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Making Sense of Integri-sense® Technology

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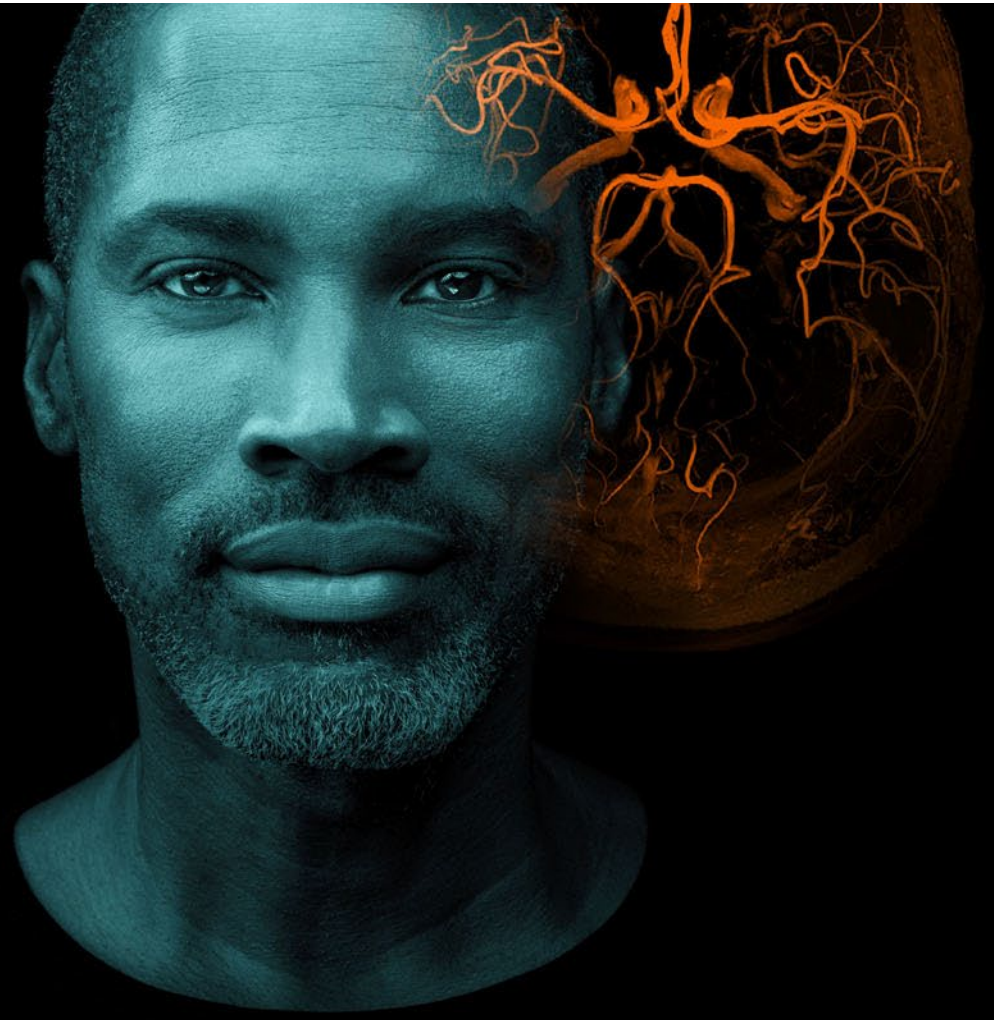

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Objectives

- **Review CLIA requirements for laboratory testing.**
- **Recognize sources of error in point-of-care testing.**
- **Recognize design attributes that mitigate risk in point-of-care testing.**
- **Demonstrate best practices in design control.**
  - Examples: epoc® Blood Analysis System and RAPIDPoint® 500e Blood Gas System

Type of CLIA certification depends on test complexity

Certification[1]

All laboratories are required to obtain CLIA certification prior to testing. Additionally, laboratories must meet any requirements imposed by state law.

The type of certification required and the associated process depend on test complexity as defined in the CLIA regulations.

Seven criteria for test complexity categorization[2]

1. Knowledge
2. Training and experience
3. Reagents and material preparation
4. Characterization of operational steps
5. Calibration, quality control (QC), and proficiency testing materials
6. Test system troubleshooting and equipment maintenance
7. Interpretation and judgment

1. https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493. Accessed 9/13/23.
2. https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clia-categorizations#Scorecard. Access 9/13/23.

CLIA moderate complexity testing: general requirements[1]

Test categorization

Tests are classified in two general categories depending on test complexity.

Waived

Nonwaived

- Moderate complexity
- High complexity
  - Specialized scientific knowledge and training are required.

POCT blood gas testing is categorized as moderately complex.

Moderate complexity

Tests requiring basic lab knowledge and training for personnel performing the test.

- To perform moderate complexity testing, labs must:
  - Have a CLIA certificate.
  - Be inspected.
  - Meet specific CLIA quality requirements.
- These laboratories also require a CLIA Certificate of Compliance (CoC) or Certificate of Accreditation (CoA).

1. https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493. Accessed 9/13/23.

CLIA certification and CMS-approved accreditation[1]

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Certificate of Accreditation (CoA)

- Many laboratories choose to apply for a CoA.
- Laboratories partner with a CMS-approved accrediting organization and must comply with the standards set by that organization.
- An accreditation organization inspects laboratories once every 2 years.
  - Citations during an inspection may put the laboratory's ability to perform this critical testing in jeopardy.

CMS-approved Accrediting Organizations[2]

- American Association of Blood Banks (AABB)
- American Association for Laboratory Accreditation (AALA)
- Accreditation Association for Hospitals and Health Systems/Healthcare Facilities Accreditation Program (AAHHS/HFAP)
- American Society for Histocompatibility and Immunogenetics (ASHI)
- COLA, Inc.
- College of American Pathologists (CAP)
- The Joint Commission

Notes:

- Laboratories select the accrediting organization at time of CLIA application.
- Some accrediting organizations offer resources to assist in the CLIA application process. Contact the organization for more details.

1. https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493. Accessed 9/13/23.
2. https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/aolist.pdf. Accessed 9/13/23.

CLIA quality standards[1]

In general, CLIA standards center on policies and procedures designed to monitor and evaluate the ongoing and overall quality of the total testing process, including:

- **Personnel Requirements: Positions & Qualifications**
- **Personnel Competency Assessment**
- **Proficiency Testing Performance**
  - Externally validate the quality of the laboratory's performance.
- **Verification of Performance Specifications**
  - Verify accuracy, precision, reportable range, reference intervals /range.
- **Calibration and Calibration Verification**
  - Verify accuracy and performance.
- **Quality Control Procedures**
  - Monitor and evaluate the testing process to assure accurate and reliable patient results.

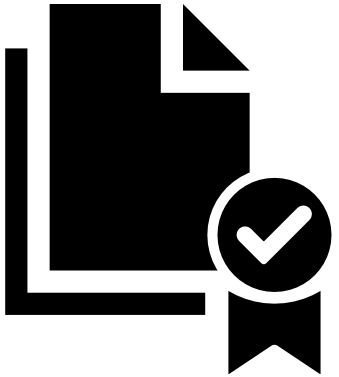
The laboratory is responsible for managing the blood gas program and for ensuring the program meets CLIA quality standards.

1. https://www.cdc.gov/mmwr/preview/mmwrhtml/00016177.htm. Accessed 9/13/23.

Quality control (QC) procedures[1,2]

Follow established written procedures to monitor and evaluate the entire analytical testing process to assure accurate and reliable patient results.

- QC consists of the activities used to detect errors that occur due to:
  - Test system failure
  - Adverse environmental conditions
  - Variance in operator performance
- Laboratories can:
  - Follow CLIA quality control requirements, or
  - Can meet CLIA quality requirements with the development and implementation of an Individual Quality Control Plan (IQCP).



1. https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493. Accessed 9/13/23.
2. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/CLIAbrochure12.pdf. Accessed 10/19/23.

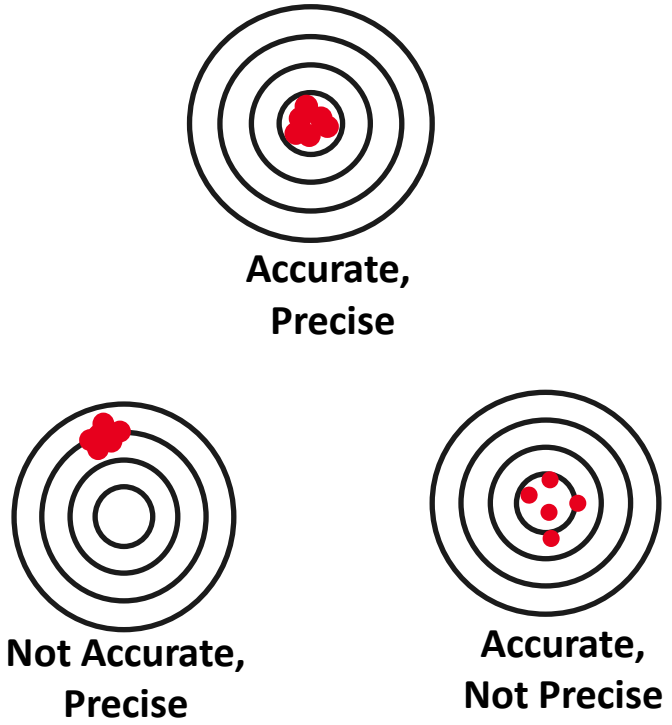
Considerations in diagnostic testing

Providers and patients rely on clinical tests to inform their treatment decisions, making it critically important that tests are reliable.

- Test reliability is measured by the test performance measures: accuracy and precision.
  - Accuracy is how close a value is to its true value.
  - Precision is how repeatable a measurement is.

Laboratory tests are subject to many factors, or variables, that could adversely affect test performance.

- It is important to mitigate variables *throughout* the diagnostic testing process to maintain test reliability.



https://www.testing.com/articles/laboratory-test-reliability/. Accessed 10/19/23.

The total testing process

The total testing process, from ordering a test through delivering a result, is divided into the pre-analytical, analytical, and post-analytical stages.

Pre-analytical stage:
all processes performed prior to testing a specimen

Analytical stage:
all processes performed during the testing of a specimen

Post-analytical stage:
all processes performed after test analysis

Carraro P, Plebani M. Errors in a stat laboratory: types and frequencies 10 years later. Clin Chem. 2017 Jul 1;53(7):1338-42. Available from: https://doi.org/10.1373/clinchem.2007.088344

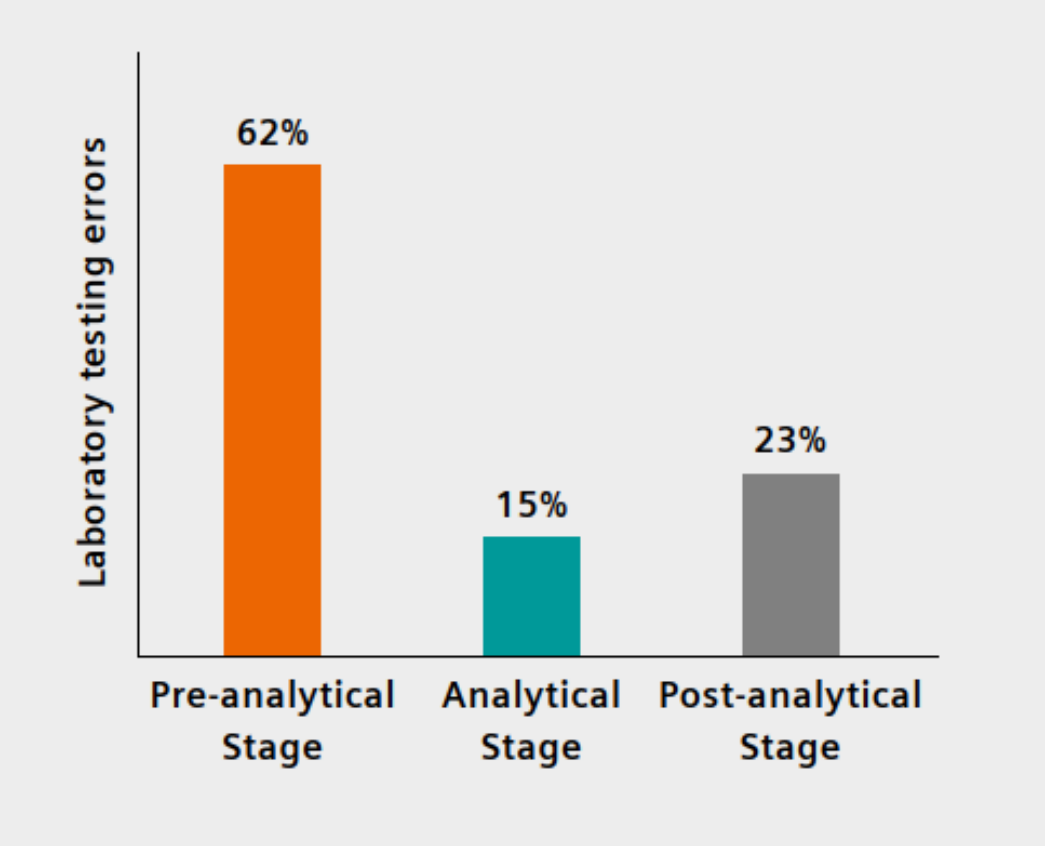
Laboratory testing errors

Errors can occur throughout the total testing process.

Most testing errors occur in the pre-analytical stage.

Pre-analytical stage:
all processes performed prior to testing a specimen

- Patient identification
- Specimen collection
- Labeling
- Transportation



Point-of-care testing (POCT) enables testing at or near the site of patient care, reducing many pre-analytical variables.

Carraro P, Plebani M. Errors in a stat laboratory: types and frequencies 10 years later. Clin Chem. 2017 Jul 1;53(7):1338-42. Available from: https://doi.org/10.1373/clinchem.2007.088344

Lippi G. Preanalytical quality improvement: from dream to reality. Clin Chem Lab Med. 2011;49(7):1113-26. doi: 10.1515/CCLM.2011.600

Mitigating risk in POCT

The Food and Drug Administration (FDA) regulates medical devices and provides guidance on risk mitigation.

FDA Risk Control

Potential sources of error for consideration:

- Operator error/human factors
- Specimen integrity and handling
- Reagent integrity (reagent viability)
- Hardware, software, and electronics integrity
- Stability of calibration and internal controls
- Environmental factors

Failsafes and Failure Alerts

Lockout functions that do not allow output of results if:

- Controls or system checks are not successfully completed.
- The device detects damage during internal electronic system checks.
- Expired reagents are used.

Internal procedural controls to flag procedural problems such as:

- Improper sample flow
- Incorrect use of components
- Improper addition of specimen

Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) waiver applications for manufacturers of in vitro diagnostic devices: guidance for industry and Food and Drug Administration staff. U.S. Food and Drug Administration. Available from: https://www.fda.gov/media/109582/download. Accessed 10/19/23..

Pre-analytical stage: sources of error and mitigations

Stage	Source of Error	Mitigation
Pre-analytical **All processes performed prior to testing a specimen**	• Test system access by unauthorized/untrained users	• Configurable operator access • User ID/password requirements • Operator lockout
	• Patient identification • Specimen labeling	• Bar-code readers for positive patient identification and specimen labeling
	• Specimen collection Examples: air bubbles, clots, hemolysis	• Easy-to-use companion collection devices • Blood collection training guides/videos • Ability to test samples immediately after drawing
	• Specimen integrity • Specimen storage and stability • Specimen transportation	• Bedside and near-patient testing that mitigates risk of sample degradation
	• Specimen processing	• Education and training guides for specimen processing

Identifying and mitigating potential variables in point-of-care testing. Siemens Healthcare Diagnostics Inc. Order No. POC-21-NAM-2215 · Digital only · 03.2021 · © Siemens Healthcare Diagnostics Inc., 2021

Analytical stage: sources of error and mitigations

Stage	Source of Error	Mitigation
Analytical All processes performed during testing of a specimen	Reagent stability	• Systems with room-temperature stability, or • Staff training in quality processes for inventory storage and access
	Test system calibration error	• Automatic calibration with failsafes and error messages to prevent testing when failures occur
	Failed quality control	• Failsafes and error messages to prevent testing when failures occur
	Selection of correct sample type	• Sample type selection required by operator
	Reagent lot expiration	• Bar-coded reagents that enable automatic checks for lot expiration, or • Implementing and training staff on quality processes for inventory storage and access

Identifying and mitigating potential variables in point-of-care testing. Siemens Healthcare Diagnostics Inc. Order No. POC-21-NAM-2215 · Digital only · 03.2021 · © Siemens Healthcare Diagnostics Inc., 2021

Analytical stage: sources of error and mitigations

Stage	Source of Error	Mitigation
Analytical All processes performed during testing of a specimen	• Internal system operating error	• Electronic internal QC monitoring throughout test process • External QC • Failsafes and error messages to prevent testing if failures occur • IQCP
	• Operator error	• Training guides, videos, and competency assessment • Guided instructions on display screen
	• Insufficient sample volume/incorrect sample introduction	• Automatic sensor with audible and visual messages • Failsafes and error messages to prevent testing if failures occur
	• Test result out of range	• Administrator rights to set analyte reference ranges • Flagging of out-of-range results
	• Test result in critical range	• Administrator rights to set critical results • Analyzer that can flag and document critical results in record

Identifying and mitigating potential variables in point-of-care testing. Siemens Healthcare Diagnostics Inc. Order No. POC-21-NAM-2215 · Digital only · 03.2021 ·

Post-analytical stage: sources of error and mitigations

Stage	Source of Error	Mitigation
Post-analytical All processes performed after test analysis	• Undocumented or incorrectly documented result Example: transcription error	• Results displayed on and stored in instrument with associated patient/QC information, plus ability to recall results • Connectivity for secure transmission of results and associated information to data management system
	• Delayed reporting of critical results	• Connectivity for secure transmission of results and associated information to data management system
	• Confirmation of result transmission	• Flagging of errors in result transmission

Identifying and mitigating potential variables in point-of-care testing. Siemens Healthcare Diagnostics Inc. Order No. POC-21-NAM-2215 · Digital only · 03.2021 ·

Quality by design

IQCP: The Individual Quality Control Plan (IQCP) is designed to mitigate risk associated with non-waived testing, except pathology and subspecialties, in each laboratory and to provide an effective quality control program.

There are three parts in a complete IQCP:

1. Risk Assessment (RA)
2. Quality Control Plan (QCP)
3. Quality Assessment (QA)

System design can help address risk mitigation in most areas.

The five components of the RA

1. **Specimen:** Patient preparation, specimen collection, specimen labeling, specimen storage and stability, transportation, processing, acceptance, and rejection
2. **Test System:** Inadequate sampling, detection of sample errors, interferences, mechanical or electronic failure detection, optics, bar codes, calibration, internal or external controls, temperature, LIS, and result reporting
3. **Reagent:** Shipping, storage conditions, preparation, and expiration dates
4. **Environment:** Temperature, humidity, ventilation, light, noise or vibration, utilities, and space
5. **Testing Personnel:** Education, experience, training, competency, and staffing numbers

https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/iqcp-workbook.pdf. Accessed 10/19/23.

Quality by Design: RAPIDPoint 500e System

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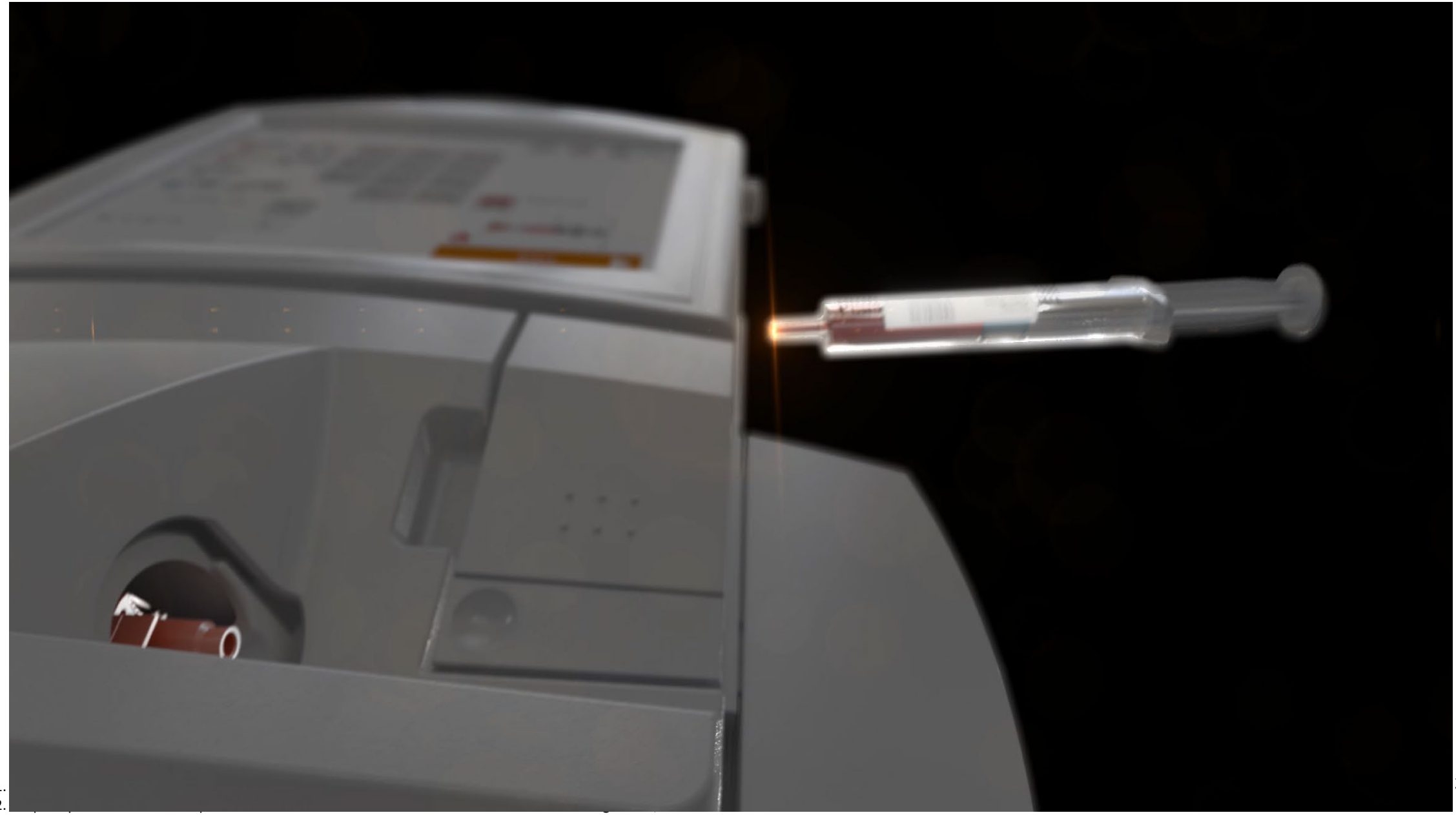

1. 2023
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Quality by design: examples

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Benchtop POCT: RAPIDPoint 500e Blood Gas System

Integri-sense Technology	A comprehensive series of analyzer functional checks and flagging mechanisms designed to deliver accurate critical care test results and efficient day-to-day operation
Automatic calibrations	Routine calibrations at prescribed intervals, for each analytical parameter for each sample, without operator involvement.
Automatic quality control	Three levels of independent automatic quality control span the clinically significant ranges. -QC follows same pathway as patient's whole blood.
System algorithm checks	Advanced software algorithms enable the analyzer to be ready to generate reliable, clinically actionable test results in approximately 60 seconds.
Universal hands-free sample port	Provides protection from biohazards during system operation and ensures consistent sample aspiration independent of operator technique.
Clot, bubble and short-sample detection	Comprehensive software algorithm checks continually monitor sample integrity. -Failsafes include built-in detection, mitigation procedures, and error messages.
Management of interfering substances	Constant monitoring of sensor response data identifies interferences, triggering automatic correction and error messages.
24-minute cartridge initialization time	A new sensor module, CO-ox chamber, and sample probe are included with every new cartridge. -Short initialization time mitigates downtime.

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Integri-sense Technology: maintenance-free cartridge technology

RAPIDPoint 500e system uses three cartridges:

- **Measurement cartridge:** Includes the planar sensors, sample probe and sample port, calibration solutions, and CO-oximeter chamber.
- **Wash/Waste cartridge:** Cleans the sample pathway after every analysis and collects the waste.
- **Automatic quality control (AQC) cartridge:** Contains three independent QC solutions and is fully programmable according to hospital requirements.

Advantages

- ☑ If a clot is detected, enters the analyzer, and is unrecoverable, only affected cartridges need replacement.
- ☑ There are a variety of measurement cartridges to accommodate different workloads/menu requirements, all with 28-day onboard use life.
- ☑ AQC cartridge is positioned so that the QC solutions follow the same pathway as the patient sample.
- ☑ AQC is fully automated and simply requires replacement every 28 days
- ☑ Wash/waste is only replaced every 10 days or as needed, with no interruption in testing workflow.

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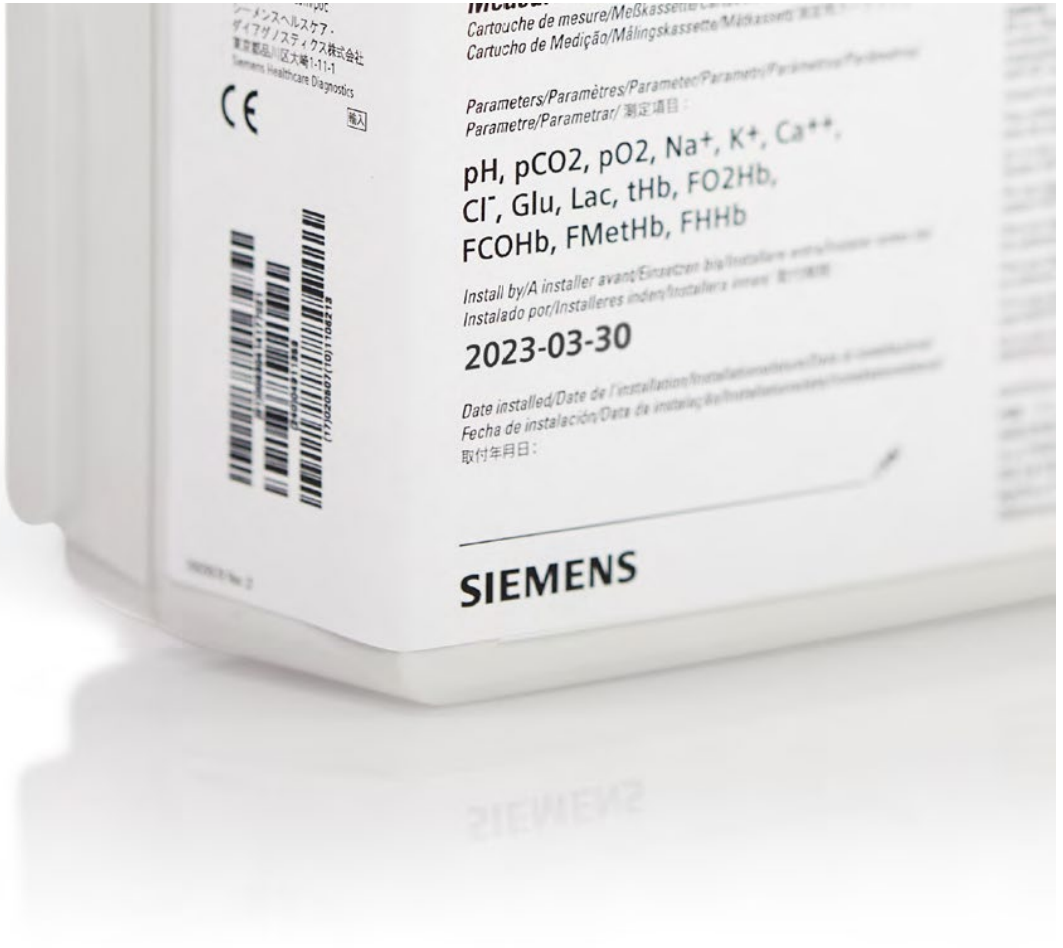
Integri-sense Technology: benefits of refrigerated storage

Refrigerated storage of the measurement cartridge ensures the integrity of the calibration solutions and planar sensors for their full 28-day use life.

- ☑ Cartridge can be installed immediately after removal from the refrigerator.
- ☑ Can be stored at room temperature for up to 24 hours before installation (full cartridge) or up to 7 days (blood gas and CO-ox only cartridge).
- ☑ Valid for up to 28 days (or the number of tests) after installation on the system.



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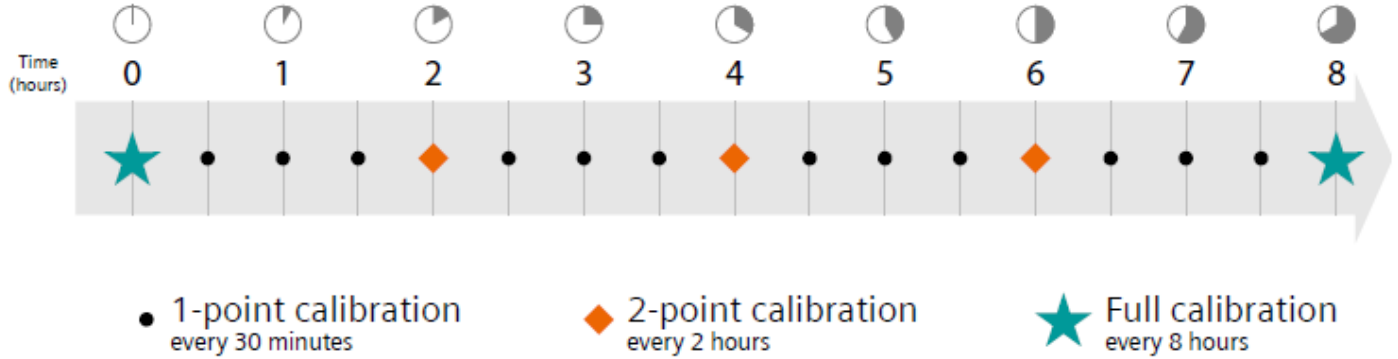
Integri-sense Technology: calibrations

Automatic calibrations

- Routine calibrations at set intervals adjust the slope and/or offset drift for each measured parameter.
  - 1 point every 30 minutes
  - 2 point every 2 hours
  - Full calibration every 8 hours
- No operator involvement required. Automatic calibrations and liquid quality control require minimal to no user intervention.
- If the calibration is not successful, the system automatically turns off the affected parameter until a successful calibration is performed.
  - Results for the other parameters may continue to be reported if calibrations are successful.



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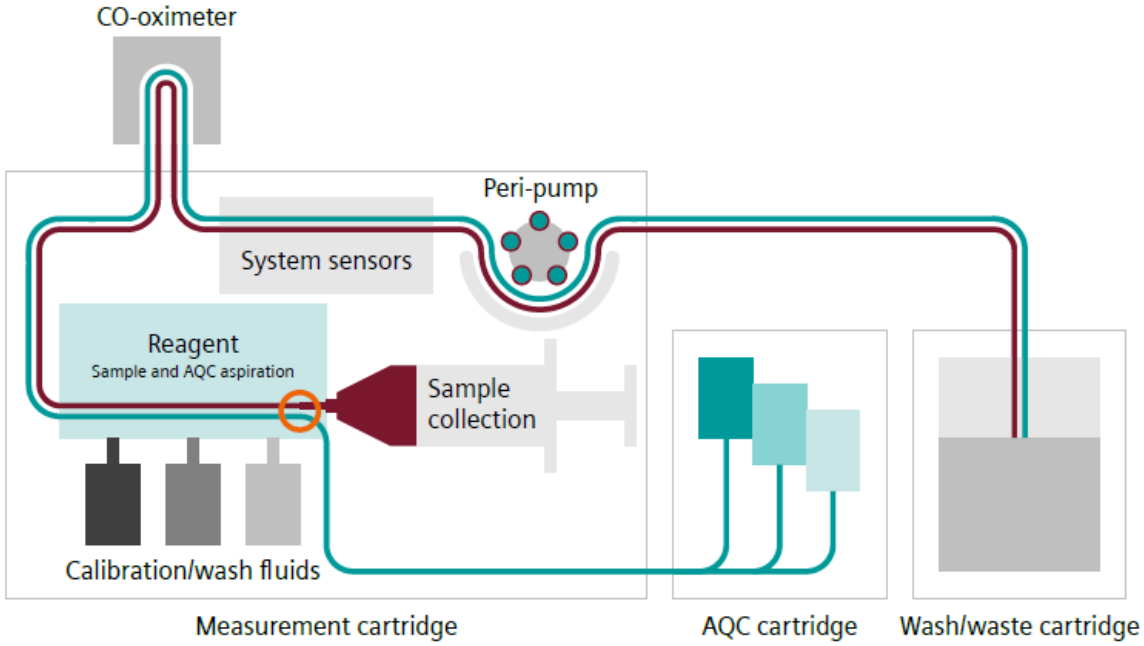
Integri-sense Technology: quality control

Automatic Quality Control (AQC)

- Three levels of independent liquid QC span clinically relevant medical decision levels.
- QC material is automatically presented to the analyzer and removes the need for operator intervention.
- Runs at scheduled intervals that can be customized to meet regulatory requirements.
- AQC solutions and patient samples follow exactly the same pathway as the patient sample.
- Consistency of the manufacturing process allows AQC solutions to be considered as one continuous lot number with no expiration date.
- Benchtop system complies with CLIA, CLSI guidelines, and ISO 15189 by allowing onboard review of Levey-Jennings charts.



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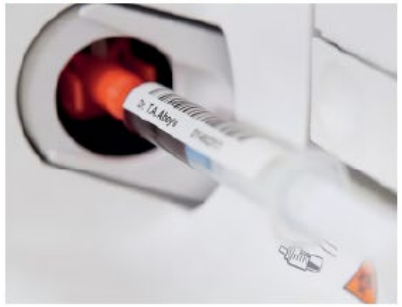
Integri-sense Technology: advanced sample management

Sample port simplifies sample introduction and minimizes instrument downtime.

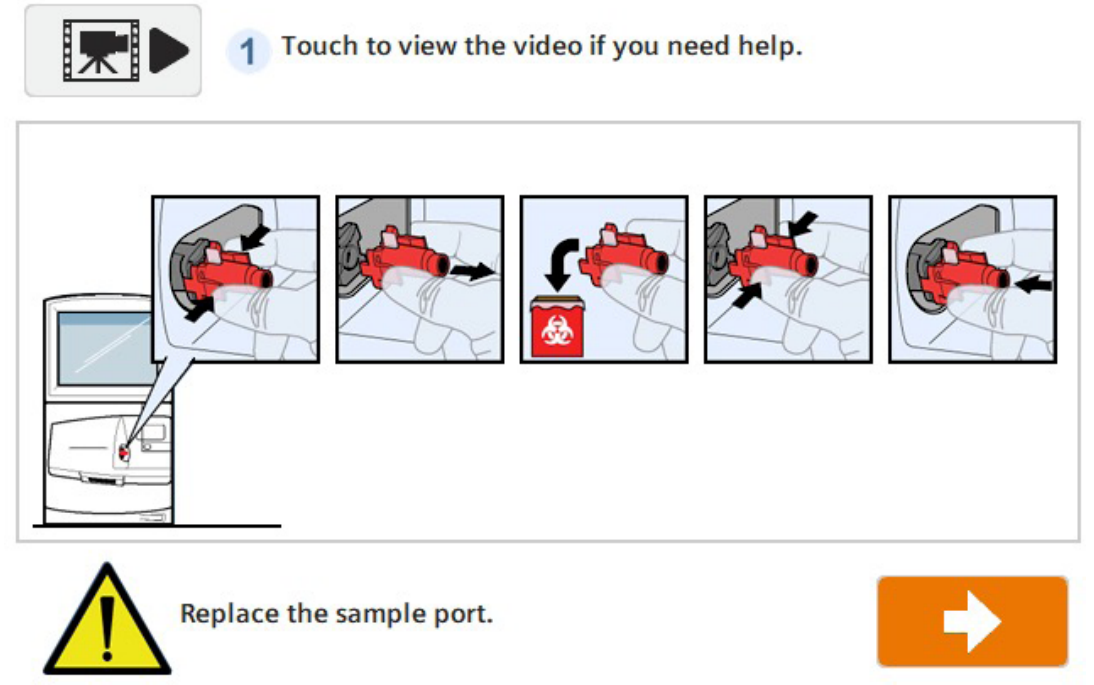
- Hands-free, universal sample port provides protection from biohazards during system operation and ensures consistent sample aspiration independent of operator technique.
- Sample aspiration is automatic and hands-free through a standardized sampling procedure for syringes, capillaries, ampules, and open-top tubes with approved adapter.

Sample port

Sample port with syringe



Sample port with capillary



- When a clot is captured in the sample port, the operator is alerted to replace the sample port. On-board system guidance walks the operator through replacement in as little as 90 seconds.

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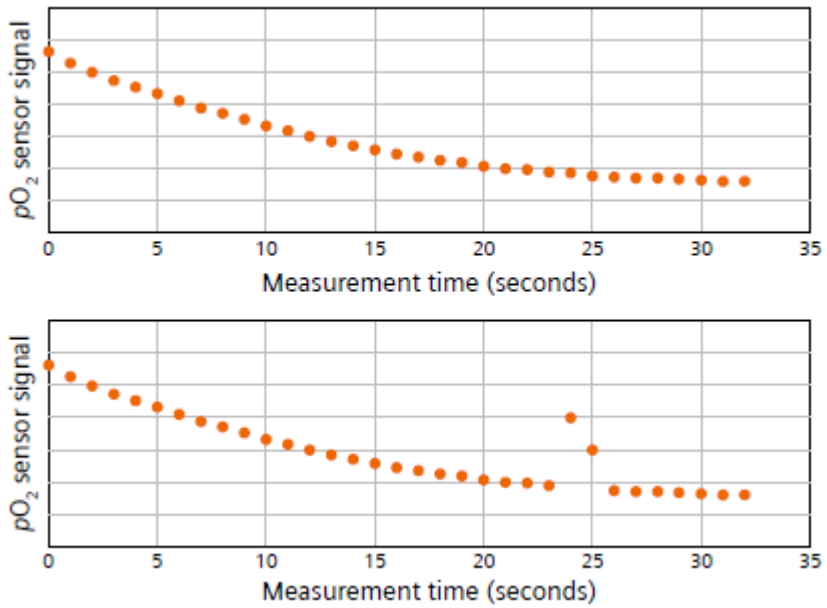
Integri-sense Technology: clot, bubble, and short-sample detection

Comprehensive software algorithm checks continually monitor sample integrity.



RAPIDPoint 500e system software maps of normal (above) and abnormal (below) analyte response curves. **Note the abnormal occurrence at the 25-second interval.**

- The patient sample is continuously monitored for clots and bubbles to help ensure accurate results and protect the measurement cartridge sensors from the potentially negative effect of excessive fibrin.
- In addition to detecting and managing samples that contain clots, the system detects bubbles early in the sample pathway as well as in the CO-oximeter sample chamber.
- The sample path is automatically monitored by fluid detectors to ensure the integrity of the patient sample fluid flow throughout the entire aspiration process.
- If a bubble is detected, the system will not analyze the sample and a “Bubbles in Sample” or “Excessive Bubbles in CO-ox sample” message will appear in the events log.
- Short samples are detected by the same fluid detectors used for bubbles.
- If a short sample is detected, an “Insufficient Sample” message will appear in the events log.

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