

Onboard Quality Controls for the CoaguChek[®] XS System

The new CoaguChek XS Anticoagulation Monitoring System incorporates a new onboard quality control system that eliminates the need for liquid controls in a CLIA-waived setting.

This paper explains the QC chemistry and profiles the performance testing results of the new system.

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INTRODUCTION

Roche Diagnostics is introducing the new CoaguChek XS System, which quantitatively determines prothrombin time (PT) in INR, %Quick or Seconds using capillary blood from a fingertip or untreated venous whole blood.

One of the key features of the new system is integrated Onboard Quality Control (OBC) technology, which is designed to provide an even higher level of quality assurance than conventional liquid control testing.

Traditionally, healthcare providers have used liquid controls to check one test strip out of every package, and then conclude that the quality of this strip is representative of all the test strips. While this approach has provided excellent quality assurance, it does not allow the user to perform a quality test on the actual strips used for the patient test.

The CoaguChek XS System's OBC technology offers a test-strip-integrated QC system that checks each individual strip while it is being used for the patient's blood testing. All the quality control tests are performed on every single test strip, in the same reagent chamber – and thus the exact physical and chemical environment – where the patient test results are determined.

A separate chemical pathway in the reaction pad of the CoaguChek XS PT test strip works with a special "misuse detector" – the chemical Resazurin and the by-product Resorufin – to confirm reagent formulation and detect exposure to high humidity, extreme temperature, light and other environmental factors that could affect strip integrity. As a result, no liquid quality controls are needed with the CoaguChek XS system when it is used in a CLIA- waived environment.

TEST CHEMISTRY

PT/INR test principle

The CoaguChek XS PT Test Strip uses a human recombinant thromboplastin with a 1.0 ISI and a peptide substrate. The enzyme thrombin (factor IIa) cleaves the peptide substrate, generating an electrochemical signal. The system converts this signal into INR by means of an algorithm and then displays the result.

Onboard Quality Control test principle

Onboard (built-in) Quality Control enables the CoaguChek XS System to automatically check for meter performance, proper strip chemistry, and test strip mishandling with each patient test.

In addition to the active substances (hrTF and Electrocyme TH), the test strip chemistry contains the blue chemical indicator Resazurin, which acts as a “misuse detector.” Resazurin is sensitive to ambient factors like light, humidity, and temperature, which create a reaction that reduces Resazurin to Resorufin.

After blood application, both Resazurin and Resorufin are quantified electrochemically using the same electrodes and the same meter functions that are used for the clot detection. This reaction is not reversible; therefore, the quantity of the Resorufin in the strip is a direct measure of any strip mishandling or damage.

This OBC test principle is unique in that it ensures that a check of the test strip integrity is performed for every single strip at the same place (same reaction chamber) and same time as the PT test.

OBC measurement principles

The Level 1 OBC test quantifies the amount of Resazurin at the test area of each individual test strip, which *corresponds directly with the amount of all components (hrTF and Electrocyme TH) in the formulation used for the clot detection*. Thus, the Level 1 OBC detects strip defects such as capillary compression and reagent problems (e.g., not enough reagent on strip, uneven coating of strip, etc.), as well as meter/electrode defects. Level 1 defects would typically be ones that occurred during the manufacturing process.

The Level 2 OBC test quantifies the amount of the by-product Resorufin, which is a direct measure of strip damage or misuse. This enables the system to check for strip mishandling, such as extended exposure to daylight or conditions of high humidity or temperature.

The Level 1 and Level 2 limits have been set to values specifically established to ensure that no unreliable result is displayed to the user due to exposure of the test strip to conditions out of specifications. The rationale is that the OBC function must provide an error message early enough to pick up the deterioration of the thromboplastin before prolonged clotting times will generate erroneous INR results. Since the OBC chemistry corresponds directly with the clot detection chemistry, the lot-specific ranges of the OBC system have been intentionally set to be more sensitive to strip mishandling than the clot detection chemistry.

PERFORMANCE TESTING PARAMETERS

The primary goal of functionality testing for the onboard quality control system was to assess the system's performance in the detection of defective and/or incorrectly handled test strips.

The expectations for system testing were a 100% detection rate of defective strips and no unreliable INR values displayed to the user. In other words, either the INR value displayed is reliable or an "ERROR QC" message is displayed by the system.

For the study, whole blood samples with a mean INR of 1.0 and an INR range of 0.7 – 1.3 were used. Test strip vials of Lot #2 were stored opened for different periods of time (0, 24, 48 and 72 hours) and at various stressed environmental conditions.

Release Testing and Lot-Specific Ranges

The Level 1 OBC and Level 2 OBC lot-specific baseline values were derived from data collected during homogeneity testing of a test strip lot using whole blood. During the homogeneity testing, the Level 1 OBC mean (electrical signal) and the Level 2 OBC mean (electrical signal) were calculated for each reagent reel. (Strips are manufactured as dried chemistry on laminated reels.) Each reel has 64 values (measured across the entire reel), and each test strip lot includes 13 laminated reels. As a result, the overall mean for each test strip lot is calculated from 832 single values (13 reels x 64 values per reel = 832 values per strip lot). This overall mean is set as the baseline for the Level 1 OBC and Level 2 OBC for the entire lot.

Like liquid control ranges, the OBC ranges are determined by the imprecision of the system. The lot-specific limits (baseline and upper thresholds) are set to be broad enough to give the OBC sufficient specificity – in this case, less than 4% wrong error messages, or $\geq 96\%$. The imprecision is determined by three major components: (1) strip imprecision over a complete test strip lot; (2) aging of the test strips over the shelf life; and (3) meter-to-meter variation.

The unit of measurement used by the CoaguChek XS meter to describe lot-specific ranges is called an "OBC Unit." An OBC Unit represents the electrochemical charge measured by the meter, which correlates directly with the concentration of Resazurin and Resorufin in a specific test strip lot.

The pre-determined baseline and upper threshold values for both Level 1 and Level 2 OBC are lot specific and are programmed into the lot-specific code chip that is packaged in every test strip box.

METHODOLOGY AND RESULTS

To simulate mishandling conditions, the CoaguChek XS PT test strips were stored open for different periods of time (0, 24, 48, and 72 hours) in three different environmental conditions:

Climate Zone IV (30°C/86°F, 70% RH)

Hottest and most humid naturally occurring environment (e.g., India and Singapore)

Extreme Climate A (32°C/90°F, 85% RH)

Maximum temperature and humidity allowed for test strip storage¹

Extreme Climate B (40°C/104°F, 85% RH)

Conditions that exceed temperature/humidity limits allowed for test strip storage

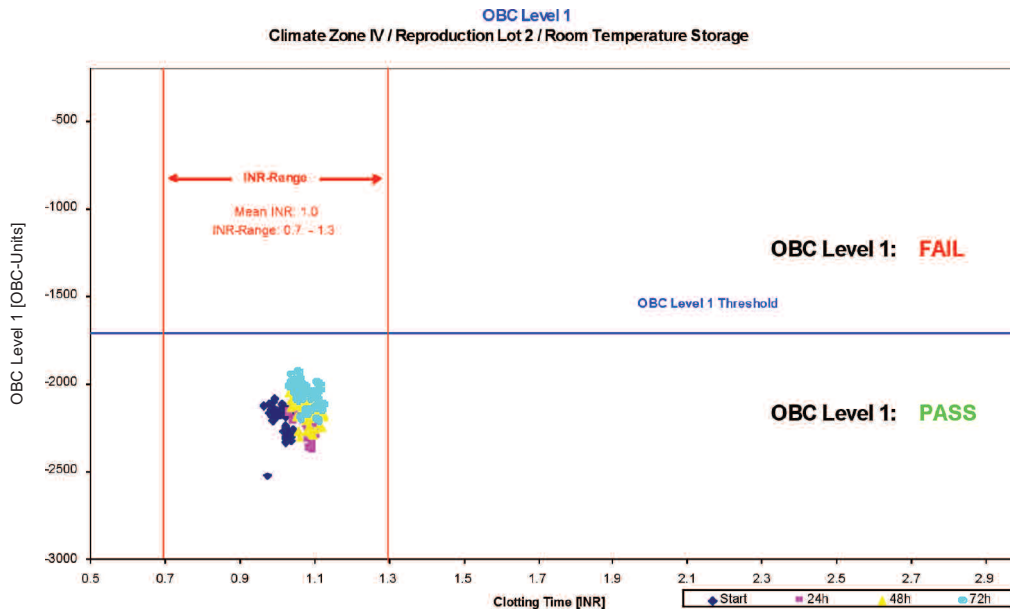
The graphs on pages 5 and 6 illustrate the OBC system performance results that were obtained in CoaguChek XS System testing.

The results are plotted on graphs that designate both the acceptable INR ranges (vertical lines) and the allowable programmed threshold in OBC Units (horizontal line).

Using Lot #2 as an example, the data in the graphs demonstrate that the Onboard Quality Controls for the CoaguChek XS System properly detected – 100% of the time – when QC results were within and outside of these pre-determined ranges.

Climate Zone IV

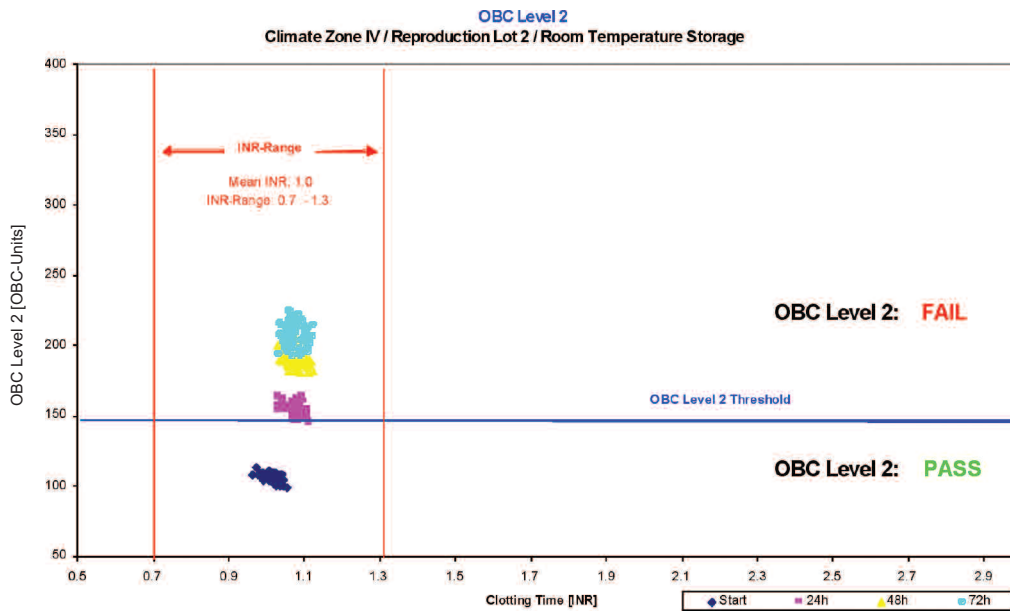
Time stressing: 0, 24, 48 and 72 hours



Level 1 OBC is in the PASS Zone: Reagent Manufacturing is Acceptable (Pass)
No INR result is out of range

Climate Zone IV

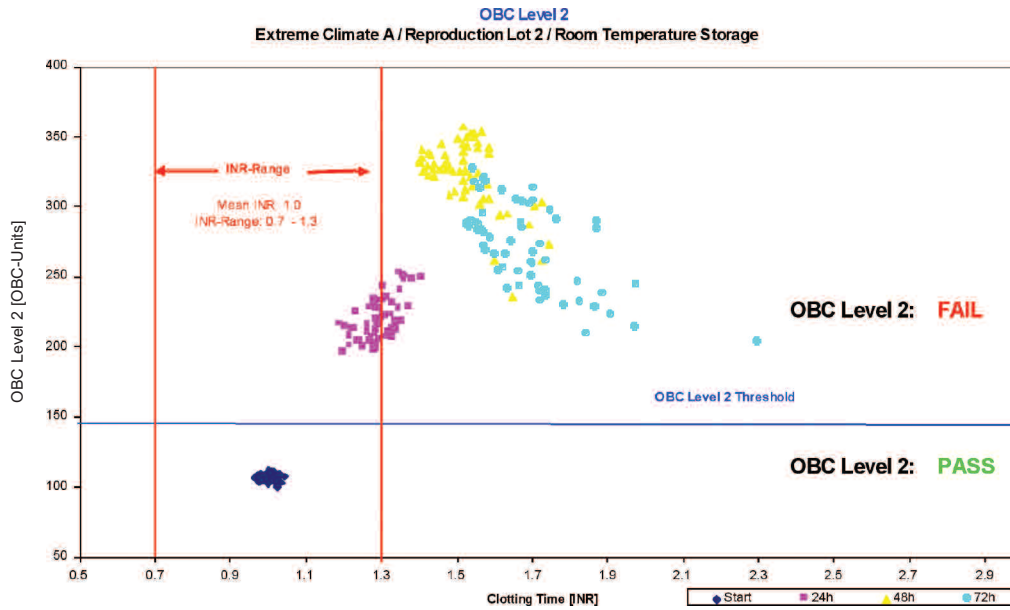
Time stressing: 0, 24, 48 and 72 hours



Level 2 OBC (amount of the by-product Resorufin) goes up over time, into the FAIL Zone, indicating the test strip has been exposed to higher temperature/humidity.
Level 2 OBC fails before the INR goes out of range.

Extreme Climate A

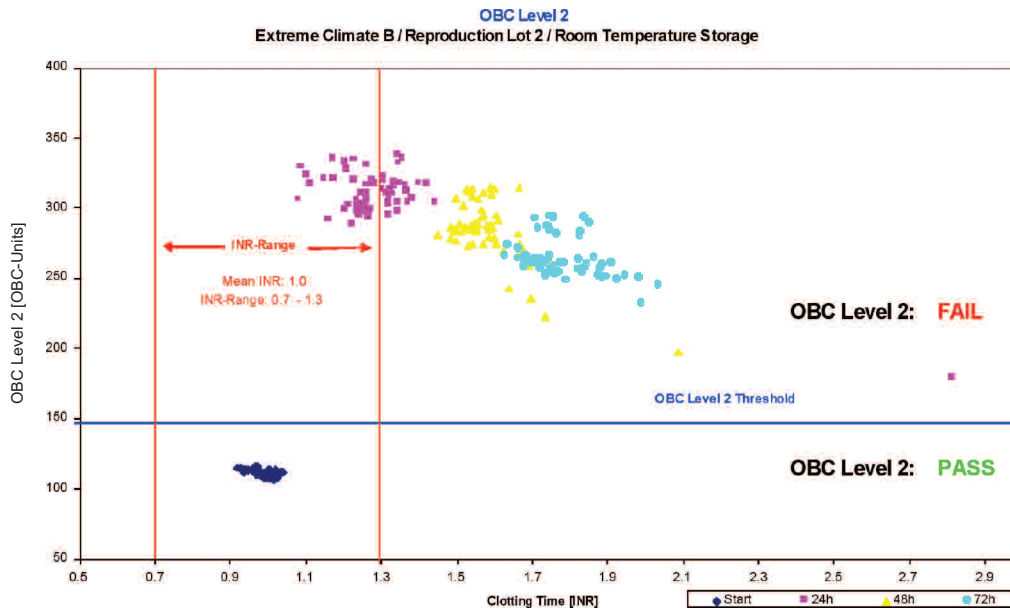
Time stressing: 0, 24, 48 and 72 hours



Level 2 OBC is well into the FAIL Zone when the INR begins to go out of range. The Level 2 OBC fails before the INR becomes unacceptable.

Extreme Climate B

Time stressing: 0, 24, 48 and 72 hours



Again, Level 2 OBC is well into the FAIL Zone when the INR begins to go out of range. The Level 2 OBC fails before the INR becomes unacceptable.

CONCLUSIONS

The Lot #2 data shown in the graphs demonstrate that the CoaguChek XS System provided 100% detection of defective or improperly handled test strips for the study sample.

As illustrated by the graphs, Level 1 OBC and Level 2 OBC failed (indicated an error) at their pre-determined threshold on every strip tested, and the OBC system always failed prior to any INR result going out of range.

In each of these instances, the meter would automatically display an “ERROR QC” message and no INR value would be displayed.

These study results indicate that strip mishandling is reliably detected by the CoaguChek XS System, helping ensure that only correct INR results are displayed to the user. And, because the OBC system checks every single test strip, liquid controls are no longer needed to check the CoaguChek XS System performance in a CLIA-waived environment.



Diagnostics

1. CoaguChek XS System package insert. Indianapolis, IN. Roche Diagnostics Corporation, 2006.

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