

VAISALA

Liquid concentration measurements in pharmaceutical and biotechnology manufacturing

eBook for improving on-site processes

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Introduction

This eBook is intended for all pharmaceutical and biotechnology professionals involved in creating, developing, and manufacturing drugs and other therapeutics.

Currently, pharmaceutical production is making the switch from batch processing towards continuous processing. Consequently, process analytical technology (PAT) supports real-time quality testing over off-line testing methods.

In this eBook we introduce new ways for pharmaceutical companies to monitor critical quality attributes in both continuous and batch processes, focusing on opportunities to reduce production cycle times, increase production capability, prevent rejects, and eliminate human error in order to ensure safe, consistently high-quality products with minimal variability. We also look at a new technology to measure liquids along with its benefits, customer testimonials, and applications.

Contact our expert team to discover our full offering and discuss how we can help you to improve your process and applications.

 [Contact form](#)

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Process analytical technology (PAT) for batch and continuous manufacturing (CM)

Batch manufacturing is still the most popular method for pharmaceutical production as it is proof tested for product quality traceability. When each step of a batch is completed before the next starts, locating and resolving quality problems is a straightforward process.

However, where suitable, continuous manufacturing is slowly gaining in popularity owing to its clear benefits, the most notable of which include the possibility to continuously manufacture products with consistent quality and to scale up more easily. Continuous manufacturing is also faster and less costly. According to U.S. Food and Drug Administration (FDA) estimates, producing a drug with continuous manufacturing takes approximately one day compared to up to 30 days for the same drug with batch manufacturing. Transferring batches between facilities, which may be in different countries, significantly increases the risk of human error, poses an extreme contamination risk due to the multiple transfer steps, and of course, takes time.

Process analytical technology (PAT)

The FDA supports the development and implementation of continuous manufacturing for drug substances, and another important initiative to boost innovation and support efficiency is Process Analytical Technology (PAT), which is a framework for innovative pharmaceutical development, manufacturing, and quality assurance. An important PAT principle is the need

for scientific knowledge. The concept behind this principle is that if pharmaceutical companies can gain sufficient process understanding from the very beginning of development, this supports the design of robust production processes and reduces both scale-up work and lead times.

PAT encourages the use of the latest scientific advances, engineering principles, and technology in pharmaceutical manufacturing as well as continuous, real-time quality assurance during processing. Process understanding is key to efficient manufacturing of quality products.

Smart instruments

PAT guidelines state that safe and efficient continuous manufacturing requires smart instruments that provide process understanding by gathering constant data from the process, providing continuous measurements without introducing contaminants.

Vaisala process refractometers were specifically designed to answer this need, taking the specific manufacturing requirements of the pharmaceutical industry into account in their design.

They measure liquid concentrations very accurately in-line, measurement is reliable and reproducible, and they provide instant process data that can be incorporated into a control system to build a control strategy. In addition, these smart measurement devices are robust and do not need regular servicing or calibration.

The most reliable digital measurement instruments, such as Vaisala's process refractometers with refractive index technology, are as accurate as laboratory measurement devices and come with the added advantage of constant measurement and the ability to feed data to the control system, which can then generate alarms if any sudden, unplanned changes in the process are detected.

Process refractometers can instantly catch even the slightest deviations from specification during production, allowing process operators to react immediately and take corrective action to prevent deviations from escalating into quality problems and expensive, time-consuming recalls. Vaisala's smart measurement devices offer continuous, real-time quality assurance, meaning that quality, safety, and efficacy can be designed into the process.



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

Smart results

Constant process feedback and data provided by smart measurement instruments contribute greatly to process understanding. This can reduce the burden of validation, as it can be demonstrated through continuous quality assurance that a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process end points.

Vaisala process refractometers support both batch and continuous manufacturing and offer clear benefits for both methods.

The perfect PAT tool

The Vaisala K PATENTS Pharma Refractometer PR-43-PC is an ideal PAT tool because it enables manufacturers to:

- reduce production cycle times
- prevent rejects, scrap, and reprocessing
- increase automation and therefore operator safety, and incorporate data into the control system
- increase process understanding using real-time data on current process conditions
- reduce human error
- improve material and energy efficiency
- increase production capacity
- consistently manufacture products of consistent, stable quality without variations

Read more in the next section:

[!\[\]\(e474458956c9a37fbf9586ddb60a7fa1_img.jpg\) The six most important things to consider when selecting an in-line liquid measurement instrument for pharmaceutical and biotechnology manufacturing](#)



The six most important things to consider when selecting an in-line liquid measurement device for pharmaceutical and biotechnology manufacturing

Real-time data for process design, scale-up, control, troubleshooting, and optimization, as well as quality control and cost savings.

1. In-line measurements

In-line measurement devices measure concentrations continuously without delay and indicate changes in process conditions immediately without consuming the measurable. They also measure from the genuine process conditions in real time without dilution or alteration, which can unfortunately happen during sampling. Real-time measurements enable continuous processing which, in turn, increases productivity and profitability, stabilizes end-product quality, and reduces both waste and production downtime.

2. Documentation

Documentation is an essential part of quality assurance and quality control systems in the pharmaceutical industry. The complete qualification process must also be fully documented.

The measurement equipment's Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) protocol documentation confirms that the correct process equipment model and parts have been ordered, delivered, and installed. It also ensures that the equipment meets its performance specification and can reliably measure typical samples using the selected measurement method. Without

the proper documentation from supplier(s), completing equipment qualification can be a complex and time-consuming process for the buyer.

3. Electronic data capture and storage

In addition to digitally documenting their production records, pharmaceutical companies must also ensure that data is kept secure by limiting access to measurement systems to authorized individuals, with a system that logs all activity.

4. Scalability

Drugs are first developed and formulated in the laboratory before being produced in progressively larger batch sizes until commercial scale is reached. These intermediate stages include, for example, pilot-scale production to simulate full-scale production and to manufacture sufficient product volumes for clinical trials and commercial-scale production.

Choosing the right measuring device is critical to enable the manufacturer to utilize the same measurement instrument in every stage of development and production, from R&D to pilot-scale to full-scale production. This avoids the risk of delays in starting manufacturing caused by results from early testing phases not representing the process-scale design. The goal is to continuously monitor the manufacturing process at full-scale.

5. Pharma-grade contact materials

Any equipment that is in contact with drugs or raw materials during the manufacturing process must be approved for the specific conditions it is operating in and must comply with contact compatibility requirements. Selecting measurement equipment with sanitary design and full tolerance to chemicals and process cleaning procedures ensures that the equipment does not introduce hazards or contaminants into the process.

Measuring devices that have the following features are suitable for pharmaceutical manufacturing processes:

- Certified sanitary contact material, for example stainless steel 316L
- Gasket materials that conform to biocompatibility standards according to USP Class VI electropolished product contact surface finishes
- Product surface roughness max Ra 0.38µm or 15µ inch
- No animal-derived ingredients (ADI) used in processing or machining
- Compatibility with CIP and SIP cleaning standards.

6. NIST traceable calibration and accuracy, and instrument verification

All automated, mechanical, and electronic measuring equipment must be calibrated, inspected, or checked according to a written quality program designed to ensure proper manufacturing performance.

Traceable measurement instruments use current international definitions of traceability and can provide assurance that measurements meet the accuracy requirements of regulatory agencies – for example, those established by the National Institute of Standards and Technology (NIST) in the US. NIST traceable calibration is an assurance program that certifies that a manufacturer is fully equipped to calibrate equipment to NIST standards and that any products offered by that manufacturer will match these standards.

Verification ensures the correct operation of equipment according to its stated operating specifications. Valid results are achieved when the instrument's calibration verification complies with international standards, such as NIST, which also ensures traceability. In addition, the calibration and accuracy traceability of the measurement device should be simple and easy to perform on-site.

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

The Vaisala K-PATENTS Pharma Refractometer PR-43-PC is an in-line measurement device that uses refractive index technology, supporting pharmaceutical drug development and manufacturing as well as biotechnology processing. The Vaisala K-PATENTS Pharma Refractometer can be used for:

- Process evaluation, validation, and troubleshooting
- Data collection to enable process understanding of different experiments and operations
- Identifying the unique process profile – a reference used during scale-up to confirm that the process behaves as designed and to ensure process equivalence
- Monitoring performance or operation in pilot and full-scale production, and monitoring the concentration and purity of solvents, raw materials, and final products
- Monitoring blending operations and achieving the correct reactants composition – the Vaisala K-PATENTS Pharma Refractometer can follow reaction degree and analyze different solvents and their suitability for the process
- Determining the supersaturation point in crystallization.

In addition, the Vaisala K-PATENTS Pharma Refractometer can send data to the control system (DCS) to support development of an automated control strategy to standardize the process, achieve consistent quality, prevent batch-to-batch variations, reduce production time and costs, increase yield, and ensure product safety.

In-line measurement of refractive index (RI) can help to immediately identify problems during scale-up and reduce development time.

Read more:

[🔗 Vaisala K-PATENTS Pharma Refractometer. A reliable measurement based on refractive index \(RI\). How does the system work?](#)



Example applications in the pharmaceutical and biotechnology industry

The Vaisala K-PATENTS Pharma Refractometer is specially designed for pharmaceutical and biotechnology processes. The device complies with pharmaceutical industry standards and guidelines including PAT, GMP, CIP/SIP, and validation.

In general terms, monitoring RI can improve the understanding of process conditions, reduce drug development time, increase production capacity and stability, improve product quality, and demonstrate compliance with regulations. Pharmaceutical manufacturers are required to demonstrate process validation from drug discovery to full production; this can be achieved through RI measurements, which provide a unique process profile that can be used for validation at any scale.

All solutions have a specific RI value, which changes as the reaction process proceeds. This means that RI monitoring can provide insights into the reaction and extraction processes and enable chemical identification. Changes in RI can therefore be used to track the progress of the reaction and to determine the endpoint. For example, where products are extracted from natural materials such as plants, RI measurements can be employed to determine the optimal time to stop the extraction process.

RI monitoring is also ideal for processes where it is necessary to conduct a solvent swap to facilitate subsequent processes such as distillation, as it can be used to help maintain the correct ratio of original and swap solvent during the various steps of the process.

TYPICAL APPLICATIONS

- **Pharmaceutical chemicals:** acetylsalicylic acid, calcium gluconate, glycerophosphates, chloral hydrate, saccharin, antihistamines, tranquilizers, antifilarials, diethyl carbamazine citrate, antidiabetics, and more
- **Active pharmaceutical ingredients:** actives, excipients, intermediates, raw material, fine chemicals, and bulk chemicals
- **Antibiotics:** penicillin, streptomycin, tetracyclines, chloramphenicol, and antifungals
- **Blood products:** blood, plasma, serum, infusion liquids, sodium chloride, and glucose
- **Proteins:** proteins and protein buffer solutions
- **Vitamins:** ascorbic acid, riboflavin, vitamin B, vitamin C, sodium pantothenate, and more
- **Synthetic hormones**
- **Syrups:** concentrated aqueous solutions of sucrose
- **Drugs of vegetable origin:** quinine, strychnine and brucine, emetine, digitalis, glycosides, and herbal extracts
- **Vaccines and sera:** sucrose gradient purification by zonal ultracentrifugation: rotor unloading and fractionation, sucrose solution
- **Acids, bases, and solvents**
- **Quality control and testing**
- **Product and CIP interfaces:** product-to-product interfaces, product-to-CIP interfaces, CIP fluids
- **Chromatographic separation:** fractionation

Active Pharmaceutical Ingredients (APIs)

APIs are often produced by crystallization from liquid phase. The aim of this process is to maximize the yield of high-quality, pure crystals that are easy to process whilst avoiding fines and conglomerates by ensuring good particle size distribution. This can be achieved by maintaining the concentration and temperature above the solubility curve or supersaturated level. Continuous monitoring of concentration by RI offers major benefits for crystallization control because this method is not influenced by crystals or bubbles, so selective monitoring of the mother liquor concentration is simple. By monitoring mother liquor saturation, it is also possible to determine the optimal seeding point.

It is normally necessary to wash produced crystals with solvent to remove impurities and any remaining mother liquor from the filter cake. This process must be carefully controlled to maximize yield and avoid product dissolution. By monitoring the RI of filtrate, it is possible to determine the endpoint of cake washing, which helps to maximize yield, save time, and avoid excessive solvent usage. These measurements also enable differentiation between clean and saturated solvents with the API and between different solvents. This means that at the end of the washing process, if the RI value is closer to the saturated value than the pure solvent value, some of the product must have been washed out, indicating that a process revision is required.

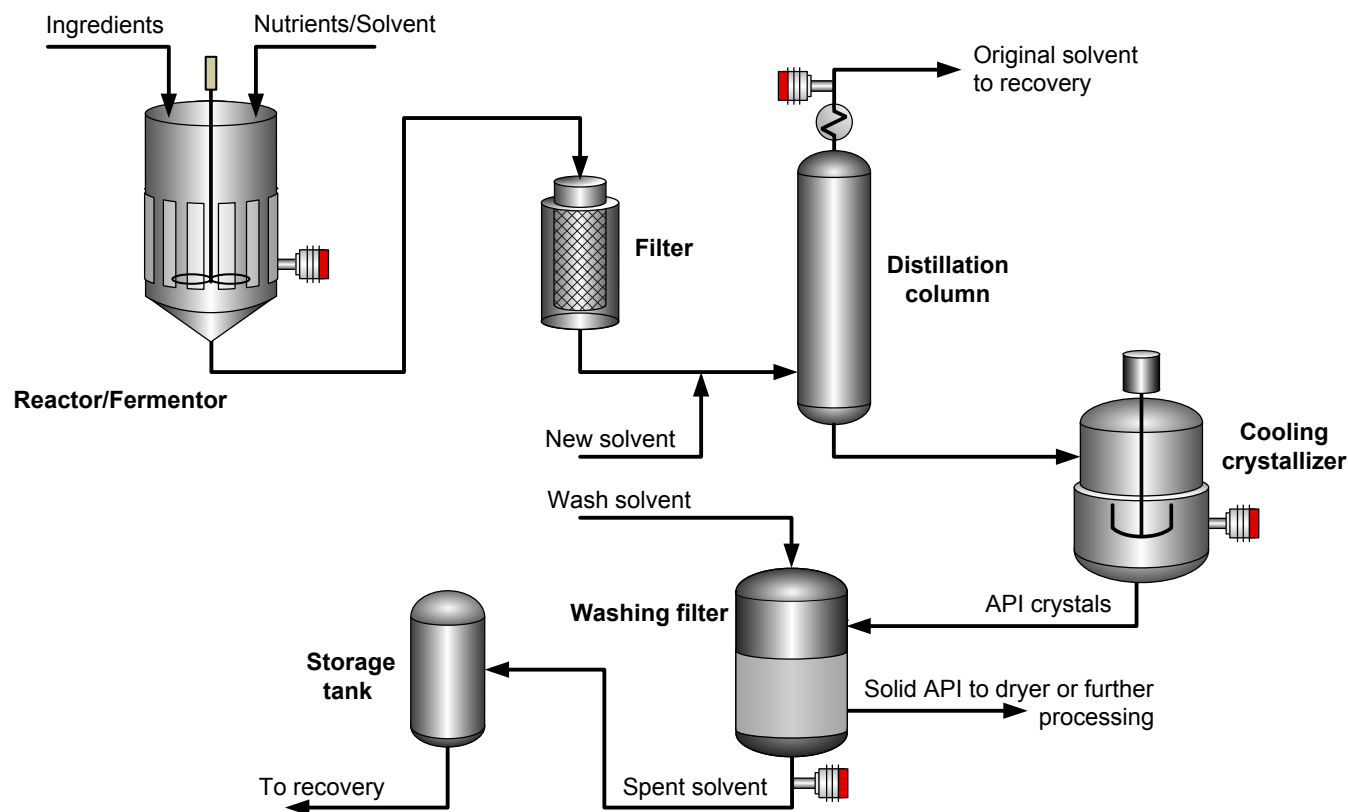


Figure 1. Development and production of an Active Pharmaceutical Ingredient (API)

Vaccine purification by sucrose density gradient

Viral vaccines are made by first growing a virus in an egg-based or cell-based process. The virus is then inactivated or attenuated, concentrated, and then purified before it is blended with other components to produce the final vaccine formulation.

Purification is one of the most important operations as it removes impurities originating from host cells or culture media and ensures the safety and efficacy of the final product. It is also one of the costliest steps in the vaccine manufacturing process.

Sucrose gradient centrifugation is widely used for the purification and concentration of viruses in large-scale production. This method has traditionally been used to produce influenza vaccines, but it can also be used for the purification of other viruses.

In sucrose gradient centrifugation, the separation of the virus and possible impurities may be rate-zonal, which is based on particle size differences, or isopycnic, which is based on particle density differences, or a combination of the two.

The concentration and purification of the virus takes place in a centrifuge – a special chamber with a rotor moving at high speed to separate mixtures by centrifugal force. The density gradient, consisting of sucrose solutions, is loaded into the rotor first. The concentration range of the density gradient is selected so that it covers the particle of interest. Next the

rotor is accelerated. The centrifugal force forms a density gradient in the form of bands in which the sucrose concentration goes from 0 to 60%. The sample fluid containing the virus is then loaded into the centrifuge. The viral particles in the sample move along the density gradient and separate out to form bands according to their sedimentation rates or differences in density. For instance, in isopycnic centrifugation the particles move to a position where their density is equal to that of the solution (buoyant density). This operation is known as isopycnic banding as the result is a solution with stable bands.



At the end of the run, the rotor inside the centrifuge is slowed to a stop and the bands are ready to be unloaded. The separation of different fractions can easily be done by measuring changes in RI or Brix with a process refractometer, which provides real-time readings that help to identify and collect the virus-rich fraction(s).

After the virus is purified, the manufacturing process continues with formulation, quality testing, filling, and finally distribution.



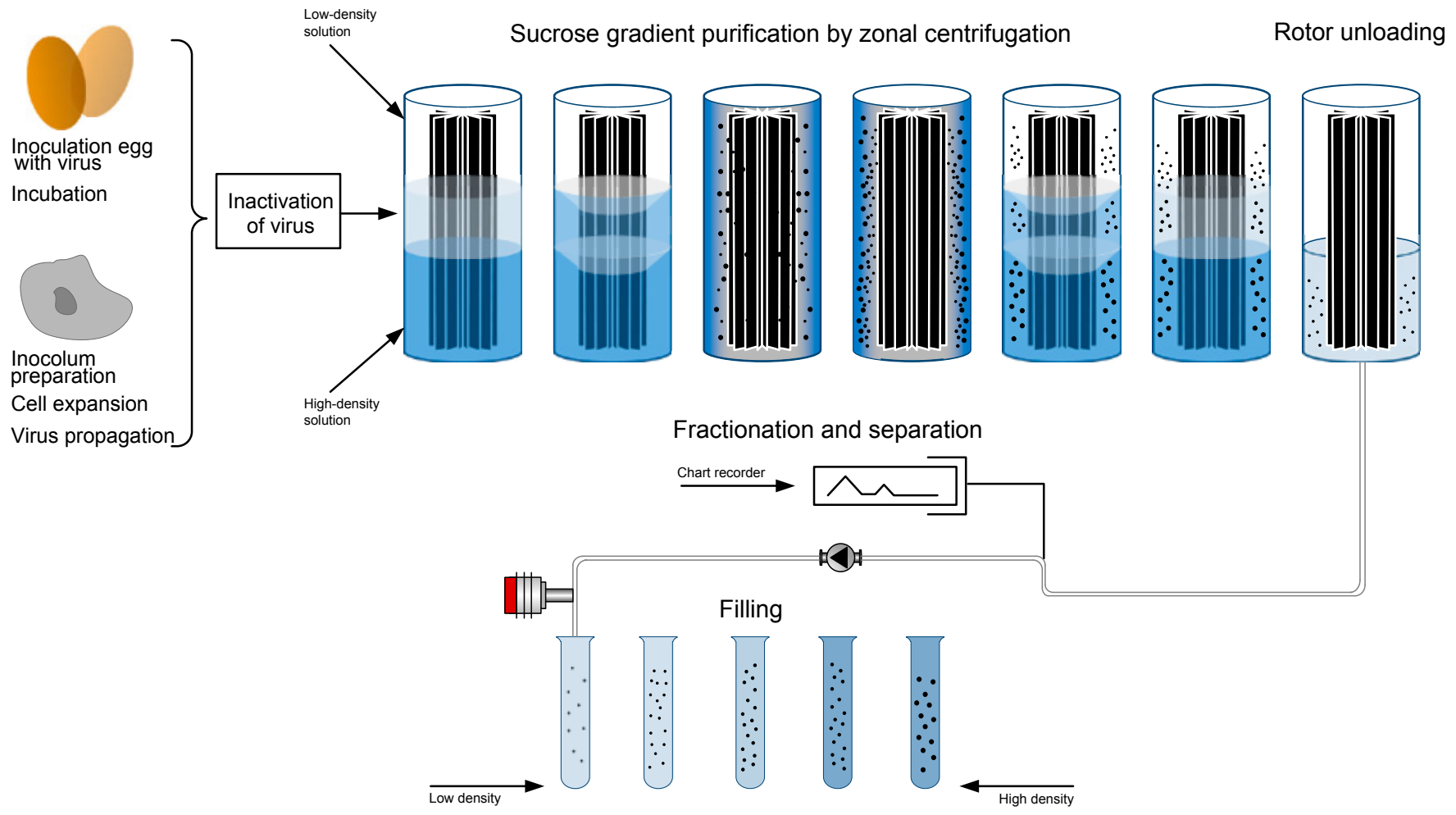


Figure 2. Vaccine production process

Pharmaceutical fermentation

Pharmaceutical fermentation is the basis for the production of a wide range of products such as antibiotics, hormones, vaccines, and specialized proteins.

Biotechnological processes, such as fermentation, are becoming increasingly important for the manufacture of APIs. It is essential in the pharmaceutical industry to standardize and automate processes to meet the requirements for consistent quality, accelerate development and production times, increase yields, and reduce costs.

Fermentation is a process for cultivating organic materials where organic material is converted into simple substances by the action of microorganisms. The key elements in fermentation are the selection of the right strain and process medium. The process conditions need to be developed and optimized throughout scale-up to maximize productivity and reduce variation in the product yield.

The fermentation process involves several phases and takes place under strictly controlled conditions.

The first step in fermentation is the preparation of the inoculum for the cell culture. The type of microorganism is selected according to the product being manufactured. For example, penicillium chrysogenum is used to produce penicillin and corynebacterium glutamicum is used to produce glutamic acid.

The cell culture is dosed to large vessels known as fermentation tanks, or fermenters, containing the process medium. The medium is an important factor in the process. It is carefully selected to ensure it is easily degradable by the microorganisms and to guarantee the viability of the cells.

The reaction regime is also designed to maximize the productivity of the organism of interest by providing optimal conditions for population growth.

The fermentation reaction (or incubation) is slow and can take several days. During incubation the nutrients in the medium (e.g. glucose) are depleted as the biomass and end product are produced.

The concentration inside the tanks is monitored throughout the reaction time to follow the degree of fermentation and detect the endpoint of the reaction. This is commonly achieved using sampling and laboratory tests, for example RI measurements.

The fermentation product, known as the fermentation broth, is processed downstream by various technologies for extracting, concentrating, and purifying the main product or API from the broth.

The Vaisala K-PATENTS Pharma Refractometer PR-43-PC provides accurate and repeatable refractive index measurements throughout the development and production of an API. At laboratory scale, the refractometer is used as a PAT tool for the creation of fermentation profiles. The correlation between the RI and nutrient concentration in the fermenter is a valuable tool for operation at larger scales and to maintain a viable medium for cell incubation. The reaction profile guarantees that the process behaves as designed and is useful for identifying and investigating deviations.

At pilot and full scale, the Vaisala K-PATENTS Pharma Refractometer PR-43-PC is installed directly in the fermentation tank to provide real-time information on the conversion rate and degree of fermentation. Continuous measurement by the refractometer combined with the fermentation profile help to identify both the reaction endpoint and the need for nutrient addition.

In-line measurement reduces the need for sampling and laboratory testing. The refractometer provides Ethernet and 4-20 mA output signals that can be connected to the process controller to enable automatic control of the feed valves to the fermenter. The Vaisala K-PATENTS Pharma Refractometer PR-43-PC is also ideal for monitoring and control of other operations upstream, for instance, for syrup dilution or nutrient solution preparation. The refractometer is installed directly in the tank or in a bypass line.

Due to its unique digital sensing technology, the Vaisala K-PATENTS Pharma Refractometer PR-43-PC is accurate and does not drift in the presence of bubbles or suspended particles. It is delivered factory calibrated and does not require recalibration. Moreover, verification is easily performed using standard refractive index liquids.

When multiple instruments are required, the Multichannel User Interface (MI) can connect with up to four refractometers, thus reducing the investment cost. The MI provides user authentication, electronic records, data logging, event log, and audit trail, all of which comply with the requirements of pharmaceutical manufacturing.

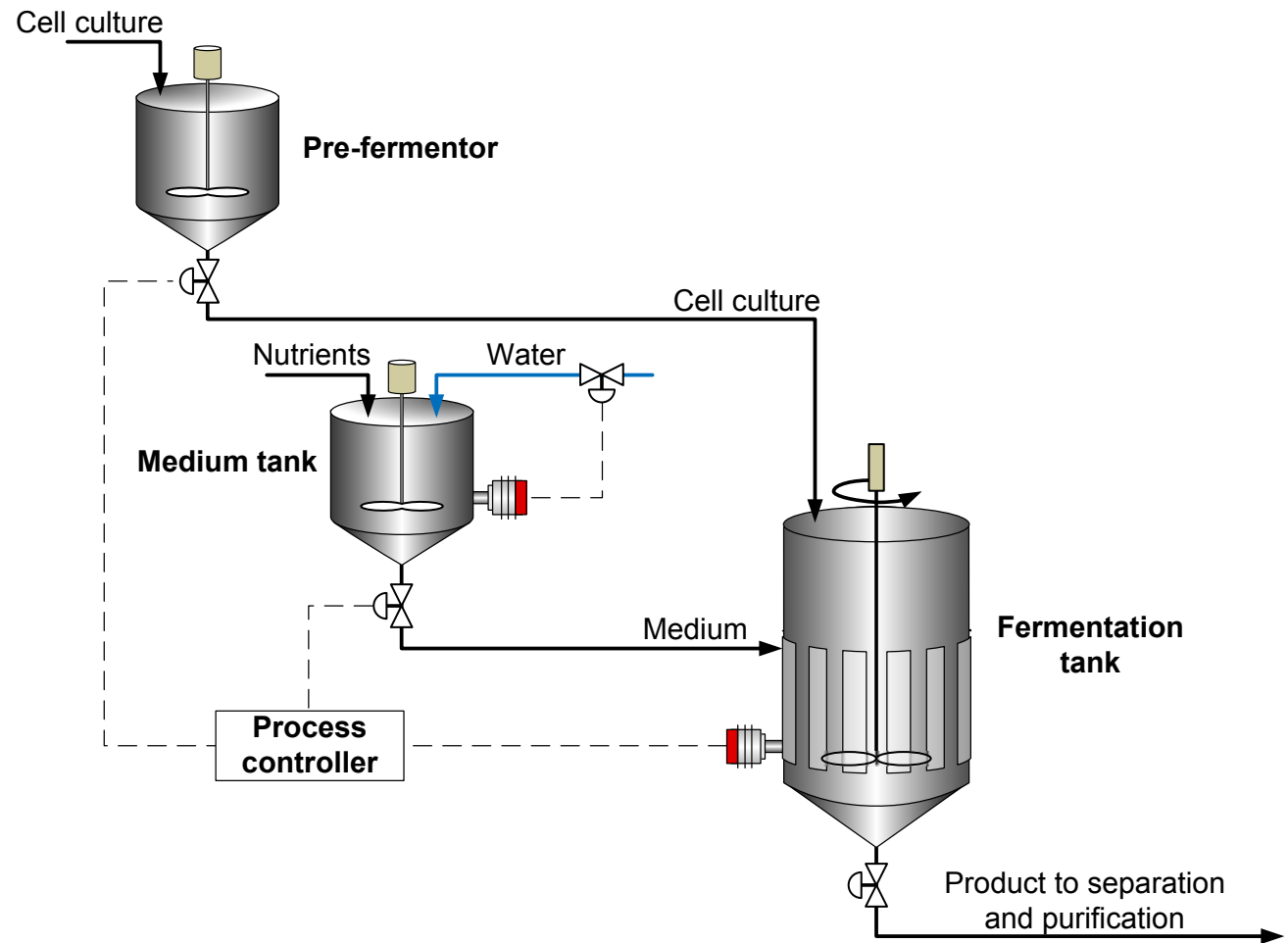
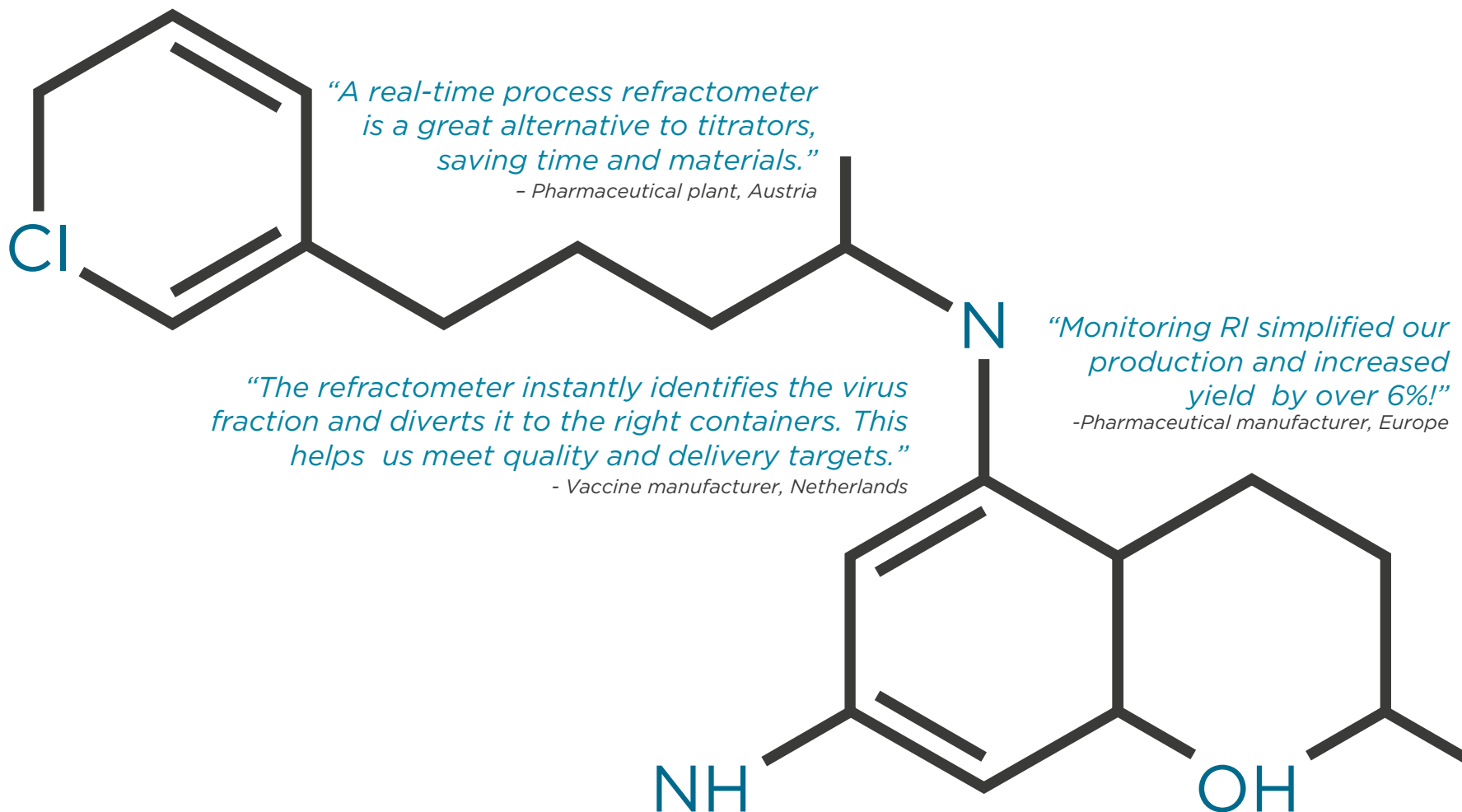


Figure 3. Pharmaceutical fermentation

Customer testimonials

There are over 600 Vaisala K-PATENTS Pharma Refractometer installations in the pharmaceutical and biotechnology field, and many customers prefer Vaisala's process refractometers over other measurement device for liquid concentrations. The testimonials below are anonymized for reasons of confidentiality.



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

A reliable measurement based on refractive index (RI)

Vaisala's process refractometers are smart measurement devices for industrial-scale manufacturing and there are tens of applications in the pharmaceutical and biotechnology industry alone. All Vaisala's pharma refractometers base their measurement on the refractive index (RI) principle.

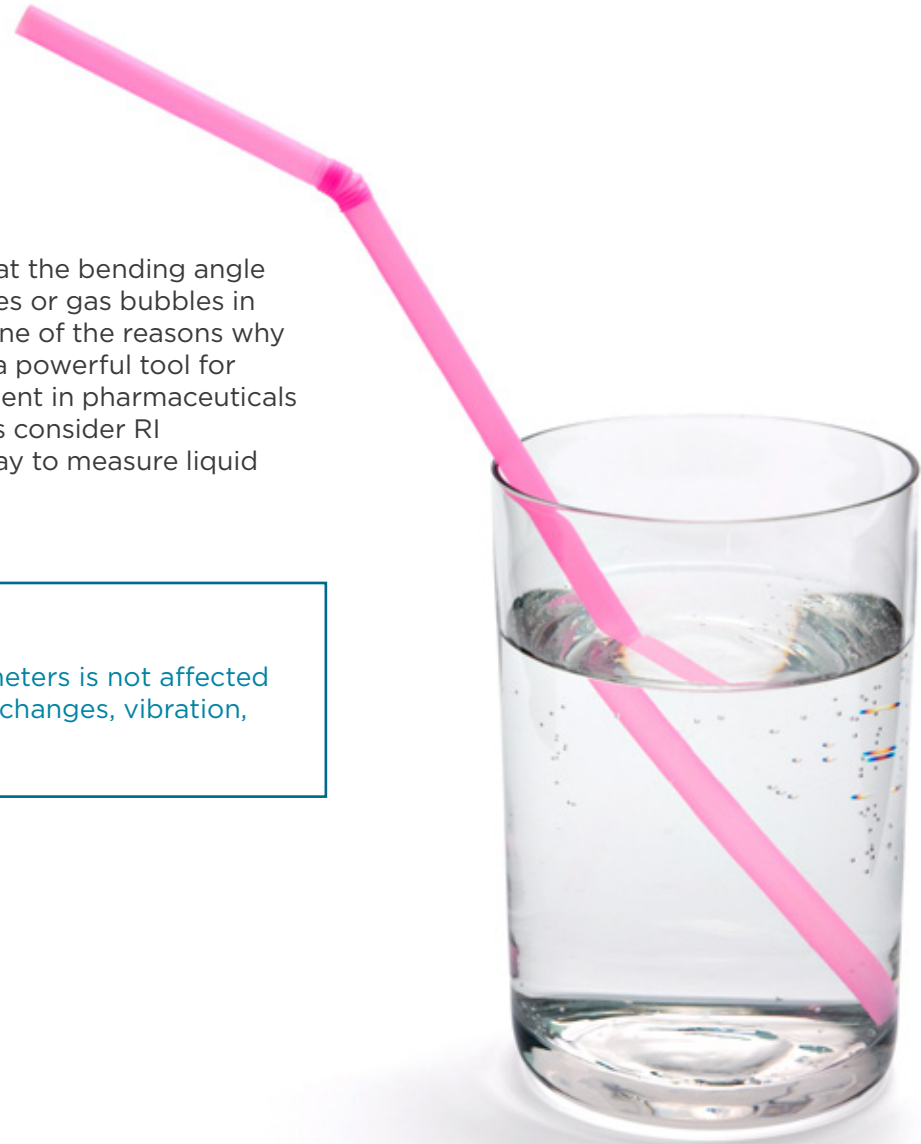
RI principle in a nutshell

RI is a property of light. Light travels at different speeds in different mediums. For example, if we put a straw in a glass of water it looks like the straw is bending at the surface, when in fact the light bends when the medium changes as the light hits the water. There are a few parameters affecting the bending angle, such as the solution's concentration and temperature.

It is important to note that the bending angle is not affected by particles or gas bubbles in the solution, and this is one of the reasons why RI measurement is such a powerful tool for concentration measurement in pharmaceuticals manufacturing. Scientists consider RI measurement an ideal way to measure liquid concentrations.

FACT

The measurement performance of Vaisala K-PATENTS Pharma Refractometers is not affected by air or gas bubbles, color, suspended particles, flow changes, pressure changes, vibration, or temperature shocks.



How does the system work?

A process refractometer instantly measures changes in concentration and therefore in the bending angle as it is a function of RI.

Inside the refractometer there is a light source, a prism, and an image detector. The light source sends light to the interface between the prism and the process solution, where light rays hit the interface at different angles. Depending on

the angle, some rays undergo a total internal reflection; the rest of the light is refracted into the process solution. This creates an optical image with a dark area and a light area. The angle corresponding to the borderline is called the critical angle of total internal reflection.

A CCD camera detects the optical image, which is then transformed pixel-by-pixel into a

digital signal. Digital signal processing is used to locate the exact shadow line position and to determine the refractive index (nD). A built-in temperature sensor measures the temperature (T) on the interface of the process liquid. The refractometer converts the nD and T into Brix units and the diagnostics program ensures that the measurement is reliable.

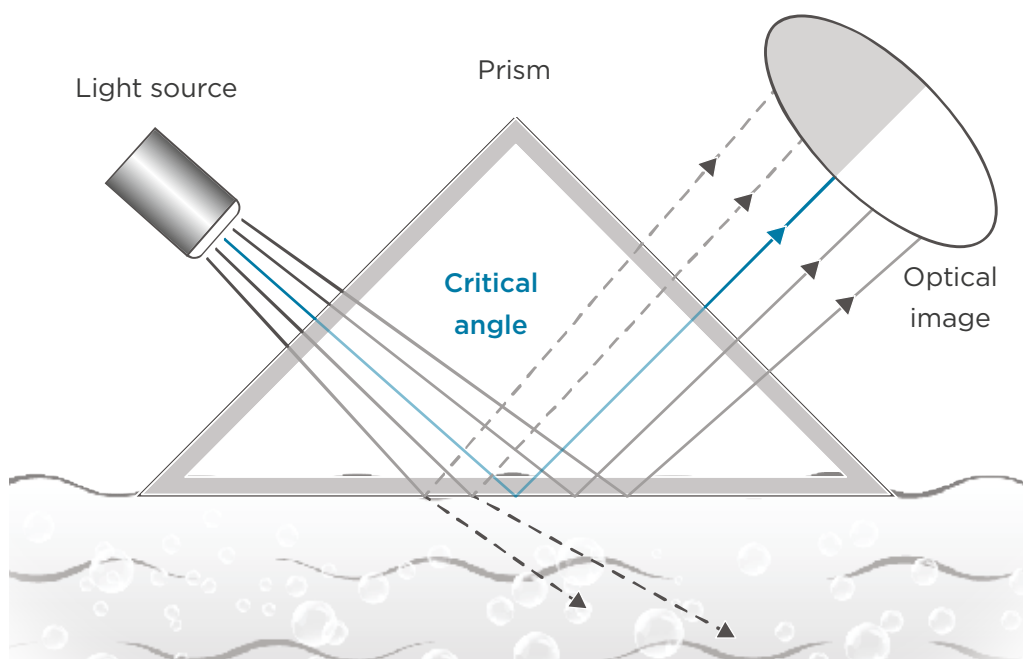
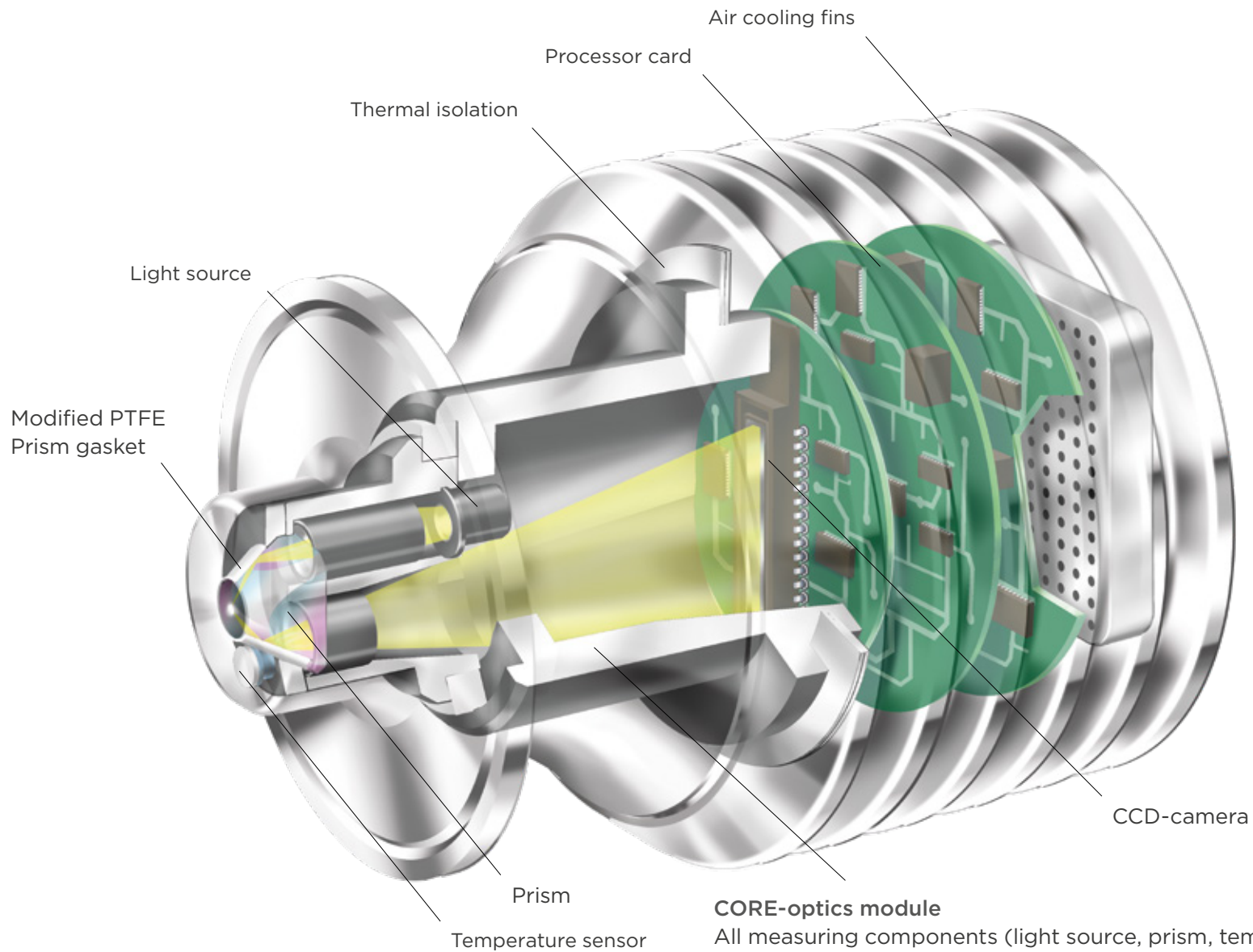


Figure 4. Critical angle measurement



CORE-optics module

All measuring components (light source, prism, temperature sensor, and CCD-camera) are in one solid CORE-optics module.

The CORE-optics module is mechanically isolated from the influence of external forces and vibrations. The CORE-optics module requires no mechanical adjustments.

Figure 5. Vaisala K-PATENTS Sanitary Refractometer PR-43-A design

Highly accurate concentration measurements

The Vaisala K-PATENTS Pharma Refractometer PR-43-PC provides the temperature-compensated concentration of a solution as an output of 4 to 20 mA DC current or Ethernet signal, covering the full concentration range. The device has built-in web connectivity with an instrument homepage, which enables configuration, monitoring, verification, and diagnosis via an Ethernet connection. In addition, the standard Ethernet communication solution allows for simultaneous data logging and continuous monitoring of the measurement values and diagnostic data.

Pharma compliance CFR FDA 21, Part 11

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 paper-based methods. Part 11 applies to all computerized systems that create, modify, maintain, archive, or retrieve records required by the FDA. It describes four basic system elements that must be addressed:

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

The requirements of Part 11 can be divided 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.). The FDA's validation requirements leave it up to the manufacturer to determine what data is essential to prove control over their processes. Therefore, it is not possible to supply a ready system that is automatically in compliance with Part 11.

The Vaisala K-PATENTS Pharma Refractometer generates electronic records via Ethernet connection. These records can be stored as digital files and printed out to be signed, or filed and maintained as hard copies. The computer files are subject to the requirements of Part 11, and the instrument parameter and configuration changes also fall into this category.



3-A and EHEDG certified

Standardization and certification verify hygienic equipment design and engineering. The Vaisala K-PATENTS Pharma Refractometer is Sanitary 3-A approved and EHEDG (European Hygienic Equipment Design Group) Type EL Class I certified.



3-A SANITARY STANDARD APPROVAL

The 3-A symbol guarantees that the Vaisala K-PATENTS Sanitary Refractometer PR-43-A conforms to 3-A Sanitary Standard number 46-04 for refractometers and energy-absorbing optical sensors and that it has passed the independent third party verification inspection for 3-A symbol authorization.



EUROPEAN HYGIENIC ENGINEERING & DESIGN GROUP

EHEDG certification authorizes the compliance of the Vaisala K-PATENTS Sanitary Refractometer PR-43-A with the EHEDG hygienic design criteria according to EL Class I for closed equipment, wet cleaned-in-place (CIP) without dismantling.

The built-in instrument verification is a very important tool that allows us to verify the measurement performance whenever needed – not just on a yearly basis.

– Pharmaceutical manufacturer in Europe

- Sanitary design with material certificates for pharma-grade materials
- Universal calibration of each sensor
- Full range nD = 1.3200...1.5300 corresponds to 0-100 % bw
- Process temperature range: -40°C...130°C (-40°F...266°F), for higher temperatures consult Vaisala
- IP67, Type 4X
- CIP, NaOH, and H₂O₂ dry fog compatible
- Small-volume flow cell also suitable for hose connection
- Fully digital system: particles and bubbles do not affect operation or accuracy
- CORE-optics module: no drift, no re-calibration, no mechanical adjustments
- Built-in web connectivity allows for configuring, monitoring, verifying, and diagnosing the refractometer via an Ethernet connection
- Fast process temperature measurement using built-in Pt1000 and automatic temperature compensation
- Easy on-site instrument verification within users' own quality-assurance system and standard refractive index liquids

Building on over 80 years of experience, Vaisala provides observations for a better world. We are a reliable partner for customers around the world, offering a comprehensive range of innovative observation and measurement products and services. Headquartered in Finland, Vaisala employs approximately 1,800 professionals worldwide and is listed on the Nasdaq Helsinki stock exchange.

K-Patents Oy, an industry leader and supplier of K-PATENTS[®] Process Refractometers, was acquired by Vaisala at the end of 2018. Following the acquisition, all K-Patents group companies are part of Vaisala.

Contact our expert team to discover our full offering and discuss how we can help you to improve your process and applications.



[Contact form](#)

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