URGENT FIELD SAFETY NOTICE
IMMEDIATE ACTION REQUIRED

Ref No:	**PFSN18 Deviations of high (>4.5) CoaguChek INR values due to masterlot calibration issue SBN-CPS-2018-014-v2.0**
Date:	**17.09.2018**
Type of Action:	**Field Safety Corrective Action (FSCA)**
Product Affected:	CoaguChek XS PT Test PST CoaguChek XS PT Test CoaguChek PT Test
System Affected:	CoaguChek® XS system CoaguChek® INRange system CoaguChek® XS Plus system CoaguChek® XS Pro system CoaguChek® Pro II system
Software Version:	N/A

Product No	Material No	Lot No (1st 6 digits as below)
CoaguChek XS PT Test PST	07671679190, 07671687019	from 272167xx up to 334498xx
CoaguChek XS PT Test	04625374190, 04625358019, 04625315019	from 272167xx up to 334498xx
CoaguChek PT Test	06688721019	from 272170xx up to 353606xx

Summary of Issue

Reason for Version 2 Expanded workaround options, due to inquiries about the use of other thromboplastins or unaffected CoaguChek test strips for comparison measurement. This version 2 notice supercedes the version 1 notice 'PFSN18 Deviations of high (>4.5) CoaguChek INR values due to calibration with WHO reference standard rTF/16 SBN-CPS-2018-014' .

We wish to inform you that Roche Diagnostics has decided to implement a temporary re-calibration of our CoaguChek PT, XS PT and XS PT PST test strips to the previous WHO Standard rTF*/09. At the same time, we can confirm that all CoaguChek test strips in the market which have been calibrated to the latest WHO standard rTF/16 (please refer to the lot numbers mentioned above) are safe to use for results up to 4.5 INR.

**(rTF = human, recombinant thromboplastin / recombinant human tissue factor reagent)*

Reason for Notice

Description of Situation

Since the market introduction of CoaguChek, test strips have been calibrated against standard

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reference thromboplastin provided by the WHO. In 2016, a new WHO reference Thromboplastin, rTF/16, was established. This new WHO reference standard is calibrated to INR values between 1.5 and 4.5 INR and is derived from human tissue factors. Compared to the previous WHO standard of human based thromboplastin (rTF/09), it leads to a slight increase in INR values and shows a higher International Sensitivity Index (ISI)[1]:

WHO Standard	ISI
rTF/09	1.08
rTF/16	1.11

Table 1: ISI values of WHO standards

As the global leader for INR Point-of-Care solutions, Roche was one of the first companies to switch to the new WHO standard. CoaguChek test strips calibrated to this new (rTF/16) standard were delivered to markets worldwide from January 2018 onward.

Roche Diagnostics has received an increased number of complaints regarding deviations of CoaguChek test strips against non-Roche controls as well as laboratory methods during the last weeks. Therefore, we initiated an in-depth analysis in order to determine the reasons for the observed differences.

Our findings:

- For values up to 4.5 INR and calibrated to the new (rTF/16) WHO standard (1.5-4.5 INR), a mean difference of +6% was found when we compared in an internal validation study the new CoaguChek test strips against test strips calibrated to the previous (rTF/09) reference WHO standard.
- In our complaint investigation we have seen an unexpected additional increasing positive bias in the upper INR range (> 4.5 INR).
- Due to these findings, it was decided to limit the use of the currently available CoaguChek (XS PT, XS PT PST, and PT) strips to the range of up to 4.5 INR which is in accordance to the validation of the WHO standard.
- In general, several influencing factors e.g. lot to lot differences, pre-analytics (e.g. sample tubes) can have a significant influence on the comparison of different methods (see graph below).

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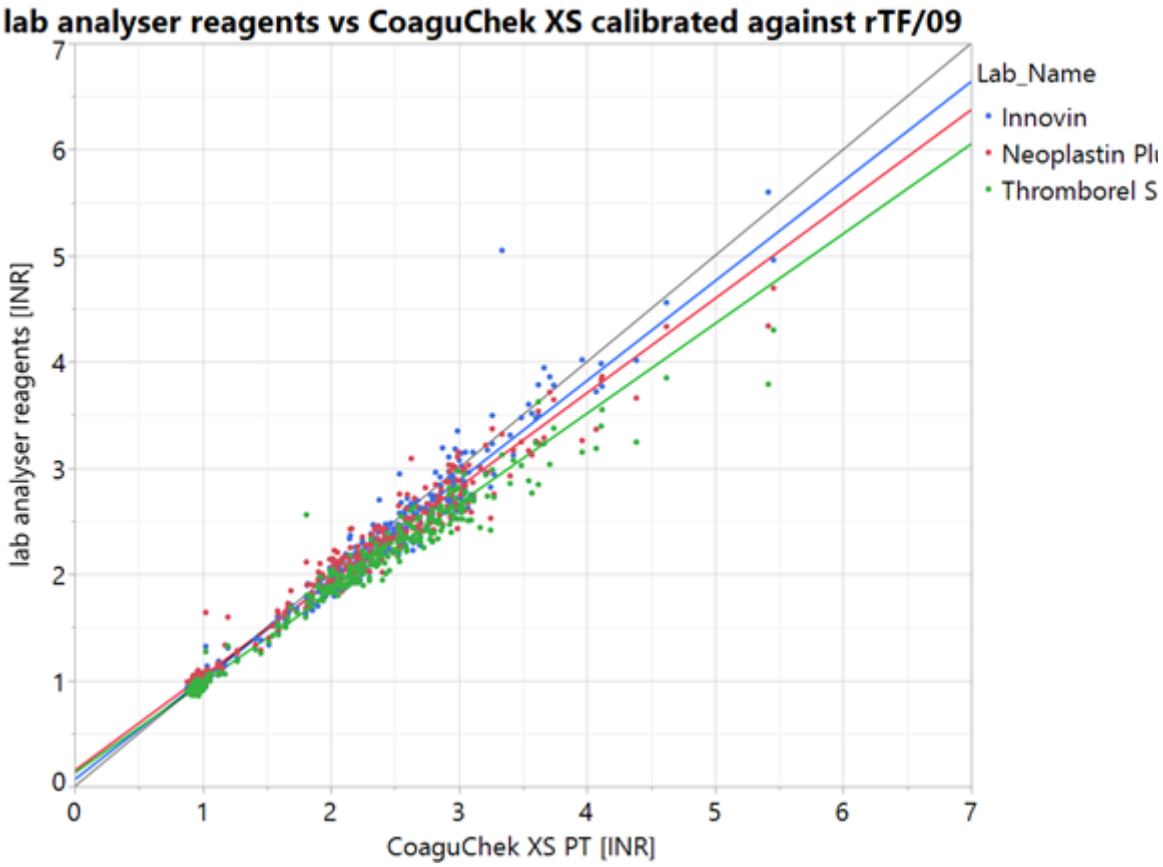

Graph: Roche Diagnostics, External Masterlot calibration study CoaguChek XS PT, 2017

- No deviations have been experienced with the CoaguChek test strips referenced to the previous WHO standard rTF/09. Most laboratory methods are still calibrated against the previous (rTF/09) WHO standard.
- Internal analysis of complaints showed that after therapy changes (change of dosage, additional medication, hold of medication) the frequency of testing was not always adapted. Therefore, we recommend to follow the local medical guidelines regarding an increased testing frequency after therapy changes.

Actions taken by Roche Diagnostics

Since a medical risk, due to inadequate therapeutic measures, for INR ranges >4.5 INR, cannot be excluded, it was decided to re-calculate the calibration for upcoming CoaguChek strip lots according to the previous WHO standard (rTF/09). Moreover, the current CoaguChek test strips, calibrated to the new WHO standard rTF/16, can still be used but are limited to INR values up to 4.5 INR. For all values above 4.5 INR, measured with CoaguChek test strips of the affected lot numbers, the advice under “actions to taken by the customer/user” must be followed.

The first test strips re-calibrated to rTF/09 will be available from **November 2018** for the following lot numbers:

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REF-Number	Product Name	Lot Number (Code Key)
07671679190	CoaguChek XS PT Test PST, 6 tests	≥334499xx (S_344)
07671687019	CoaguChek XS PT Test PST, 24 tests	≥334499xx (S_344)
04625374190	CoaguChek XS PT Test, 6 tests International	≥334499xx (S_344)
04625358019	CoaguChek XS PT Test, 24 tests	≥334499xx (S_344)
04625315019	CoaguChek XS PT Test, 2 x 24 tests	≥334499xx (S_344)
06688721019	CoaguChek PT Test, 2 x 24 tests	≥361433xx (S_062)

Table 2: Availability rTF/09 Lots

With the above mentioned lots in Table 2 the issue is resolved and you can return to your usual testing and treatment procedures.

Until the new lots are available, rTF/16 calibrated test strips continue to be distributed for the following reasons:

- values are reliable up to 4.5 INR
- the difference in the ranges between 0.8 to 4.5 INR, caused by the rTF/16 calibrated test strips when compared to rTF/09 based test strips, does not expose patients to a medical risk

A re-calibration to the new rTF/16 standard will be carefully evaluated.

In 2019 as an additional measure the respective CoaguChek test strip method sheets will be updated, with regard to method comparison.

The "Patient-Information-Letter" attached will be provided to patients that have purchased CoaguChek XS PT Test PST and CoaguChek XS PT Test strips directly from Roche.

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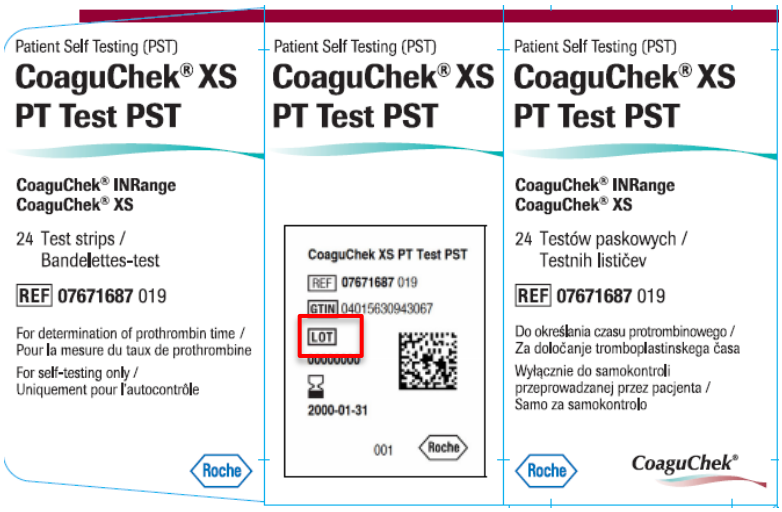
Actions to be taken by the customer/user

Check the lot number on the box of strips to see if it is included in the list of affected lots.
The lot number is printed on the label applied to the test strip box, see below illustration:



In order to prevent any risk to your and our valued patients we ask you for the following actions:

1. Health Care Professionals using one of the affected lots in their GP office/hospital:
   - Values ≤4.5 INR: Values are valid and can be used without a comparison test.
   - Values >4.5 INR: If values >4.5 INR are measured a comparison measurement shall be performed with either a laboratory method or unaffected CoaguChek test strips. In addition, the testing frequency shall be increased according to local medical guidelines until results in the therapeutic range of that individual are obtained until recalibrated material is available.

2. Health Care Professionals (HCP) with patients performing self-testing/self-management:
   - Values ≤4.5 INR: Values are valid and can be used without a comparison test.
   - Values >4.5 INR: If values >4.5 INR are measured a comparison measurement shall be performed with either a laboratory method or unaffected CoaguChek test strips. In addition, the testing frequency shall be increased according to local medical guidelines until results in the therapeutic range of that individual are obtained, until recalibrated material is available.

HCPs are requested to please **reactively** hand out the attached "Patient-Information-Letter" at their discretion, if patients use CoaguChek tests strips of the affected lots calibrated against rTF/16.

3. Insurers & Retailers (wholesalers, pharmacies etc.):
   If patients contact you regarding INR results above their therapeutic range, please advise your customer to contact their local Health Care Professional.

Once you have received the new rTF/09 calibrated test strip lots you can return to your usual testing and treatment procedures.

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Please complete and return the Acknowledgement Form which accompanies this Field Safety Notice by Oct 3rd 2018

Please bring this notice to the attention of all personnel in your hospital or Health Care facility who need to be aware of this safety issue.
If you have forwarded the affected product(s) listed above to another laboratory, please provide a copy of this notice to them.

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

References:

1) van den Besselaar AMHP, Chantarangkul V, Angeloni F, Binder NB, Byrne M, Dauer R, Gudmundsdottir BR, Jespersen J, Kitchen S, Legnani C, Lindahl TL, Manning RA, Martinuzzo M, Panes O, Pengo V, Riddell A, Subramanian S, Szederjesi A, Tantanate C, Herbel P, Tripodi A. International collaborative study for the calibration of proposed International Standards for thromboplastin, rabbit, plain, and for thromboplastin, recombinant, human, plain. J Thromb Haemost 2018; 16: 142–9.

Attachments Patient-Information-Letter
Acknowledgement Form

This action is being conducted with the knowledge of the Medicines and Healthcare Products Regulatory Agency (MHRA), the Health Products Regulatory Authority (HPRA), and other International Regulatory Agencies.

Roche Diagnostics operates a vigilance system that complies with the IVD Directive 98/79 EC

A copy of this notice can also be found on the Roche Dialog Portal

If you require any further information please contact our

Technical Support Hotline

UK: 0808 100 19 20
Ireland: 1800 40 95 64

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