Urgent Field Safety Notice
SBN-RMD-2020-002

RMD / **cobas**® 4800
Version 1
19-Nov-2020

cobas z 480 dirty lens: Potential for invalid or false positive results

Product Name	**cobas z** 480 analyzer
GMMI / Part No **Device Identifier**	GMMI: 05200881001 Device Identifier : 04015630929016
Production Identifier (Lot No./Serial No.)	Not Applicable
SW Version	Not Applicable
Type of Action	Field Safety Corrective Action (FSCA)

Dear Valued Customer,

Description of Situation

Roche received 15 complaint cases alleging false positive or invalid results with select **cobas**® 4800 IVD assays. The complaint investigations confirmed the presence of dirty lenses within the **cobas z** 480 analyzer in 10 of the 15 escalated cases. After lens cleaning by local Field Service Engineers, no additional false positive results were observed. The false positive results were attributed to spatial cross-talk, due to a dirty lens, where the fluorescent signal from true positive wells scattered to adjacent wells.

Impacted assays were identified based on assay-specific algorithm parameters.
The affected full workflow assays include:

- **cobas**® CMV Quantitative nucleic acid test for use on the **cobas**® 4800 System,
- **cobas**® HBV Quantitative nucleic acid test for use on the **cobas**® 4800 System,
- **cobas**® HCV GT HCV genotyping test for use on the **cobas**® 4800 System,
- **cobas**® HCV Quantitative nucleic acid test for use on the **cobas**® 4800 System,
- **cobas**® HIV-1 Quantitative nucleic acid test for use on the **cobas**® 4800 System
- **cobas**® HIV-1 Nucleic acid test for use on the **cobas**® 4800 System,
- **cobas**® HSV 1 and 2 Test for use on the **cobas**® 4800 System,
- **cobas**® HPV Test for use on the **cobas**® 4800 System,
- **cobas**® 4800 CT/NG Test,
- **cobas**® CT/NG v2.0 Test,
- **cobas**® Cdiff Test for use on the **cobas**® 4800 System.

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The affected PCR only workflow assays include:

- **cobas**® EGFR Mutation Test v2,
- **cobas**® 4800 BRAF V600 Mutation Test,
- **cobas**® KRAS Mutation Test.

Root Cause Analysis

Internal studies including the use of multiple **cobas z** 480 analyzers, over 200 test runs across the analyzers used, and a variety of AD plate sealing conditions (not sealed; partially sealed) were performed. These studies confirmed that improper sealing of the AD-plate contributes to dirty lenses. Although dirty lenses were observed in these studies, spatial cross-talk and false positive/invalid results were not reproduced. These observations suggest that dirty lenses due to improper sealing of the AD-plate alone do not cause spatial cross-talk and false positive results. There are likely additional factors, including age and usage of the instrument as well as laboratory environmental conditions, that contribute to dirty lenses, spatial cross-talk and false positive/invalid results.

Risk Assessment

The current installation base is greater than 4000 **cobas z** 480 analyzers worldwide, and there have been 15 reported cases to date where the **cobas z** 480 analyzers had dirty lenses to the extent where false positive/invalid results were generated (~0.38% complaint rate).

For Infectious Disease assays, the probability of serious adverse health effects due to a false positive or invalid/delayed result is extremely unlikely (i.e., not likely). In the case of false positive results, the risk of significant harm is mitigated by the fact that each positive test should be interpreted by the clinician in the context of the clinical situation.

In the case of invalid/delayed tests, the risk of significant harm can be mitigated by the fact that in most cases, there will not be a prolonged delay in diagnosis as residual sample is often available for another test, and if not, a new sample can usually be obtained for the repeat test. In addition, the results of parallel, secondary diagnostic tests may also reduce the risk of the invalid test.

There is, however, a remote probability of medically reversible or transient adverse health effects due to false positive results, especially since erroneous results may not be readily detectable. As a result, patients may be provided an incorrect diagnosis, resulting in psychological distress and unnecessary treatment. Side effects/toxicities could be caused by medications, but these would usually be temporary and reversible.

For Genomics and Oncology assays, the probability of serious adverse health consequences to the population at greatest risk and to the overall population from an invalid/delayed result is extremely unlikely (i.e., not likely). In most cases, an invalid result would be a minor inconvenience requiring retesting of a tissue sample or obtaining another blood sample. It would be unlikely to cause any significant delay in therapeutic decision-making. In a worst-case scenario, the tissue sample is exhausted requiring a new biopsy or the patient is not readily available for another blood draw.

There is, however, a remote probability of serious adverse health consequences to the population at greatest risk (i.e., cancer patient) from a false positive result due to exposure to potentially toxic drugs. This risk may be mitigated as any positive test should be interpreted in the context of the clinical situation and physicians would be alerted when unusual mutation patterns are reported. Additionally, if the patient was not responding to the therapeutic prescribed based on the false positive result, the patient would only be on therapy for a brief period of time before being changed to a standard of care therapy.

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Actions taken by Roche Diagnostics (if applicable)

This situation represents a potential safety concern

For Full Workflow Customers running Virology, HPV, CT/NG, C. Diff. assays:
Full-workflow assays include those that use the **cobas x** 480 instrument for automated sample preparation together with the **cobas z** 480 analyzer for real-time amplification and detection.

The affected full workflow assays include:

- **cobas**® CMV Quantitative nucleic acid test for use on the **cobas**® 4800 System,
- **cobas**® HBV Quantitative nucleic acid test for use on the **cobas**® 4800 System,
- **cobas**® HCV GT HCV genotyping test for use on the **cobas**® 4800 System,
- **cobas**® HCV Quantitative nucleic acid test for use on the **cobas**® 4800 System,
- **cobas**® HIV-1 Quantitative nucleic acid test for use on the **cobas**® 4800 System
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- **cobas**® HPV Test for use on the **cobas**® 4800 System,
- **cobas**® 4800 CT/NG Test,
- **cobas**® CT/NG v2.0 Test,
- **cobas**® Cdiff Test for use on the **cobas**® 4800 System.

For these customers, Affiliate organizations will schedule site visits to inspect the optical lens in the **cobas z** 480 analyzer detection unit and clean, if necessary. Additionally, updated inspection instructions will be included in the periodic maintenance schedule within the service documentation and will be performed yearly.

For PCR Only Workflow Customers Running EGFR, BRAF, and KRAS assays:
PCR only workflow assays include those that only utilize the **cobas z** 480 analyzer for real-time amplification and detection where sample preparation is manually performed.

The affected PCR only workflow assays include:

- **cobas**® EGFR Mutation Test v2,
- **cobas**® 4800 BRAF V600 Mutation Test,
- **cobas**® KRAS Mutation Test.

For these customers, Affiliate organizations will request Problem Reports for review, and schedule cleaning visits, if necessary. Roche is in the process of developing a service tool that will utilize customer raw data files generated with the referenced PCR only workflow IVD assays to determine whether **cobas z** 480 analyzer lens cleaning is required or not. The tool uses the raw data, found in the Problem Reports, to identify spatial cross-talk. Stringent criteria have been established to identify a dirty lens *before* false positive results are generated.

The proposed actions are short-term solutions to check and clean the lens, if necessary, and are not intended to prevent the lens from getting dirty during subsequent use. As noted above, there are multiple factors that contribute to the generation of a dirty lens in addition to the improper sealing of the AD-plate that could result in spatial cross-talk and false positive/invalids results. The proposed actions are expected to evaluate the status of the lenses and identify a dirty lens *before* false positives could occur. It is important to note that the User Assistance provides detailed instructions on how to properly seal AD-plates before amplification/detection in the **cobas z** 480 analyzer.

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Actions to be taken by the customer/user

For Infectious Disease assays:
Customers should follow laboratory standard operating procedures to investigate the potential for false positive results for assays where a change in result reporting could impact patient management. This could apply to assays utilized in the management of chronic diseases (e.g. hepatitis C) or those utilized in serial monitoring (e.g. CMV) where only the most recent result for a patient would have the potential to affect management. For assays used for the diagnosis of acute, self-limited conditions, a retrospective review of previous results or retesting would not result in a change in patient management.

For G&O assays:
While a false positive result might be difficult to detect, the clinical context of the patient, occurrence of unusual mutation patterns and ongoing laboratory quality management testing will help mitigate a false positive result.

Contact your local affiliate organization if there is any allegation of invalid or false positive results with the **cobas**® 4800 system assays.

Communication of this Field Safety Notice (if appropriate)

<If the recipient needs to forward the FSN to additional organizations/individuals then one or more of the following statements may be included:

This notice must be passed on to all those who need to be aware within your organization or to any organization/individual where the potentially affected devices have been distributed/supplied. (If appropriate).

Please transfer this notice to other organizations/individuals on which this action has an impact. (If appropriate).

Please maintain awareness of this notice and resulting action for an appropriate period to ensure the effectiveness of the corrective action. (If appropriate).>

The following statement is mandatory in FSNs for EEA countries but is not required for the rest of the World:

Include if applicable: The undersigned confirms that this notice has been notified to the appropriate Regulatory Agency.

We apologize for any inconvenience this may cause and hope for your understanding and your support.

<closing salutations>,

Contact Details

To be completed locally:
Name
Title
Company Name
Address

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Tel. +xx-xxx-xxxx xxxx
Email name@roche.com