May 24, 2022

URGENT MEDICAL DEVICE CORRECTION NOTIFICATION

Product Issue: High number of total images/unassigned events including (dual positives) and the potential for false positive results being placed into the image gallery in some patient samples for CELLSEARCH® Circulating Tumor Cell Kits (IVD), (Product Code 7900001, Lot Number S108)

Dear Valued Customer:

This is to inform you of an Urgent Medical Device Correction Notification for the following:

Product Name	Product Code	Lot	Expiry Date
CELLSEARCH® Circulating Tumor Cell Kits (IVD)	7900001	S108	04Oct2022

This an Urgent Medical Device Correction Notification has been initiated by Menarini Silicon Biosystems Inc. due to reports of an unusually high number of events (including dual positives) and the potential for (false positives) observed with some patient samples when reviewing the image gallery.

Investigation Summary

We have received reports from a number of customers about the occurrence of an unusually high number of total images/unassigned events and the potential for false positives in the image gallery for some patient samples using the CELLSEARCH® Circulating Tumor Cell Kits (IVD), (Product Code 7900001), Lot Number S108.

An internal review of data and testing has defined and confirmed the occurrence of a high number of unassigned events which includes a large number of dual positives on some patient samples. Testing has also confirmed that there is a potential for false positive images where the CTCs are still staining as expected; however on a few occasions, we have observed images that are dimmer in the PE channel, but may still fit the criteria of a CTC.

Our preliminary investigation identified the problem was related to a manufacturing process issue in one of the Antibody/Fluorochrome conjugations that was utilized in the final staining reagent of the affected kit lot S108.

See the Question and Answer section for further details and images related to this quality issue.

Required Actions

- Discontinue usage of Lot S108 and quarantine the lot in your inventory for disposal.
- Review patient samples run with Kit Lot S108 which had results that were above the cut-off. If you observe any images with the staining pattern of the false positive images shown below or there is any uncertainty regarding these images impacting the patient's outcome from below the cutoff to above the cut-off, the patient sample should be repeated.
- Report any previous occurrence of unusually high number of total images / unassigned events or potential false positive events that have not already been reported to the Customer Technical Support.
- Complete and return the enclosed Confirmation of Receipt form no later than **May 31, 2022**.

Impact to Results

The same Cell Interpretation Guidelines as described in the CellTracks Analyzer II User Guide can be followed to determine if the cells or objects in the image gallery meet the criteria of a CTC.

The unusually high number of total images / unassigned events may require additional time and effort for the operator to review all the images and may cause a delay in reporting the results. In extreme cases, the operator may declare the sample non-evaluable. There has also been reports of potential false positive CTC images related to this issue.

Based upon our investigation and evaluation of the reported complaints, we observed that CTCs are still staining as expected. However; on a few occasions, we have observed images that are dimmer in the PE channel, but may still fit the criteria of a CTC and therefore these additional images could be selected and counted as CTCs by a clinician for some patient samples.

As stated in the Instructions for Use, patient results generated using CELLSEARCH® Kits should be used in conjunction with the overall clinical information derived from diagnostic tests (i.e., imaging and laboratory tests), physical examination and the complete medical history in accordance with appropriate patient management procedures.

It is important that you are aware of the potential impact, as described above, and that you report the occurrence in patient samples to Customer Technical Support.

Resolution

A manufacturing process issue has been identified as the most likely root cause and the investigation is ongoing to further determine root cause and corrective and preventive actions.

We apologize for the inconvenience this may cause your laboratory. We have anticipated questions you may have in the following Question and Answer section.

Should you need any further information, please do not hesitate to contact us using the email address:cellsearch-emeasupport@siliconbiosystems.com or the hotline telephone number toll-free: 00800 0837 4339

Sincerely,

John Clay

John Clay
VP of Quality Assurance and Regulatory Affairs

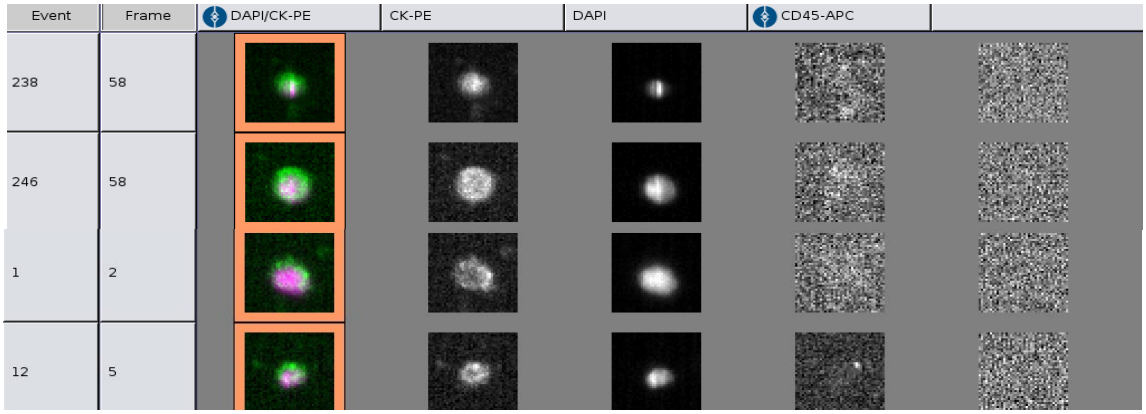
Questions and Answers

1. Can I use my current inventory of the affected lots?

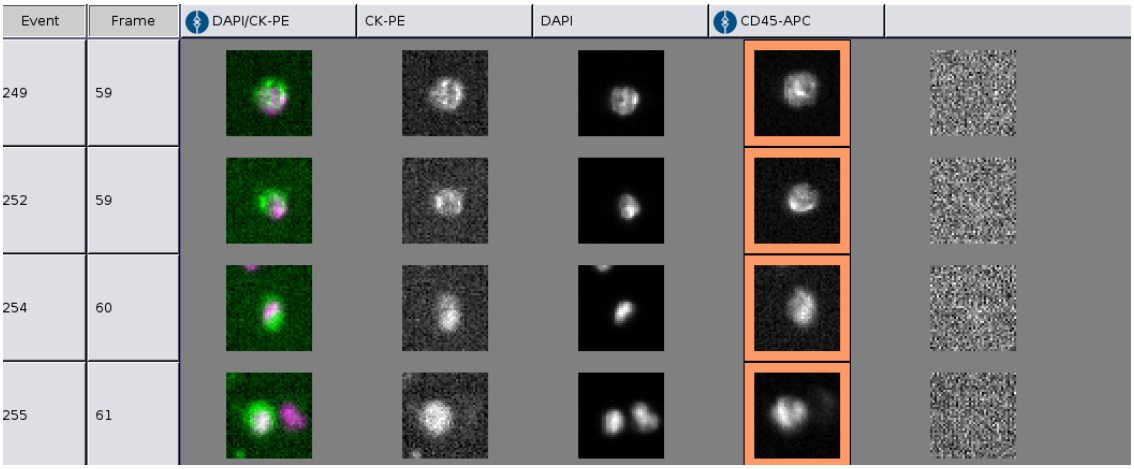
No, please dispose of any affected product in your current inventory. For tests already performed, see the **Impact of Results** and **Required Actions** sections of the letter for potential impact to results.

2. What are the characteristics of the observed images? See Photos and explanation below.

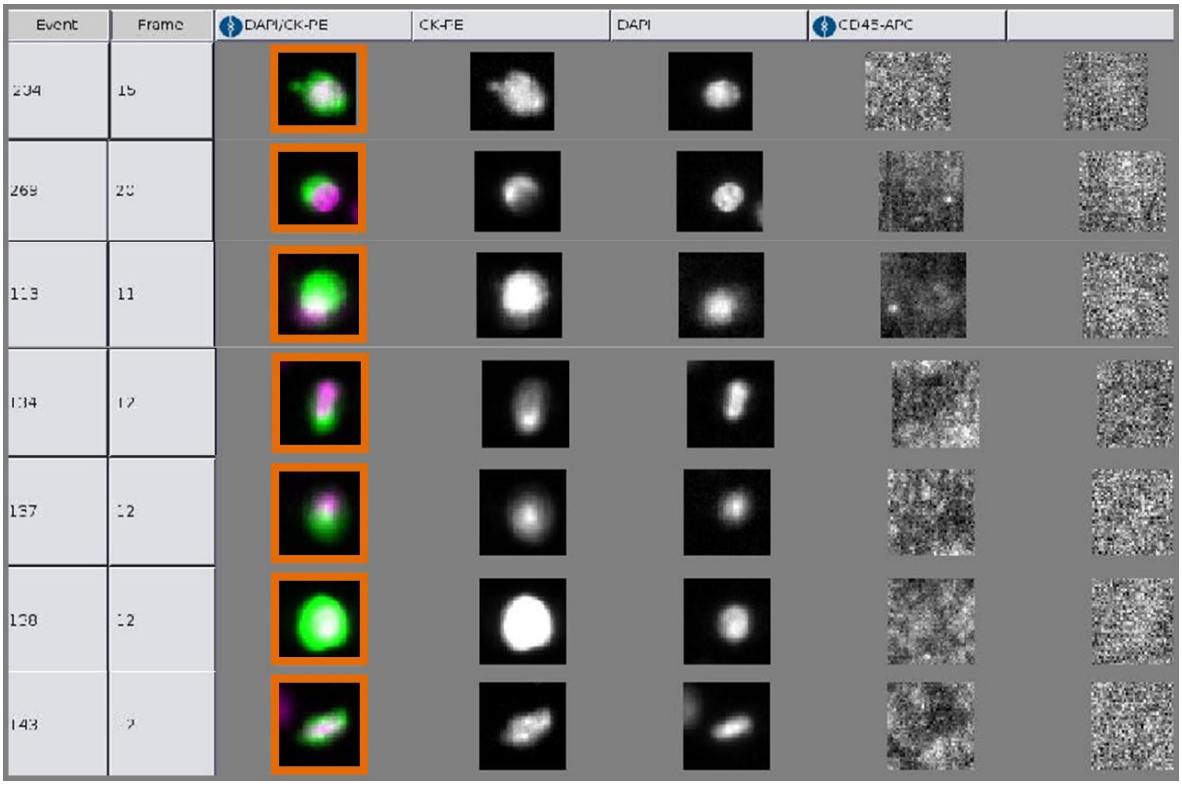
<u>Potential False Positive Images – Dimmer Images of cells fluorescing in the CK-PE, fluorescing in the DAPI, but not fluorescing or showing up well in the CD45-APC Channel.</u>



<u>Dual Positive Images - Images of cells fluorescing in the CK-PE, DAPI and the CD45-APC channels</u>



Typical CTC Images – Images of CTCs fluorescing in the CK-PE and the DAPI Channel, but not fluorescing in the CD45-APC Channel



3. What about previously reported results?

The same Cell Interpretation Guidelines as described in the CellTracks Analyzer II User Guide can be followed to determine if the cells or objects in the image gallery meet the criteria of a CTC. However, the unusually high number of total images / unassigned events may require additional time and effort for the operator to review all the images and may cause a delay in reporting the results. In extreme cases, the operator may declare the sample non-evaluable.

- Patient samples processed using Lot S108 that are below the cut-off require no further action.
- If you observe any images with the staining pattern of the false positive images shown above or there is any uncertainty regarding the images from a patient sample impacting the patient's outcome from below the cutoff to above the cut-off, the patient sample should be repeated.

INTERPRETATION OF RESULTS: Results are reported as the number of CTC / 7.5 mL of blood.

Metastatic Breast Cancer (MBC) - A CTC count of 5 or more per 7.5 mL of blood at any time during the course of the disease is associated with a poor prognosis and is predictive of shorter progression free survival and overall survival.

Metastatic Prostate Cancer (MPC) - A CTC count of 5 or more per 7.5 mL of blood at any time during the course of the disease is associated with a poor prognosis and is predictive of shorter progression free survival and overall survival.

Metastatic Colorectal Cancer (MCRC) - A CTC count of 3 or more per 7.5 mL of blood at any time during the course of the disease is associated with a poor prognosis and is predictive of shorter progression free survival and overall survival.

Patient results generated using CELLSEARCH® Kits should be used in conjunction with the overall clinical information derived from diagnostic tests (i.e., imaging and laboratory tests), physical examination and the complete medical history in accordance with appropriate patient management procedures.

You should discuss any concerns you may have regarding previously reported results with your Laboratory Medical Director or with the requesting physician.

4. Will I receive a credit if a patient sample requires re-testing?

If upon further review, re-testing is deemed necessary, a credit will be issued.

5. Are there other lots available to replace my existing inventory?

We are working on a re-supply plan to ensure you receive replacement for the existing inventory. Upon return of the enclosed confirmation form, we will communicate shortly regarding the product availability.

Customer Confirmation of Receipt and Action

URGENT MEDICAL DEVICE CORRECTION NOTIFICATION

Product Issue: High number of total images/unassigned events including (dual positives) and the potential for false positive results being placed into the image gallery in some patient samples for CELLSEARCH® Circulating Tumor Cell Kits (IVD), (Product Code 7900001, Lot Number S108)

Please return this form to us no later than May 31, 2022**.**

Attn: ***Field Action Coordinator***

EMAIL: cs-correction@siliconbiosystems.com

Section I – Acknowledgement

I read and understood the Urgent Medical Device Correction Notification and will do as instructed.

Section II – Confirmation

Your Name: _____Name of Facility: _____

Your Signature: _____

Date: _____ Telephone: _____

(Your signature provides confirmation that you have received and understood this notification.)

Section III – Reconciliation and Traceability of Products – Product Code: 7900001, CTC Kit Lot S108

Quantity of Kit Lot S108 Unopened: _____

Quantity of Kits Opened: _____ Date Opened: _____

No. of Tests Performed from Opened Kit: _____

Quantity of Kits quarantined for disposal: _____

Your Name: _____Title: _____

Your Signature: _____

Date: _____ Email: _____

(Your signature provides confirmation that you have destroyed the remaining inventory at your site.)