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CN-2018-05
06-Jun-18

URGENT SAFETY CORRECTIVE ACTION

Sysmex XN-Series: Erroneous Automated Eosinophil Count Discrimination

Dear Customers, Healthcare Professional;
Cc : Chairman Medical Board and relevant Head of Department

This letter is to inform you concerning issue on Erroneous Automated Eosinophil Count Discrimination occurred in Sysmex XN-Series.

Product Name	: XN-10 and XN-20 (Cat Nr. AP795756 and AE797961)
Affected S/N	: [redacted]
Intended Use	: The XN series is an automated hematology analyzer for in vitro diagnostic use in clinical laboratories. Only human blood, human body fluids or control blood should be run. Any other use is regarded as non-specified.
Product Owner	: Sysmex Corporation
Address	: 1-5-1, Wakinohama Kaigandori, Chuo-ku, Kobe 651-0073, Japan

Associated AE in Singapore: HSA 600:41/11-146/18/03_22; HSA 600:41/11-146/18/01_33; HSA 600:41/11-146/18/02_65

Problem Description

Please refer to the attached document for more detailed information.

Action to be taken

1. Please sign & return the acknowledgement form 1 that you have received & understood the content of this FSCA letter.
2. Please disseminate the letter to relevant people within your organization.
3. Sysmex representative will coordinate the Ver. 22.07-00 software installation time with you. Upon the installation please sign & return the acknowledgement form 2 to acknowledge that your system has been upgraded into this new software version. Amendment to the product registration to the authority might be required prior the software can be installed into your system.
4. As indicated in the attached letter, please activate the "Action Message" to flag for retest. Kindly ask your local Sysmex representative if you have any doubt.

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Contact Reference

If you have question concerning this information, please contact your local Sysmex Representative. We would be glad to assist you further.

We deeply apologize for any inconvenience caused, and we thank you for your kind patience and continued support.

Yours sincerely,

[redacted] 6 June 2018

Shingo Maeda
VP Business Admin and Planning
Sysmex Asia Pacific

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Sysmex XN-Series

Erroneous Automated Eosinophil Count Discrimination

Make reference to previous issue (Notification March 2017)

Attention

Hematology Lab Manager, Laboratory Director

Introduction

[redacted] Sysmex has become aware of an issue regarding incorrect discrimination in the XN-Series differential (WDF) channel between the Eosinophil and the Neutrophil cell populations. This may result in discrepancies between the automated Eosinophil count and the manual differential Eosinophil count.

Issue

The WDF channel has improved classification over legacy Sysmex systems by employing the Sysmex adaptive flagging algorithm based on shape-recognition (SAFLAS) method of analysis. This method has shown an improved overall flagging performance within the lymphocyte and monocyte cell populations as well as abnormal cell populations with an increase in both sensitivity and specificity in these areas. With this improvement, Sysmex has realized that in some situations [redacted], there may be misclassification between the neutrophil and eosinophil cell populations. Due to a decrease in separation between the neutrophil and eosinophil clusters, the cells may be erroneously counted as a single cell population.

The misclassification has been shown to occur when reactive eosinophils, with an increase in membrane permeability, come in contact with the reagents in the WDF channel. The reaction may induce degranulation of the eosinophils in the WDF channel causing the eosinophil cluster to overlap with the neutrophil cluster. The result of the overlap results in a falsely increased neutrophil result and an eosinophil result of zero.

Clinical Relevance & Impact

Eosinophils normally amount to about 0.24 – 10.24% or 0.01-0.59 x10^9/L [1] of the total circulating leukocytes. The cells proliferate in response to inflammatory stimuli such as in parasitic infestation and allergic reactions, the latter being more common in developed countries [2]. High eosinophil count or eosinophilia (>500 cells/uL) [2] may also be seen in neoplastic condition, in some rare

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conditions or can be of unknown etiology.

Typically, significant changes in the cell counts are interpreted in conjunction with other supporting clinical workups and testing. In cases of chronic eosinophilic leukemia (CEL), a rare type of chronic myeloproliferative disorder, leukocytosis and changes in other cell lineage, such as the appearance of blast cells, could be present [3]. Nonetheless, the laboratory has to be aware that results from a screening method such as the XN, may at times, have to be further investigated with other laboratory techniques and additional clinical assessment to come to a definitive clinical decision.

Corrective Action

With software (SW) version 22.07-00 , Sysmex has improved the algorithm that discriminates degranulated eosinophils, for better differentiation between the neutrophil and eosinophil clusters. The improvement from the original version 00-20(Build9) to ver. 22.07-00 is illustrated in the Figure 1 and Table 1:

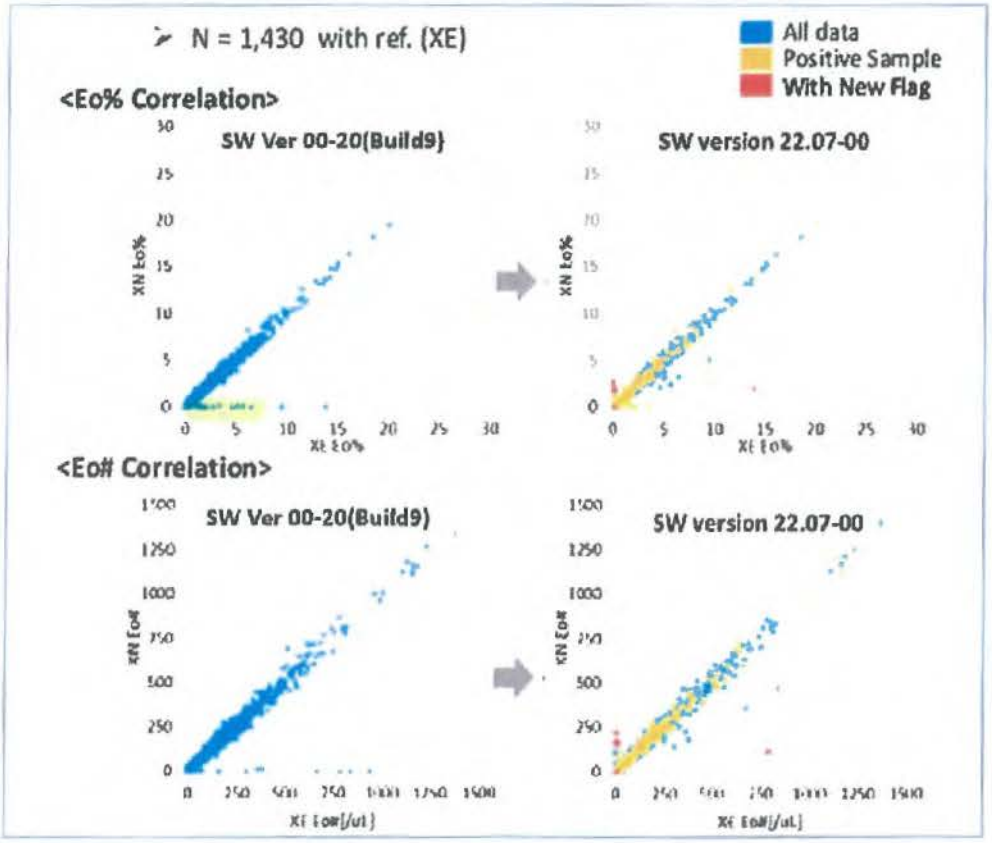

Figure 1: Correlation data between XN and XE (reference analyzer) using the SW 00-20(Build9) and the SW version 22.07-00

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Improved Detection rate on SW version 22.07-00
(No. of samples analyzed: 1430)

SW version 00-20(Build9)	SW version 22.07-00
Incidence of Erroneous Eosinophil count: **N=11 (0.77%)**	Incidence of Erroneous Eosinophil count: **N=7 (0.49%)**

Improved detection rate: 36.36% (4/11)

In cases where discrimination is deemed unreliable, an IP message, *"WBC Abnormal Scattergram"* and an Action message, *"Confirm eosinophil and neutrophil count by other method"* will be displayed and the sample will be judged POSITIVE. The customer has the option to mask the results (---) or mark with an asterisk to indicate unreliability, refer to figure 3 and 4 for screenshots of above mentioned settings:

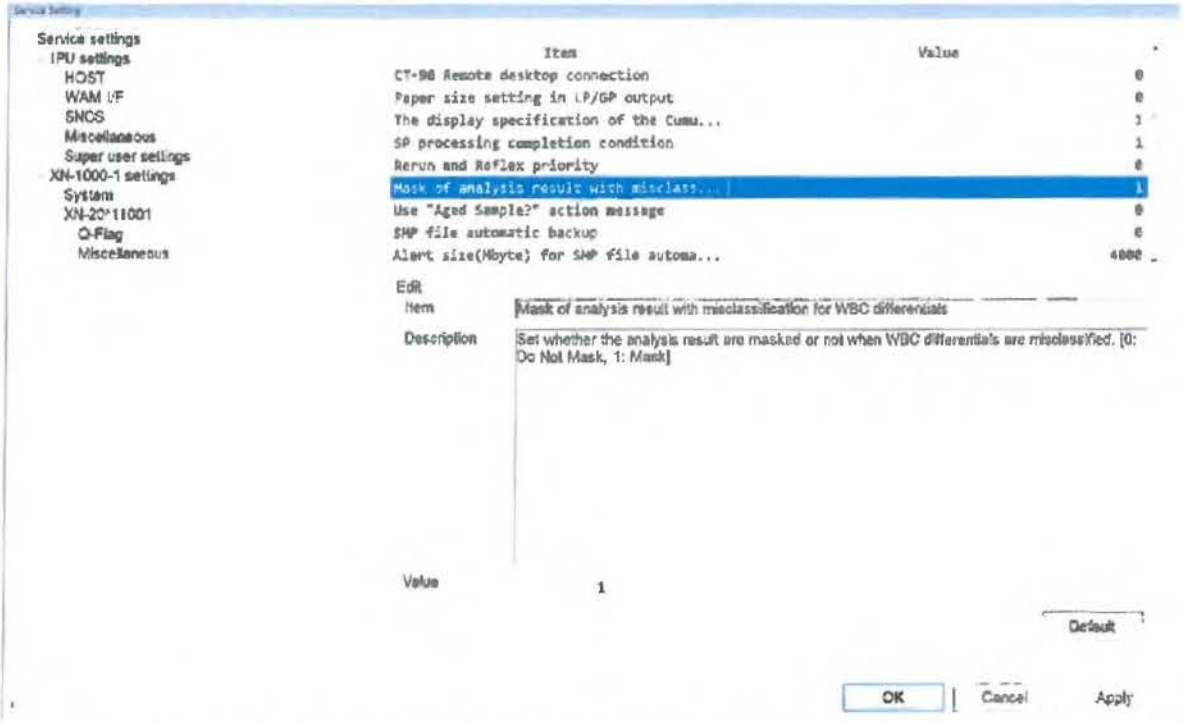

Figure 3: Screenshot of service setting on XN SW version 22.07-00 on selection of setting to mask of analysis result with misclassification for WBC differentials (0: Do Not Mask, 1: Mask)

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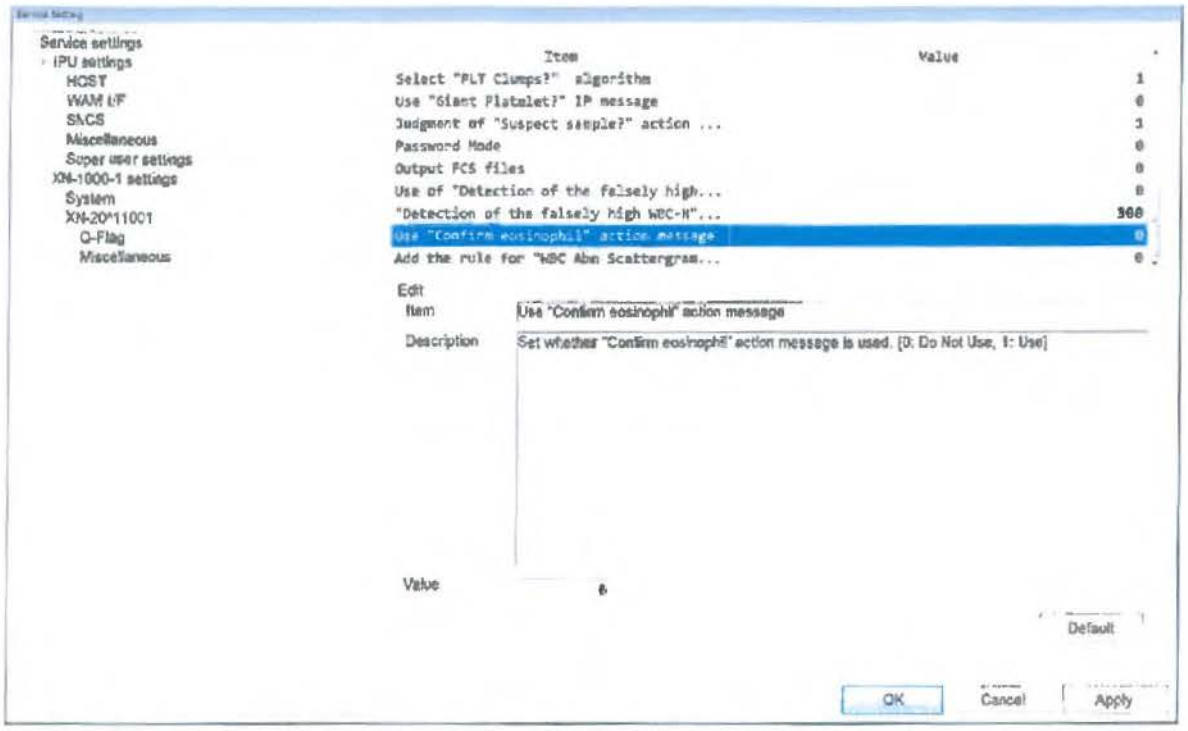

Figure 4: Screenshot of service setting on XN software version 22.07-00 on selection to use "Confirm eosinophil" action message (0: Do Not Use, 1: Use)

With the activation of the new action message "*Confirm eosinophils*", the simulated increase in the review rate based on a database of N=1,430 is 12/1,430 (0.84%).

The operator should follow the laboratory's protocol for further evaluation of the sample.

Action Required:

1. Software ver. 22.07 is available. Your local Sysmex representative will coordinate with you for the installation starting 25 May 2018.
2. Upon installation, Sysmex recommends user to activate Action Message to flag for retest.
3. Please distribute this Product Notification as appropriate to your laboratory and IT staff.
4. File this Product Notification as a part of your laboratory's Quality System as required

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References:

[1] Park SH, Park CJ, Lee BR, Kim MJ, Han MY, Cho YU, et al. Establishment of age-and gender-specific reference ranges for 36 routine and 57 cell population data items in a new automated blood cell analyzer, sysmex XN-2000. Ann Lab Med. 2016;36(3):244–9.

[2[O'Connell EM, Nutman TB. Eosinophilia in Infectious Diseases. Vol. 35, Immunology and Allergy Clinics of North America. 2015. p. 493–522.

[3] Kumar A, Sinha S, Tripathi AK. Chronic eosinophilic leukemia: a case report and review of literature. Indian J Hematol Blood Transfus [Internet]. 2007;23(3–4):112–5. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3453119&tool=pmcentrez&rendertype=abstract

[4]. Montgomery ND, Dunphy CH, Mooberry M, Laramore A, Foster MC, Park SI, et al. Diagnostic complexities of eosinophilia. Vol. 137, Archives of Pathology and Laboratory Medicine. 2013. p. 259–69.

Sysmex Corporation

[redacted] 17 MAY 2018

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CUSTOMER ACKNOWLEDGEMENT FORM 1

Dear Customer, Business Partner & Affiliates,

This acknowledgement form is to confirm the receipt of the enclosed Sysmex Urgent Safety Corrective Action letter dated 6 Jun 2018 regarding Sysmex XN-Series: Erroneous Automated Eosinophil Count Discrimination.

Kindly scan and send the completed form back to Kelvin Fan (email: [redacted]) upon your acknowledgement.

Product	XN-10 and XN-20
CAT No.	AP795756 and AE797961
S/N	[redacted]

Please indicate the amount of XN-10 and XN-20 system you have:

XN-10: _____unit

XN-20: _____unit

By acknowledging this form, you confirm that you have received the enclosed Urgent Safety Corrective Action letter and the content is understood.

Company Name	
Address	
Name of staff	
Designation	
Signature & Company Stamp	
Date	

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CUSTOMER ACKNOWLEDGEMENT FORM 2

Dear Customer, Business Partner & Affiliates,

This acknowledgement form is for you to confirm that the Ver 22.07-00 software has been installed in the XN-10/XN-20 in your facility as per corrective action indicated in the Sysmex Urgent Safety Corrective Action letter dated 6 Jun 2018 regarding Sysmex XN-Series: Erroneous Automated Eosinophil Count Discrimination has been performed.

Kindly scan and send the completed form back to Kelvin Fan (email: [redacted]) upon your acknowledgement.

Product	XN-10 and XN-20
CAT No.	AP795756 and AE797961
S/N	[redacted]

XN-10: Software Ver. 22.-07-00 installed? Yes/ No, _____unit
XN-20: Software Ver. 22.-07-00 installed? Yes/ No, _____unit

Have you activated the "Action Message": Yes / No
If No, please state reason: _____

Company Name	
Address	
Name of staff	
Designation	
Signature & Company Stamp	
Date	