethernet connection

### Description of requirements

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

### Requirement acceptance values

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

		<input type="checkbox"/>	<input type="checkbox"/> *	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

\*Conditional pass:

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## 7.10 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.

		<input type="checkbox"/>	<input type="checkbox"/> *	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

\*Conditional pass:

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## 7.11 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)



# 8

## Onsite Qualification Protocols and Records: Operational Qualification

Operational Qualification (OQ) is documented verification 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 K-Patents Pharma refractometer meets predefined specifications, and that all system components function correctly and according to specification within a specific environment.

### 8.1 Individual module and system components check

Checking the operation of the refractometer as an individual module, and as system that comprises also of the Laboratory Test Cuvette, the sample mixer, the Ethernet connection, software and ancillary equipment such as thermostatic bath.

- 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 testing the system components, a functional challenge, which tests 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.

### 8.2 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.

## 8.3 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 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 Laboratory Test Cuvette have 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.

## 8.4 Authorized officiator

Selection of the individual authorized to carry out the Operational 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 Operational Qualification log and reports.

Name: \_\_\_\_\_

Function: \_\_\_\_\_

Date: \_\_\_\_\_

Signature: \_\_\_\_\_

Initials: \_\_\_\_\_

## 8.5 System qualification

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

### Definition of requirements

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

Date	Signature	<input type="checkbox"/> Pass	<input type="checkbox"/> Conditional Pass	<input type="checkbox"/> Fail
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Conditional pass:

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## 8.6 Setting up the system components and devices

### Description of requirements

The Pharma Refractometer system comprised of Refractometer sensor, Laboratory Test Cuvette LTC 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 thermostatic bath and the sample delivery system (if required) are connected in accordance with the **Section 3** (this document). 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	<input type="checkbox"/> Pass	<input type="checkbox"/> Conditional Pass	<input type="checkbox"/> Fail
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Conditional pass:

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## 8.7 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 settle 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).

		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

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 (no 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.

		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Date</b>	<b>Signature</b>	<b>Pass</b>	<b>Conditional Pass</b>	<b>Fail</b>

Conditional pass:

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## 8.8 Instrument verification with Laboratory Test Cuvette for Static sampling and Refractive Index Liquids

Successful completion of the preceding Instrument verification indicates that this instrument performs as per the accuracy specifications, and it may now be submitted for off-line laboratory testing using Laboratory Test Cuvette with static sampling feature.

### Description of requirements

The verification procedure is performed at the temperature of 25 °C (77°F) (with max. temperature deviation of 1°C) and with all five liquids using a sample volume of 2-5 ml (0.07 -0.17 fl oz) and verification instructions at **Section 4.1** (this document) and 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 (no more than + 0.0004 of the nominal values) are received for each sample using a sample volume of 2-5 ml (0.07 -0.17 fl oz). 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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Pass	Conditional Pass	Fail

Conditional pass:

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## 8.9 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: \_\_\_\_\_

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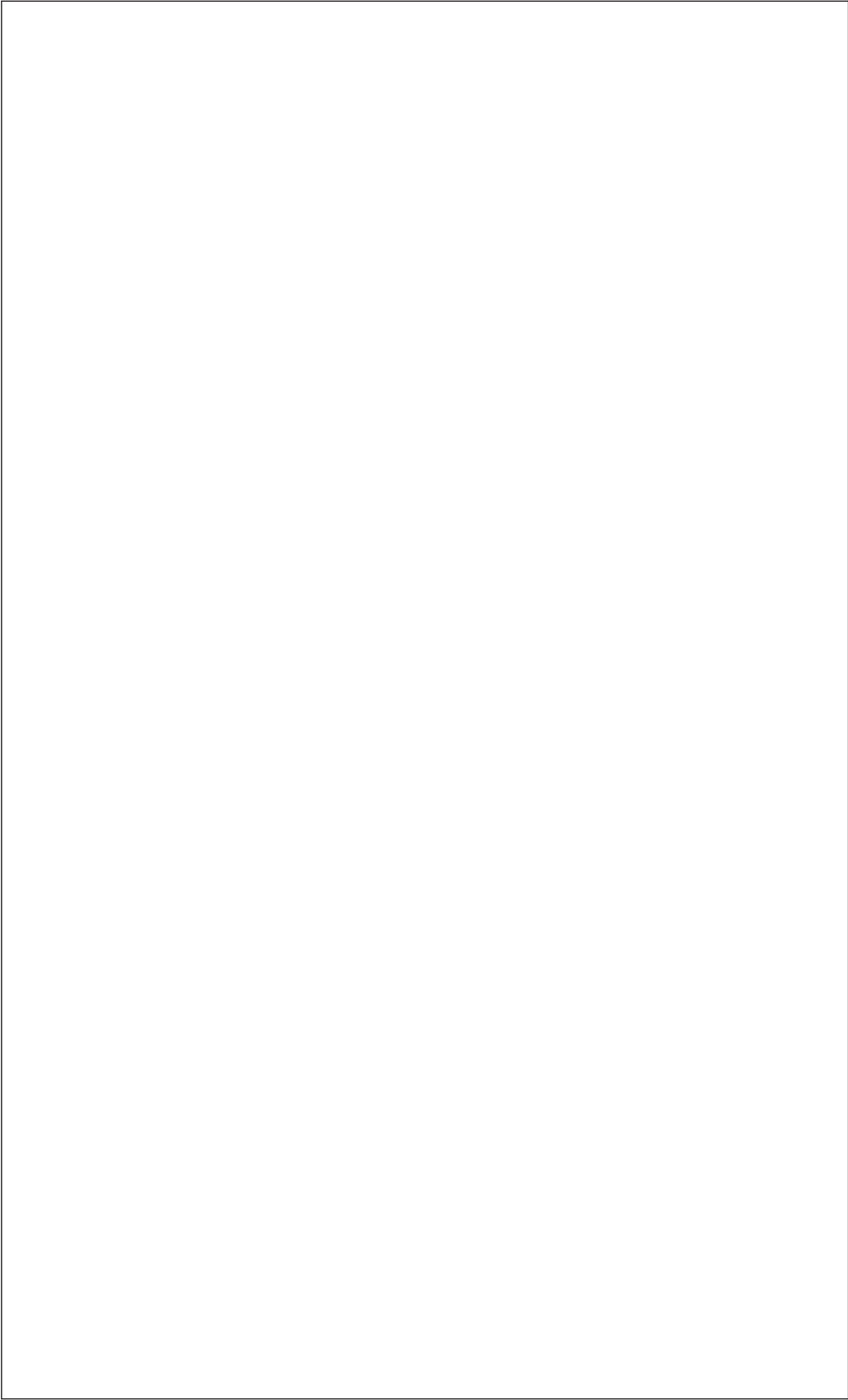
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### Comments (including discrepancies)





# Analytical Method Validation: Establishing product refractive index monitoring validation protocols

An essential element of pharmaceutical product development, manufacturing process design and process scale-up design is the knowledge of how the product behaves during all stages of manufacture. This requires establishing the analytical parameters required to monitor the process. Awareness of product Refractive Index changes are extremely important as it can facilitate in-line monitoring and control of the full-scale manufacturing process. The Refractive Index's relevance to acceptable variations in the process must first be established.

Once the refractometer system has passed the qualification with refractive index liquids, the accuracy of an analytical method may be determined by applying that method to samples or mixtures of excipients to which known amounts of analyte have been added both above and below the normal levels expected in the samples. The accuracy is then calculated from the test results as the percentage of analyte recovered by the assay. Robustness tests (sample temperature and/or concentration parameters are deliberately varied to give an indication of method reliability).

## 9.1 Validation of Analytical Method

Analytical methods are validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference.

Methods should be validated to include consideration of characteristics included within The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on validation of analytical methods. The United States Food and Drug Administration (USFDA) have also proposed guidelines on submitting samples and analytical data for methods validation. And The United States Pharmacopoeia (USP) has published specific guidelines for method validation for compound evaluation.

The validity of an analytical method can be verified only by laboratory studies. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

## 9.2 Protocol objectives

Method validation is the process by which it is established that performance characteristics of the method meet the requirements for the intended analytical applications.

The protocol objectives for analytical method validation are:

- Product knowledge, establishing Critical Quality Attributes (CQA) and parameters for the manufacturing process.
- Protocol acceptance values: Establishing proven acceptable ranges.
- Product validation protocols carried out in compliance with the relevant authority's regulations and procedures.

To obtain the relevant knowledge of Refractive Index behavior, multiple readings should be taken and recorded with the different variables applied. Compilation of the obtained knowledge requires a rigorous recording and documentation protocol to be first established. These documenting procedures must be carried out in compliance with all the relevant authorities' documentation requirements.

Testing samples from progressive stages of a process is essential in designing a valid refractive index monitoring regime.

The Static sampling LTC is used to establish the refractive index of the product solutions at various temperature settings through adjustment of the Thermostatic Bath feed to the heating/cooling jacket. The test samples should be in accordance with process values. Insertion into the LTC and testing follow the same procedures given in **Section 4** Refractive index  $n_D$  verification of Laboratory Test Cuvette.

Thorough cleaning of all wetted surfaces is required between each sample test as described in the relevant section. Once a valid set of Refractive index parameters has been established using the static LTC, the Continuous sampling LTC can be used to monitor and verify laboratory pilot production batches.

## Routine Operation Phase

After the instrument is qualified, the instrument 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 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 requalification.

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 instances.

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 K-Patents Pharma Refractometer is recommended to have a calibration verification label applied with the relevant status information for the system, date of the last calibration verification, who carried out the verification and the scheduled date for the next verification.





## Preventive Maintenance

The need for K-Patents 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 Laboratory Test Cuvette LTC at suitable intervals in accordance with an established schedule:

- Check the condition of the O-rings (PR-9254 O-ring, 21x2 EPDM; PR-9253 O-ring, 20.2x3 EPDM) of the Laboratory Test Cuvette LTC
- Check the condition of the PR-12152 Mixer paddle
- Check and test the condition of PR-10956 Universal power adapter for Sample mixer

### 11.1 Spare parts

The following spare parts are available for the Laboratory test cuvette LTC:

Description	Model
PR-7603-SS Table top stand for Indicating transmitter (contains a set of two M5x10 A2 DIN screws)	PR-7603-SS
PR-8820 Crossover cable for Ethernet connection between Indicating transmitter and computer, length 5 m (16 inch)	PR-8820
PR-12151 Sample mixer	PR-12151
PR-12152 Mixer paddles ( Set includes 2 paddles)	PR-12152
PR-10956 Universal power adapter for mixer	PR-10956
PR-9254 O-ring 21x2 EPDM	PR-9254
PR-9253 O-ring 20.2x3 EPDM	PR-9253



## Other Documentation

You may want to include the following documents in your files concerning this 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.
- K-Patents ISO 9001 certificate  
(can be obtained from [www.kpatents.com](http://www.kpatents.com) ► Documents downloads)







[www.kpatents.com](http://www.kpatents.com)

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