December 18, 2018

FIELD SAFETY CORRECTIVE ACTION NOTICATION

COULTER® EPICS® XL™ Flow Cytometer with System II Software
COULTER EPICS XL-MCL™ Flow Cytometer with System II Software

Product	Part Numbers	Software Versions
COULTER® EPICS® XL™ Flow Cytometer (new, reconditioned or refurbished) with System II Software	All	All
COULTER EPICS XL-MCL™ Flow Cytometer (new, reconditioned or refurbished) with System II Software		

Attention Beckman Coulter Customer,
*Copy: Chairman Medical Board/Head of Departments of Affected consignees

**Applicable to Affected consignees of Singapore only*

Beckman Coulter is initiating a field action for the product listed above. This letter contains important information that needs your immediate attention.

ISSUE:	As a result of customer complaints and subsequent internal investigations, Beckman Coulter has determined that an internal electronic component on the circuit "Amplifier" boards in the EPICS XL/XL-MCL Flow Cytometry systems may be affected by a manufacturing defect. Each EPICS XL/XL-MCL system contains up to seven (7) of the potentially affected Amplifier boards. All instruments are potentially impacted.
IMPACT:	There may be impact to patient results due to this issue when using the EPICS XL/XL-MCL for any application. This manufacturing defect may result in failures causing signal loss and/or signal drifting as follows: ▪ The failure could present itself as signal loss and/or signal drifting resulting in absence of data or a shift in the population in the data plots. ▪ Customers have reported sudden loss of signal, intermittent signal loss, sudden upward or downward shift in signal, upward or downward drift in signal over time, fluctuating signal, suboptimal compensation, erroneous results on affected parameters, and/or increased coefficients of variation (CV) of Flow-Check beads (see **Attachment 1** – FAQ for more details).
ACTIONS:	Implement the following actions for the applications you use * - 1. <u>For All Applications including Laboratory Developed Tests:</u> a. As per the product documentation all data must be reviewed by a laboratory professional prior to the release of reported results from the lab. b. Immediately implement the collection of TIME as a parameter and create TIME versus Parameter plots which will allow the

monitoring of signal integrity as instructed in **Attachments 2 and 3**.

c. Review data as described below:
   i. Review of all TIME plots for each parameter.
   ii. Monitor consistent Forward Scatter, Side Scatter and all fluorescence data over time as shown in **Attachment 3**.
   iii. Unexpected fluctuations in the events over time may indicate compromised fluidics, signal integrity or data acquisition conditions.
   iv. All data must be reviewed prior to the release of any results from the laboratory, via an LIS or any other mechanism.

2. For tetraONE:
   a. As it is not possible to add TIME as a parameter to these protocols, discontinue use of the automated tetraONE application.
   b. You can continue to use the tetraCHROME reagents with the manual gating instructions provided in the product labeling. Refer to CYTO-STAT tetraCHROME IFU, PN B90108 (for tetraCHROME CD45-FITC/CD4-RD1/CD8-ECD/CD3-PC5, PN 6607013 and tetraCHROME CD45-FITC/CD56-RD1/CD19-ECD/CD3-PC5, PN 6607073).
      i. Ensure to follow the instructions in the preceding step to add time as a parameter and create the TIME vs Parameter plots.
      ii. If your laboratory uses Panel Reports, the panels and corresponding panel report templates will need to be constructed as well.
      iii. Create a separate Data Review TIME Plot protocol for data review including TIME, for the manual tetra application (**Attachment 3**).
      iv. Follow the Data Review instructions in the IFU and respective System Guides, as well as the instructions attached to this notification (**Attachment 4).**

3. For stemONE:
   a. By default, the stemONE IVD locked protocols have TIME included as a parameter. There are no additional requirements to create a manual stemONE IVD protocol.
   b. Create a separate Data Review TIME Plot protocol for data review including TIME, for the stemONE application (Attachment 3).
   c. Follow the Data Review instructions in the stemONE System Guide, PN 4277322, Chapter 4 as well as the instructions attached to this notification (**Attachment 5**).

4. For Laboratory Developed Tests:
   In addition to the actions described above, follow the instructions in **Attachment 4** to:

	a. Ensure that the appearance of the data patterns are reviewed and look for suboptimal compensation. b. Ensure that the pattern appearance matches the statistical data reported. 5. Contact Beckman Coulter Customer Technical Support Center or your local Beckman Coulter Representative if you observe any of the issues described. 6. Consult with your Medical Director to determine if a retrospective review of results is warranted.
RESOLUTION:	Beckman Coulter discontinued the manufacturing of new EPICS XL/XL-MCL units in 2011. In 2018 we are discontinuing the service support and the supply of spare parts and system-specific reagents/ controls/ assay target values. We will be contacting you regarding available options to completely retire the units which are not actively used and/ or to assess options to migrate your existing flow sample workload to a more modern research or clinical cytometer. * Continue following the above actions for the applications you use, as long as you use your system.

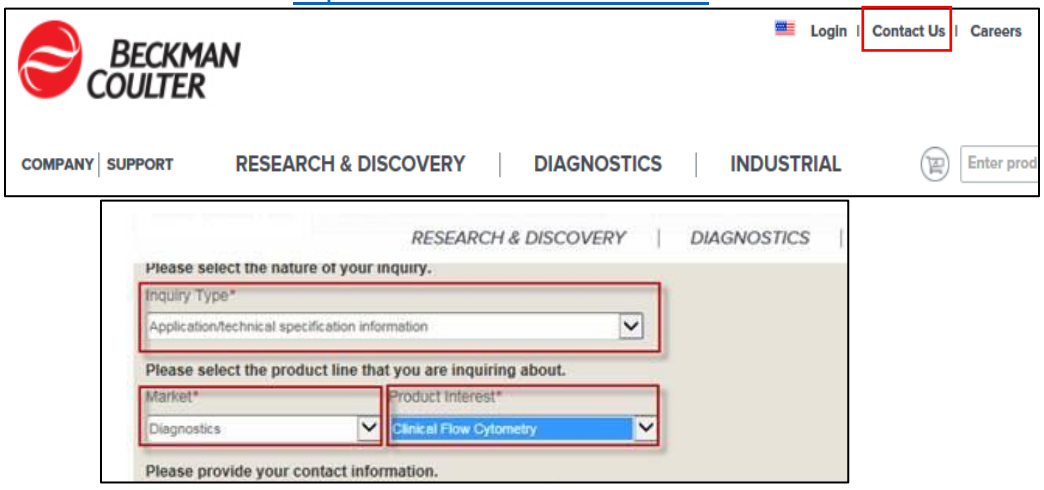
Please share this information with your laboratory staff and retain this notification as part of your laboratory Quality System documentation. If you have forwarded any of the affected product listed above to another laboratory, please provide them a copy of this letter.

So that we are assured you have received this important communication, please respond within 10 days in one of the following ways:

- Electronically, if you received this communication via email.
- Manually, complete and return the enclosed Response Form.

If you have any questions regarding this notification, please contact:

- From our website: http://www.beckmancoulter.com



- By phone: call 800-369-0333 in the United States and Canada (Monday – Friday, 8:00 am EST – 8:00 pm EST).

- Outside the United States and Canada, contact your local Beckman Coulter representative.

We apologize for the inconvenience that this has caused your laboratory.

Sincerely,

[redacted]
Marwan Fathallah
Vice President, Quality Assurance and Regulatory Affairs
Enclosure: Response Form

Attachment 1
Frequently Asked Questions (FAQ)

1. **What is the impact of the issue?**
    - There may be impact to patient results due to this issue when using the EPICS XL/XL-MCL for any application.
    - Implementation of the actions provided in this letter allow for the detection of signal loss and/or signal drifting that could impact patient results.

2. **Is my instrument potentially impacted?**
    - There is the potential that it could be impacted.
    - Implementation of the actions provided in this letter allow for detection of signal loss and/or signal drifting that could impact patient results.

3. **How can I confirm if my instrument has this issue?**
    - This issue may be intermittent.
    - Implementation of the actions provided in this letter allow for the detection of signal loss and/or signal drifting that could impact patient results.
    - Review of these plots, in addition to those used for assay/application result determination, should be part of routine data review, prior to reporting results. Please see additional information in the Attachments.

4. **If my instrument demonstrates symptoms of this issue after the implementation of the actions in this letter, what are the next steps to resolve the issue?**
    - If your instrument displays the indicated issues contact BEC Customer Support or your local Beckman Coulter Representative for additional guidance and support.

5. **Where can I find the instructions how to implement the immediate recommendations?**
    - See Attachments 2 through 5 of this communication.

6. **How can I confirm there is no issue with previous data if TIME parameter was not selected?**
    - Unexpected fluctuations in the events over time may indicate compromised data acquisition conditions (see Special Procedures and Troubleshooting Manual for the EPICS XL/XL-MCL (PN 4237296)) for instructions on handling compromised fluidics or optics conditions).

7. **How can I get updates on the resolution of this issue?**
    - Beckman Coulter will be contacting you regarding available options for resolution of this issue.

Attachment 2

Instructions for Creating TIME Plots in System II Unlocked Protocols

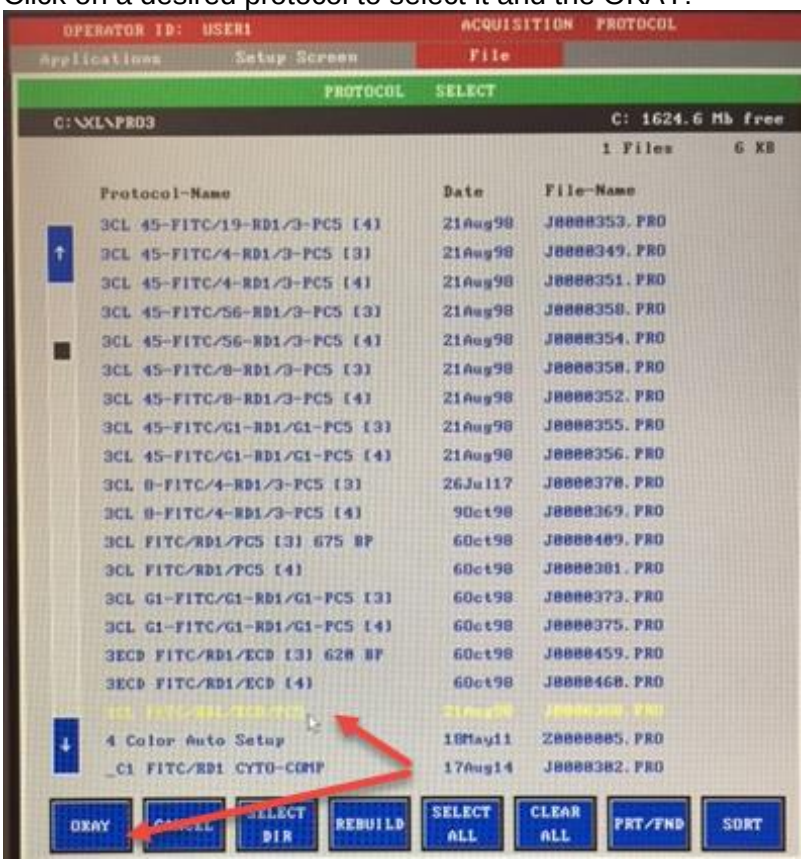
Please refer to COULTER® EPICS® XL Flow Cytometer COULTER EPICS XL-MCL Flow Cytometer SYSTEM II Software Getting Started manual, PN 4237238**,** Chapter 4, Creating Protocols for additional instructions. The following instructions apply to any unlocked protocol in the System II Software.

A. Adding Time Plots to Unlocked Protocols

1. Select Setup Screen >> Protocols

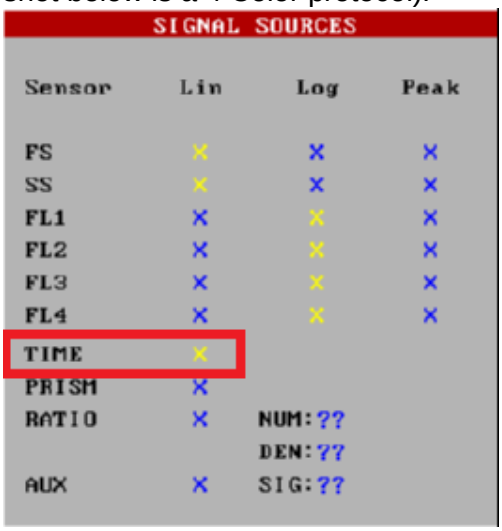
2. Select **File>> Select** to view the Protocols.

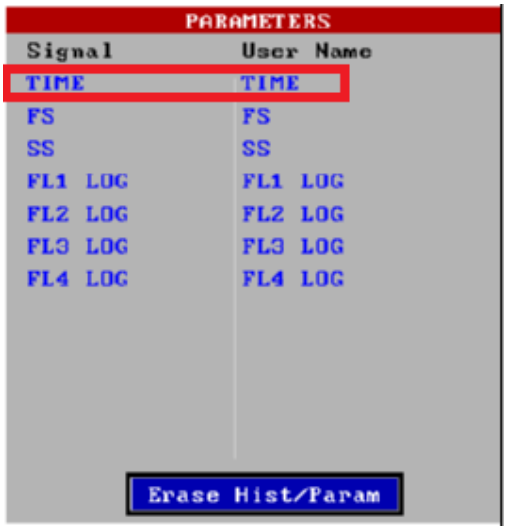
3. Click on a desired protocol to select it and the OKAY:



4. The protocol will display (this example is a 4 color protocol). Make note of the Signal Sources box at the lower right of the display.

   Edit the protocol to ensure that TIME is selected as a parameter for data collection by selecting the "X" next to TIME in the Signal Sources box. Observe that TIME is now listed in the protocol parameters as an added signal to be acquired. (Example in screen shot below is a 4 Color protocol).





5. Select **File >> Save**.

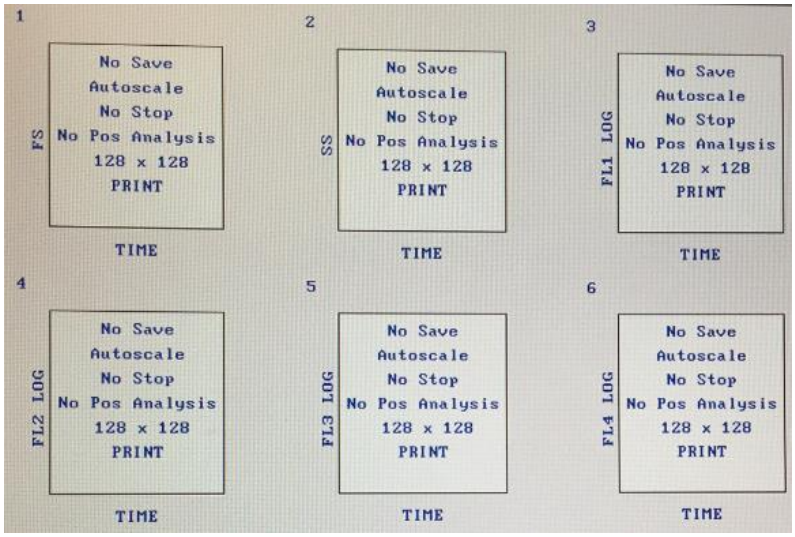
Note: **System II protocols allow a maximum of 8 plots**. If the unlocked protocol just updated cannot accommodate an individual TIME plot for each parameter, a separate Data Review protocol using 2-parameter histograms of TIME versus each parameter (i.e. FS/TIME, SS, TIME, FL1/TIME, FL2/TIME, FL3/TIME, and FL4/TIME) is created per the instructions in Attachment 3.

Attachment 3

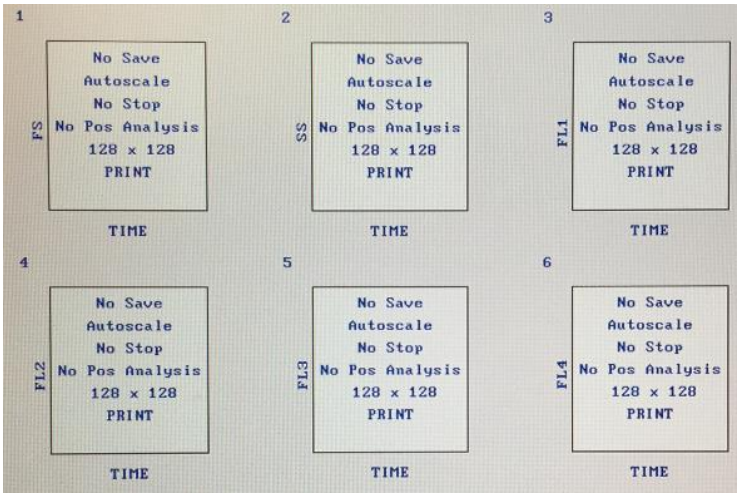
Instructions for Creating a Data Review Protocol with Time Plots For Listmode Replay Data Review

A. Creating a Data Review Protocol with Time Plots

1. Select **Setup Screen >> Protocol**.
2. Either open an existing 4 color (log fluorescence) protocol or create a new 4 color protocol following the instructions beginning in Section 4-2 to create the protocols. Ensure this protocol has the following signals selected:
    a. FS Lin
    b. SS Lin
    c. FL1 Log
    d. FL2 Log
    e. FL3 Log
    f. FL4 Log
    g. TIME
3. Assign parameters to plot axes:
    a. Click on TIME in the Parameter box and assign TIME to the X-axis of Plots 1 through Plot 6.
    b. Click on the next Parameter Signal, for example, FS, and click on the Y-axis of Plot 1.
    c. Repeat Step 3b to assign the remaining parameters (SS, FL1, FL2, FL3 and FL4) to the Y-axis of the remaining histograms. The protocol should appear as shown below:



4. Select **File >> Save As** … and enter a name for the protocol: i.e. Data Review Log FL-TIME Plots.
5. If Linear fluorescent signals are selected to be collected, repeat Step 1 through Step 4 selecting FS-Lin, SS-Lin, FL1-Lin, FL2-Lin, FL3-Lin, FL4-Lin and TIME. When saving the protocol, enter a name for the protocol: i.e. Data Review Lin FL-TIME Plots:

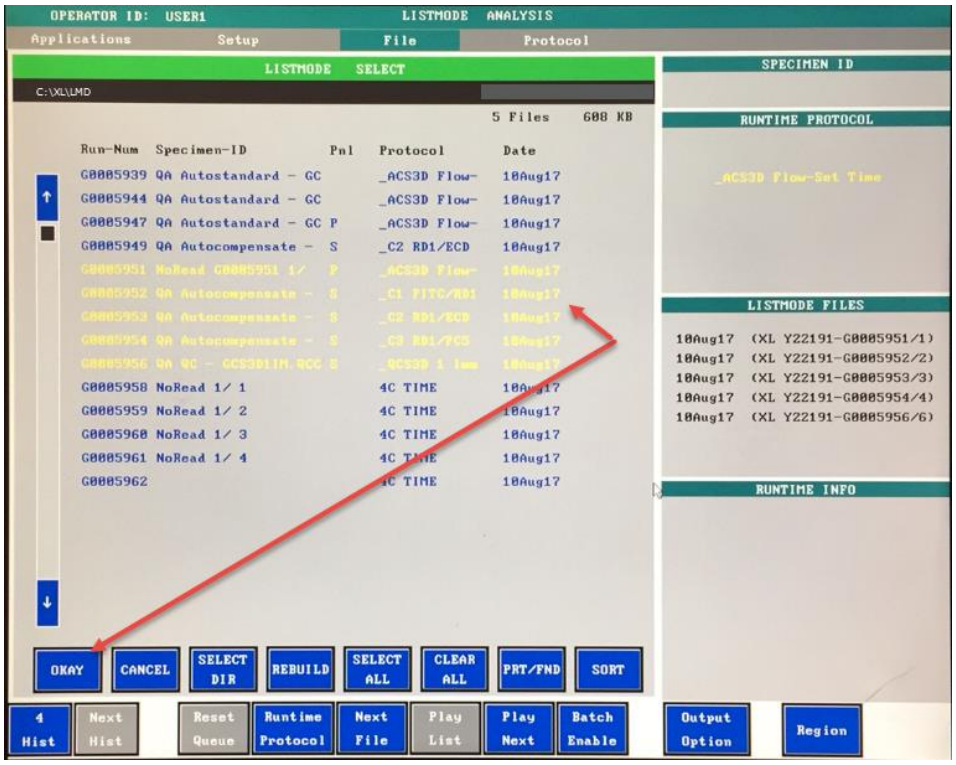


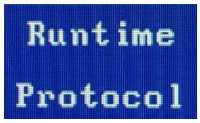
6. If your laboratory uses panels to acquire samples, refer to the COULTER® EPICS® XL Flow Cytometer COULTER EPICS XL-MCL Flow Cytometer SYSTEM II Software Getting Started manual, PN 4237238**,** Chapter 6, Creating Panels for additional instructions.
7. If your lab uses panel reports, please refer to the COULTER® EPICS® XL Flow Cytometer COULTER EPICS XL-MCL Flow Cytometer SYSTEM II Software Data Management manual, PN 4237237**,** Chapter 4, Creating Reports for the necessary instructions.
8. Refer to Procedure B of this document for instructions on Listmode Replay using the Data Review using TIME Plots.

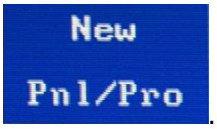
B. Listmode Replay using the Data Review Protocol with TIME Plots

Refer to COULTER® EPICS® XL Flow Cytometer COULTER EPICS XL-MCL Flow Cytometer SYSTEM II**,** Instructions for Use Manual, PN 4237297, Chapter 5, Listmode Analysis, for additional instructions regarding Listmode replay in System II software.

- Select **Applications >> Listmode.**
- Select **File >> Select** and click on all desired listmode files for data review, then select **OKAY**:



- Click on the 

button at the bottom of the screen to toggle to 

.

4. Select **Protocol >> Select** and select the Data Review Protocol (i.e. Data Review Log FL-TIME Plots created in Procedure B of this Attachment) and then select **OKAY**.

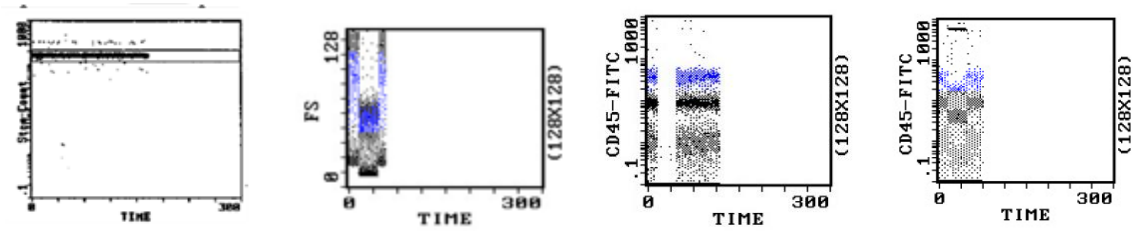
- Click on the 

to review each listmode file data on each Time versus parameter plot.

Data review must include the following:

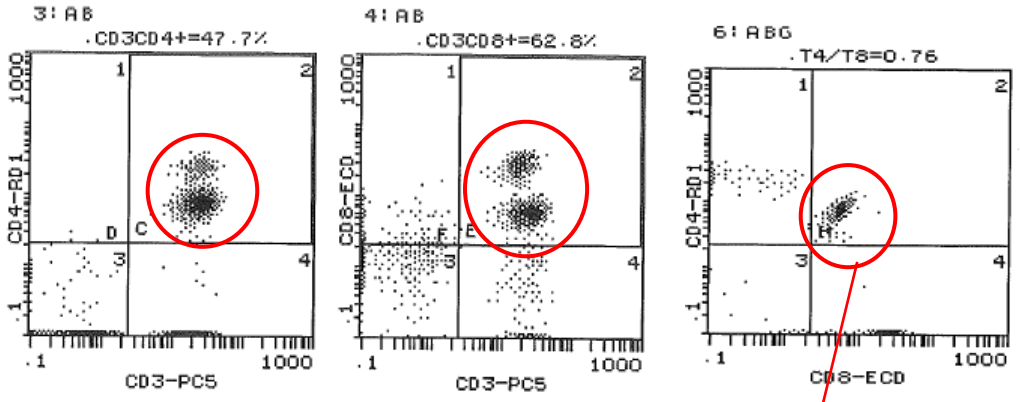
a. Review of all TIME plots for each parameter.
b. Monitor consistent Forward Scatter, Side Scatter and all fluorescence data over time as shown in the example below.

Examples: Stable Acquisition Examples: Compromised Acquisition



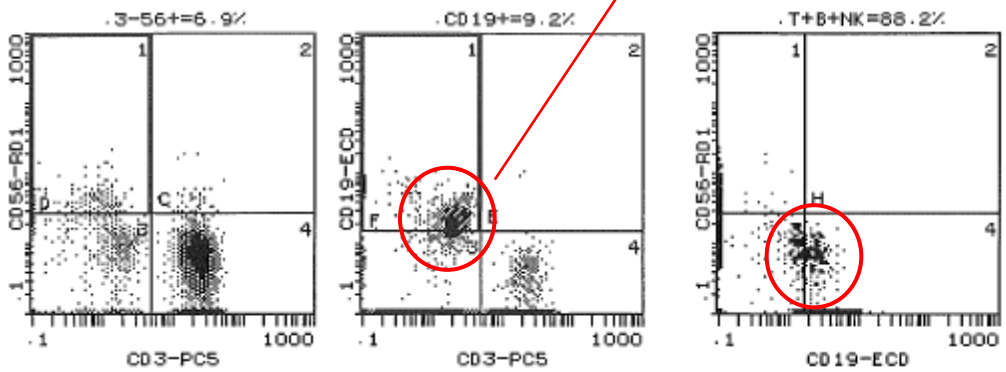
- Unexpected fluctuations in the events over time may indicate compromised data acquisition conditions (see Special Procedures and Troubleshooting Manual for the EPICS XL/XL-MCL (PN 4237296) for instructions on handling compromised fluidics or optics conditions).
- Review the data plots for the application in question. Below are examples of data plots from the tetraONE application demonstrating signal loss:

tetraONE 45/4/8/3



This also demonstrates an example of suboptimal compensation

tetraONE 45-56-19-3

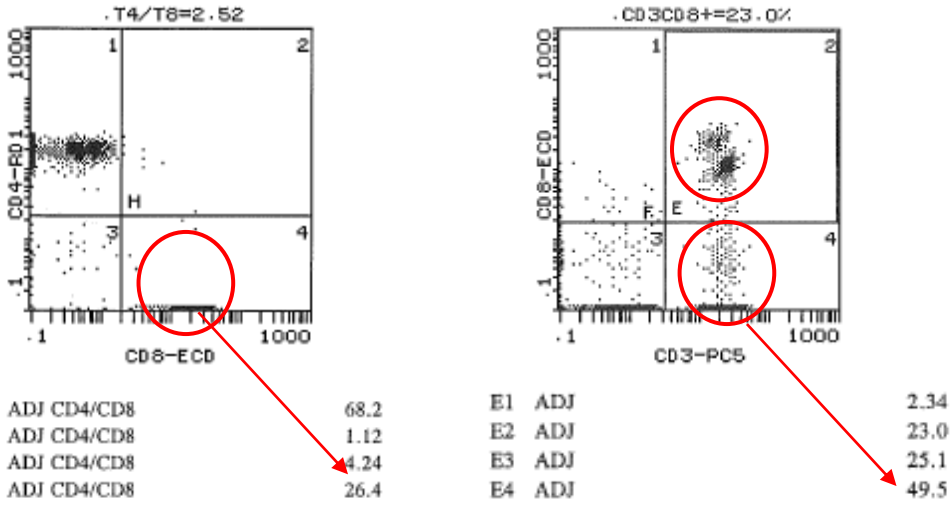


Attachment 4

Additional Information for Laboratory Developed Tests

In certain applications, the implementation of the TIME vs Parameter plots may not always result in detection of the failure. Therefore:

- Ensure that the appearance of the data patterns are reviewed, look for suboptimal compensation (as shown on the previous page). In some instances, the finding may be especially subtle. In this case, a similar pattern could be due to a small compensation error. Consider the possibility that this may be an Amplifier board failure.
- Ensure that the pattern appearance matches the statistical data reported. The following are examples of data where the pattern appearance does not match the statistical data reported below the plots, and the population appearance is not appropriate:



H1	ADJ CD4/CD8	68.2
H2	ADJ CD4/CD8	1.12
H3	ADJ CD4/CD8	4.24
H4	ADJ CD4/CD8	26.4

E1	ADJ	2.34
E2	ADJ	23.0
E3	ADJ	25.1
E4	ADJ	49.5

- Follow the Data Review instructions in the respective IFU(s) and System Guides, as well the instructions included in this notification.

Attachment 5

Instructions for IVD Locked Protocols stemONE / tetraONE

Manual IVD Protocol Creation

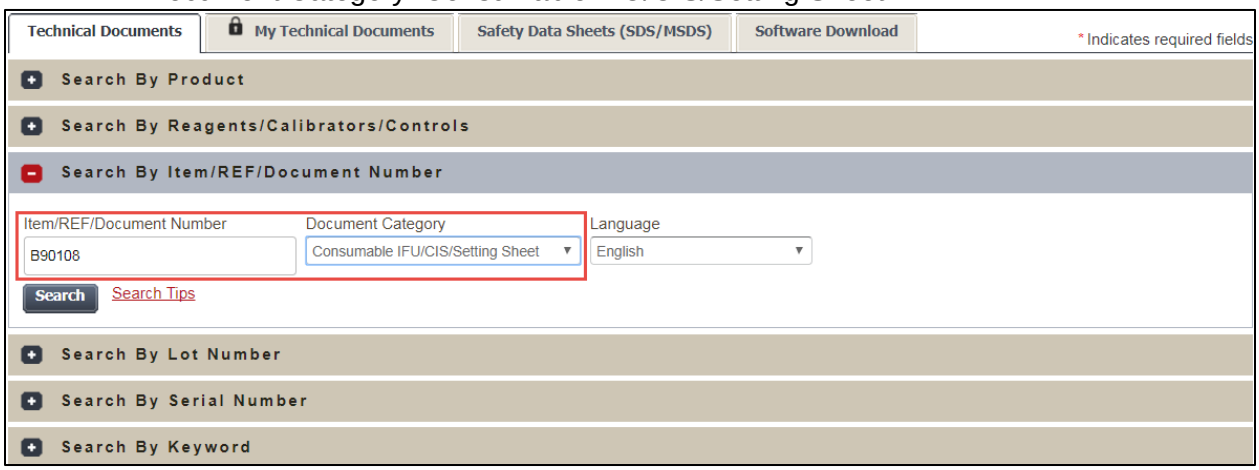
These instructions provide guidance for the tetraONE and stemONE locked IVD applications for the purpose of data review with TIME plots.

A. stemONE IVD locked protocols

1. By default, the stemONE IVD locked protocols have TIME included as a parameter. There are no additional requirements to create a manual stemONE IVD protocol. Attachment 3 addresses creating a separate Data Review TIME Plot protocol for data review including TIME, for the tetraONE and stemONE applications. Refer to Attachment 3 for instructions on 'Creating a Data Review Protocol with TIME Plots' for data review.
2. For all stemONE listmode data, perform listmode replay using the Data Review Protocol with TIME Plots instructions provided in this document (Attachment 3).

B. tetraONE IVD locked protocols

1. Locate the indicated product instructions for use at www.beckmancoulter.com.
2. Scroll down to the option to search by Item/REF/Document Number
1. Enter the following information to locate the tetraCHROME IFU:
   - Item/REF/Document Number: B90108 CYTOSTAT tetraCHROME IFU
   - Document Category: Consumable IFU/CIS/Setting Sheet



3. Follow the CYTOSTAT tetraCHROME reagent IFU for instructions on creating unlocked manual protocols.
4. Ensure TIME is selected as a parameter for data collection in the unlocked tetraCHROME manual protocol(s). The unlocked tetraCHROME protocol(s) will be used for data collection.
5. If your laboratory uses panels to acquire samples, refer to the COULTER® EPICS® XL Flow Cytometer COULTER EPICS XL-MCL Flow Cytometer SYSTEM II Software Getting Started manual, PN 4237238**,** Chapter 6, Creating Panels for additional instructions.

6. If your lab uses panel reports, please refer to the COULTER® EPICS® XL Flow Cytometer COULTER EPICS XL-MCL Flow Cytometer SYSTEM II Software Data Management manual, PN 4237237**,** Chapter 4, Creating Reports for the necessary instructions.
8. For all tetra application listmode data, perform listmode replay per the *Listmode Replay using the Data Review Protocol with TIME Plots* instructions provided in this document (Attachment 2).

December 18, 2018

FIELD SAFETY CORRECTIVE ACTION NOTIFICATION
FC 500 Series Flow Cytometers

Product	Part Number	Software Versions
FC 500™ Series Flow Cytometers (new, reconditioned or refurbished)	All	All

Attention Beckman Coulter Customer,
*Copy: Chairman Medical Board/Head of Departments of Affected consignees
**Applicable to Affected consignees of Singapore only*

Beckman Coulter is initiating a field action for the products listed above. This letter contains important information that needs your immediate attention.

ISSUE:

As a result of customer complaints and subsequent internal investigations, Beckman Coulter has determined that an internal electronic component on the circuit "Amplifier" boards in the FC 500 system may be affected by a manufacturing defect. Each FC 500 system contains seven (7) of the potentially affected Amplifier boards. All instruments are potentially impacted.

IMPACT:

There may be impact to patient results due to this issue when using the FC 500 for any application.

This manufacturing defect may result in failures causing signal loss and/or signal drifting as follows:

- The failure could present itself as signal loss and/or signal drifting resulting in absence of data or a shift in the population in the data plots.
- Customers have reported sudden loss of signal, intermittent signal loss, sudden upward or downward shift in signal, upward or downward drift in signal over time, fluctuating signal, suboptimal compensation, erroneous results on affected parameters, and/or increased coefficients of variation (CV) of Flow-Check beads (see **Attachment 1** – FAQ for more details).

ACTIONS:

Implement the following actions for the applications you use*.

1. For All Applications including Laboratory Developed Tests:
    a. As per the product documentation all data must be reviewed by a laboratory professional prior to the release of reported results from the lab.
    b. Immediately implement the collection of Time as a parameter and create Time versus Parameter plots which will allow the monitoring of signal integrity during data acquisition as instructed in **Attachment 2**.
    c. Review data as described below:
        i. Review of all Time plots for each parameter.

ii. Monitor consistent Forward Scatter, Side Scatter and all fluorescence data over time as shown in **Attachment 2**.
iii. Unexpected fluctuations in the events over time may indicate compromised fluidics, signal integrity or data acquisition conditions.
iv. All data must be reviewed prior to the release of any results from the laboratory, via an LIS or any other mechanism.

2. For tetraCXP and stemCXP:
   a. As it is not possible to add time versus parameter, discontinue use of the automated tetraCXP and stemCXP applications.
   b. You can continue to use the tetraCHROME reagents and Stem Kit reagents with the manual gating instructions provided in the product labeling. Refer to CYTO-STAT tetraCHROME IFU, PN B90108 (for tetraCHROME CD45-FITC/CD4-RD1/CD8-ECD/CD3-PC5, PN 6607013 and tetraCHROME CD45-FITC/CD56-RD1/CD19-ECD/CD3-PC5, PN 6607073) and the Stem-Kit IFU, PN B60229 for PN IM3630 or stemCXP 7HPCM protocols as applicable.
      i. Ensure to follow the instructions in the preceding step to add time as a parameter and create the Time vs Parameter plots.
      ii. If your laboratory uses Panel Reports, the panels and corresponding panel report templates will need to be constructed as well.
      iii. Follow the Data Review instructions in the IFU and respective System Guides, as well as the instructions attached to this notification (**Attachment 3).**

3. For ClearLLab Reagents, CytoDiff Application and Laboratory Developed Tests:
   In addition to the actions described above, follow the instructions in **Attachment 4** to:
   a. Ensure that the appearance of the data patterns are reviewed and look for suboptimal compensation.
   b. Ensure that the pattern appearance matches the statistical data reported.

4. For CytoDiff Application:
   In addition to the actions described above, compare the results obtained from the cytometer to the results from the hematology analyzer for the same sample, and verify that there is concordance with the results.

5. Contact Beckman Coulter Customer Technical Support Center or your local Beckman Coulter Representative if you observe any of the issues described

6. Consult with your Medical Director to determine if a retrospective review of results is warranted.

RESOLUTION:

- As an additional interim solution, Beckman Coulter will be releasing software updates for tetraCXP and stemCXP which will include the additional Time versus Parameter plots.
- Beckman Coulter is actively working on a long term resolution in the form of a software upgrade to fully detect this issue.

  * Continue following the above actions for the applications you use, until the software upgrade to fully detect the issue is installed in your system.

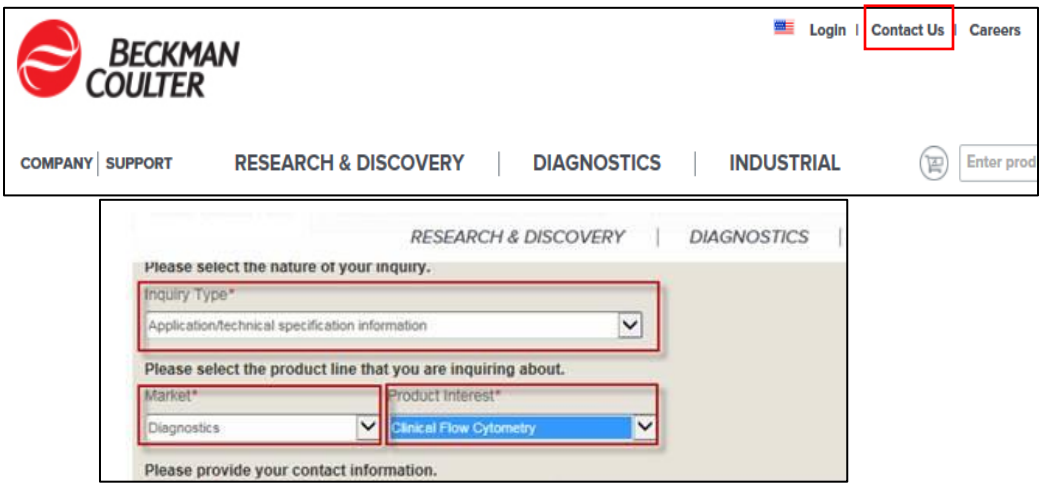
Please share this information with your laboratory staff and retain this notification as part of your laboratory Quality System documentation. If you have forwarded any of the affected product listed above to another laboratory, please provide them a copy of this letter.

So that we are assured you have received this important communication, please respond within 10 days in one of the following ways:

- Electronically, if you received this communication via email.
- Manually, complete and return the enclosed Response Form.

If you have any questions regarding this notification, please contact:

- From our website: http://www.beckmancoulter.com



- By phone: call 800-369-0333 in the United States and Canada (Monday – Friday, 8:00 am EST – 8:00 pm EST).
- By email – US and Canada only: LScustomerLetter@Beckman.com
- Outside the United States and Canada, contact your local Beckman Coulter representative.

We apologize for the inconvenience that this has caused your laboratory.

Sincerely,

[redacted]

Marwan Fathallah
Vice President, Quality Assurance and Regulatory Affairs
Enclosure: Response Form

Attachment 1

Frequently Asked Questions (FAQ)

1. **What is the impact of the issue?**
   - There may be impact to patient results due to this issue when using the FC 500 for any application.
   - Implementation of the actions provided in this letter allow for the detection of signal loss and/or signal drifting that could impact patient results.

2. **Is my instrument potentially impacted?**
   - There is the potential that it could be impacted.
   - Implementation of the actions provided in this letter allow for detection of signal loss and/or signal drifting that could impact patient results.

3. **How can I confirm if my instrument has this issue?**
   - This issue may be intermittent.
   - Implementation of the actions provided in this letter allow for the detection of signal loss and/or signal drifting that could impact patient results.
   - Review of these plots, in addition to those used for assay/application result determination, should be part of routine data review, prior to reporting results. Please see additional information in the Attachments.

4. **If my instrument demonstrates symptoms of this issue after the implementation of the actions in this letter, what are the next steps to resolve the issue?**
   - If your instrument displays the indicated issues, contact BEC Customer Support or your local Beckman Coulter Representative for additional guidance and support.

5. **Where can I find the instructions on how to implement the immediate recommendations?**
   - See Attachments 2, 3 and 4 of this communication.

6. **How can I confirm there is no issue with previous data if TIME parameter was not selected?**
   - Unexpected fluctuations in the events over time may indicate compromised data acquisition conditions (see Special Procedures and Troubleshooting Manuals for the FC 500 with CXP (PN 175572) or FC 500 MPL (PN 177580)) for instructions on handling compromised fluidics or optics conditions).

7. **How can I get updates on the resolution of this issue?**
   - Resolution of this issue will be communicated via the release of a Corrective Action Release Letter.

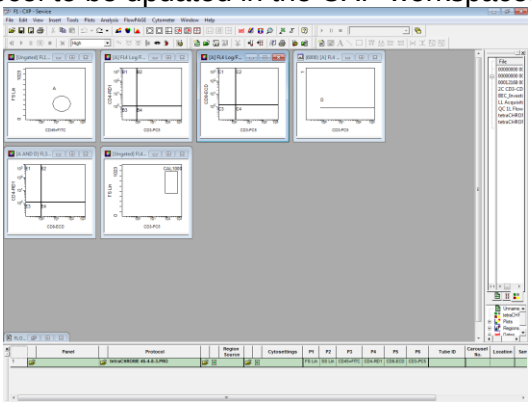
Attachment 2

Instructions for Creating Time Plots in CXP and/or MXP Unlocked Protocols

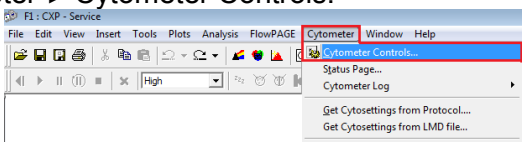
Please follow the instructions below to include Time as a parameter for collection in all unlocked protocols, including QC auto setup protocols. Create a Time versus Parameter X density plot (FS/Time, SS/Time, FL1/Time, etc.) and save each protocol. The following instructions use a tetraCHROME 45-4-8-3 FC protocol as an example. The same steps apply to any unlocked protocol.

A. Adding Time Plots to Unlocked Protocols

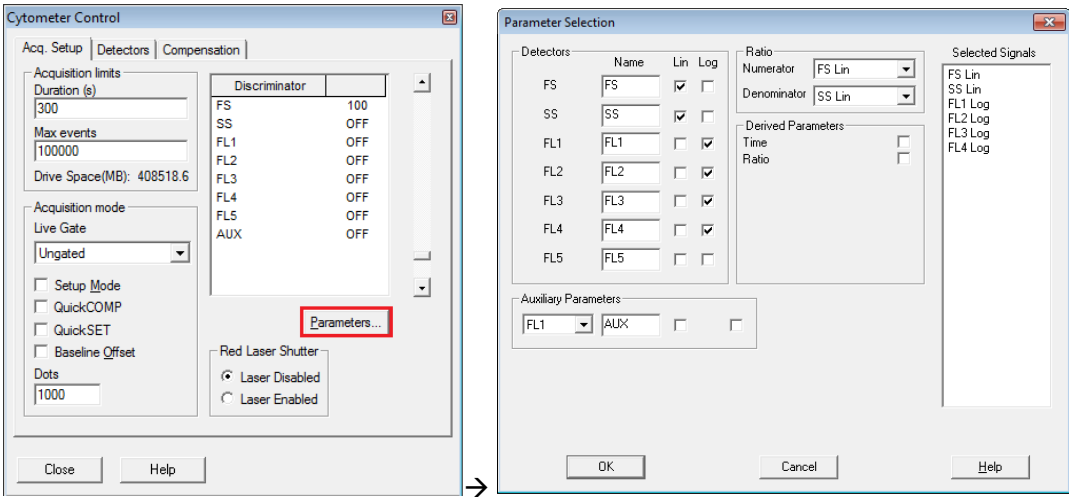
1. Open the protocol to be updated in the CXP workspace.



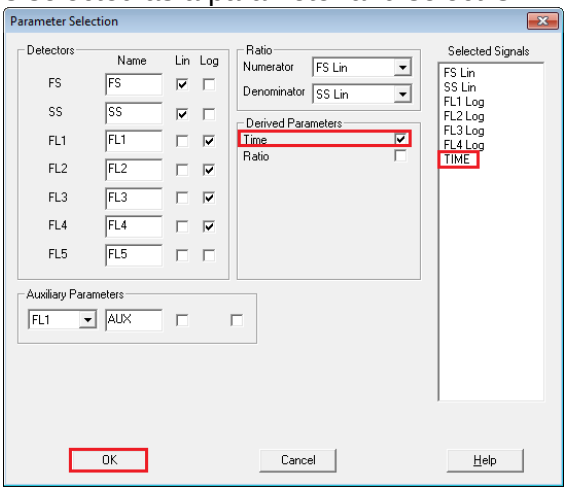
2. Select Cytometer ►Cytometer Controls:



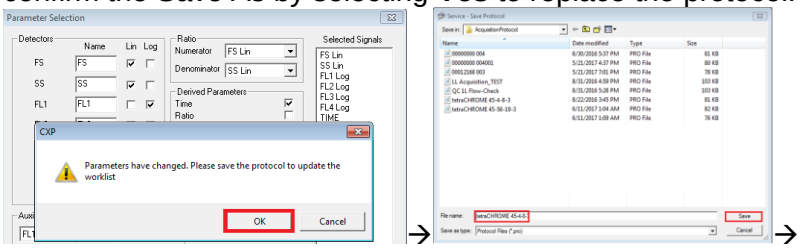
3. From the Cytometer Control screen, select the Parameters button to view the Parameter Selection screen:

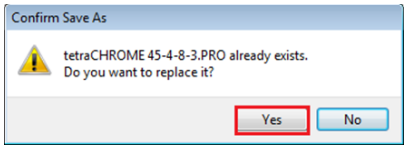


4. Ensure Time is selected as a parameter and select **OK**.



5. If CXP prompts that the parameters have changed, select **OK**. Note: This prompt only displays when TIME is not already selected as a parameter. Select **Save** and then confirm the Save As by selecting **Yes** to replace the protocol.



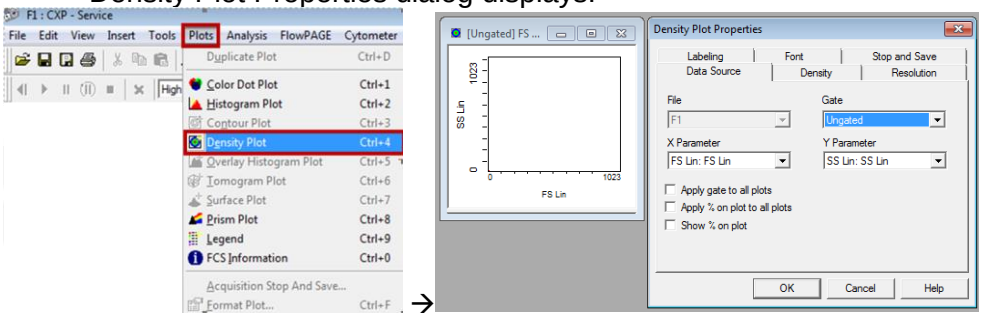


If CXP does not prompt that the parameters have changed, then TIME was already selected as a parameter. Proceed to Step 6.

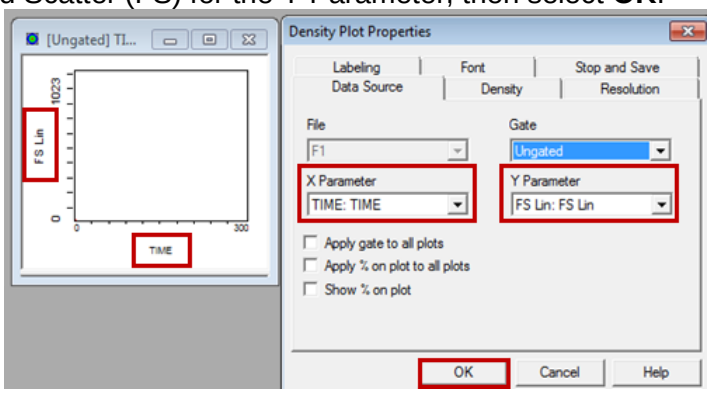
6. Select **Close** on the Cytometer Control dialog.

7. To add Time Plots for each parameter:

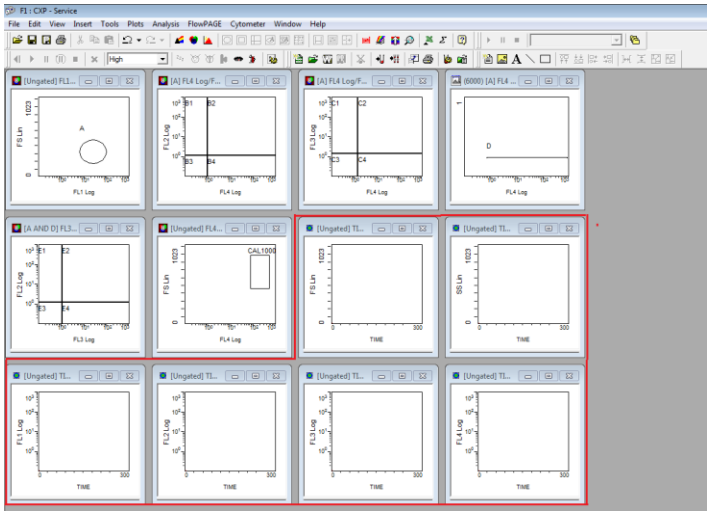
   a. From the Plots Menu, select Plots ► Density Plot. A new Density Plot and Density Plot Properties dialog displays:



b. From the Density Plot Properties screen, select Time for the X Parameter and Forward Scatter (FS) for the Y Parameter, then select **OK**.

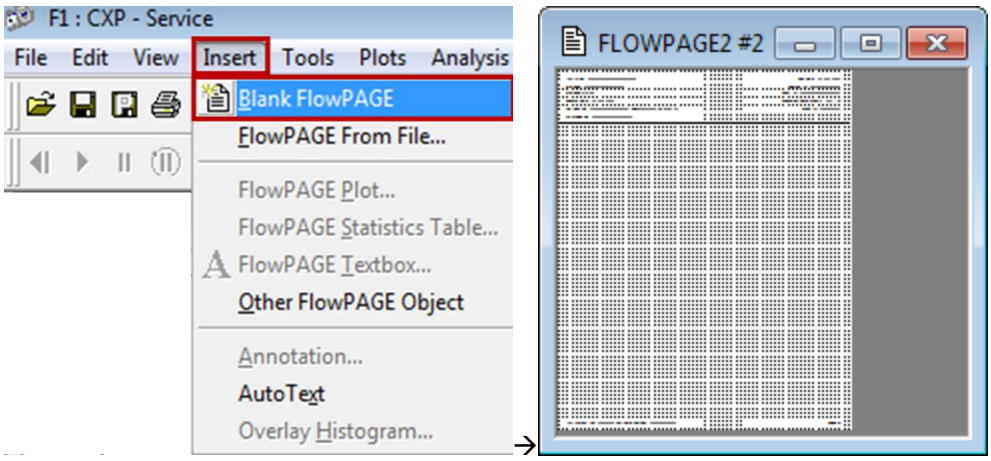


c. Repeat steps 7a and 7b to create a Time versus Parameter Density plot for all remaining parameters in the protocol: i.e. Side Scatter and each fluorescence parameter.

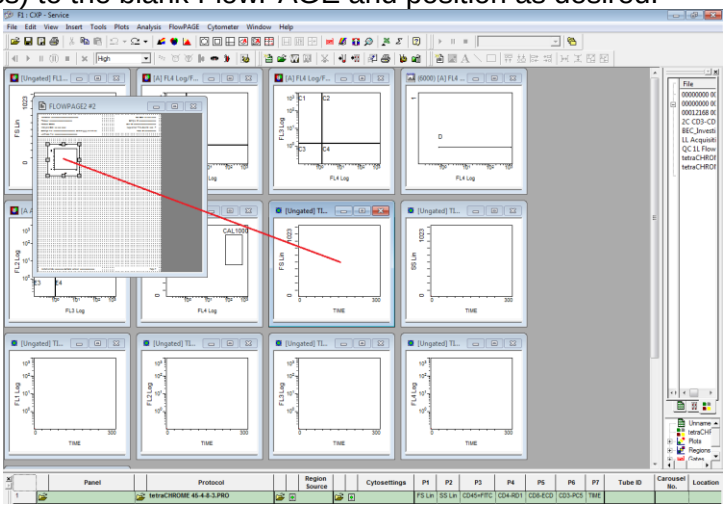


8. To add a FlowPAGE with the newly created Time Plots:

a. Select ► Insert ► Blank FlowPAGE. A blank FlowPAGE displays.

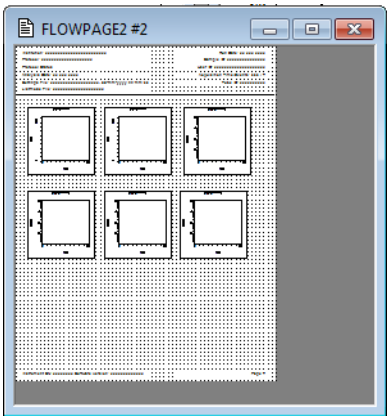


b. Hold the <Ctrl> key down and drag and drop the FS versus Time Plot (with no statistics) to the blank FlowPAGE and position as desired.

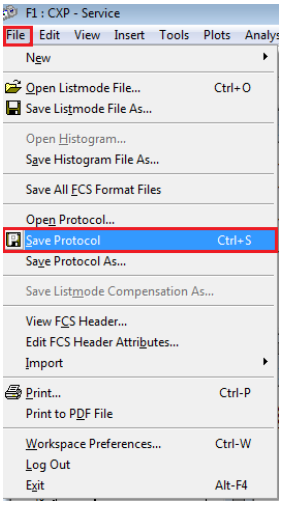


c. Repeat steps 8a and 8b to add all remaining Time versus Parameter plots to the FlowPAGE.

i. For CXP Win7 - Maximize the FlowPAGE by clicking on the  button on the upper right of the FlowPAGE, then minimize the FlowPAGE by clicking on the  button.



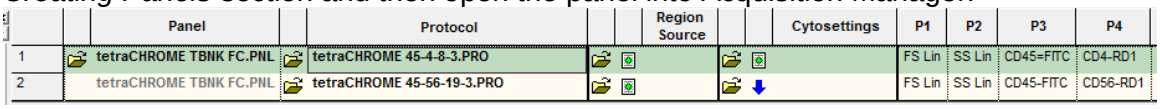
9. Select File ►**Save Protocol**.



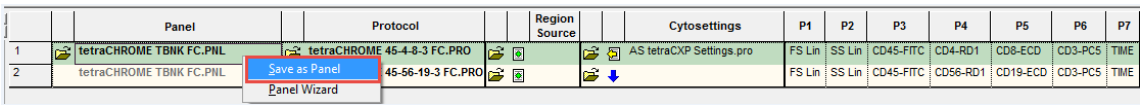
10. Repeat Steps 1 through Step 9 for all unlocked CXP and/or MXP protocols.

B. Saving Panels Associated with Newly Updated Protocols:

1. Create the panel associated with the newly updated protocols per the applicable IFU *Creating Panels* section and then open the panel into Acquisition Manager:

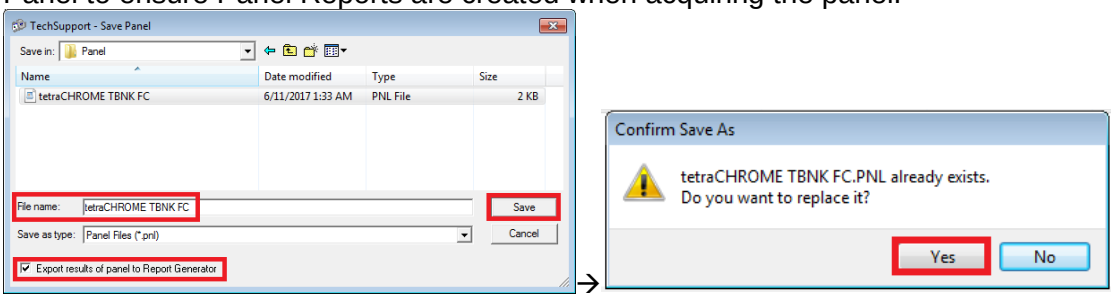


2. Ensure that AS tetracxp setting.PRO is the settings file selected for the panel constructed with the manual protocol.
3. Right click on any row in the panel and select **Save as Panel**.



4. On the Save Panel dialog, select **Save**. When prompted to confirm the Save As, select **Yes** to save the panel.

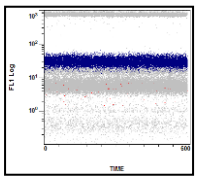
Note: Ensure the Export results of panel to Report Generator checkbox is selected when saving an Export Panel to ensure Panel Reports are created when acquiring the panel.



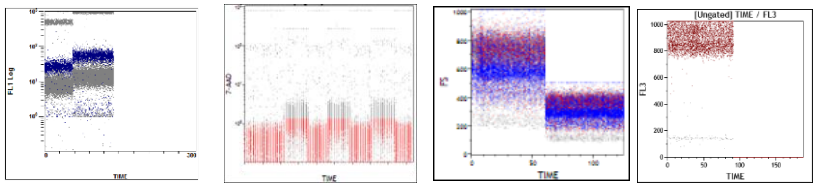
C. Data Review Instructions

- Data review must include a review of all Time plots. Monitor consistent Forward Scatter, Side Scatter and all fluorescence data over time as shown below.
- Unexpected fluctuations in the events over time may indicate compromised data acquisition conditions (see Special Procedures and Troubleshooting Manuals for the FC 500 with CXP (PN 175572) or FC 500 MPL (PN 177580)) for instructions on handling compromised fluidics or optics conditions).

Example: Stable Acquisition

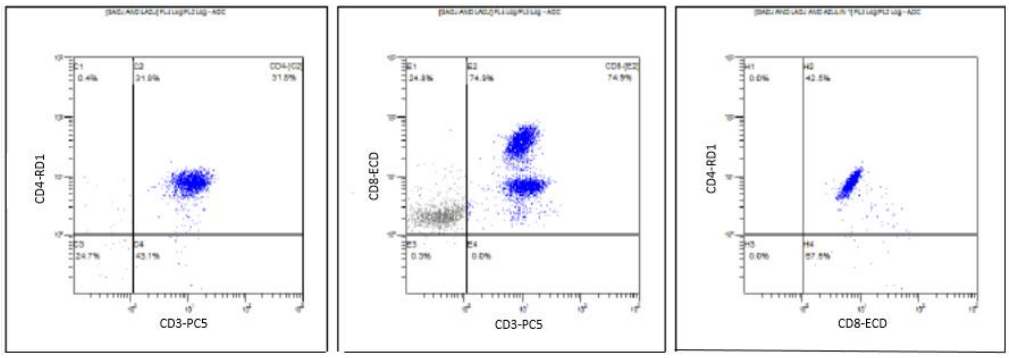


Examples: Compromised Acquisition

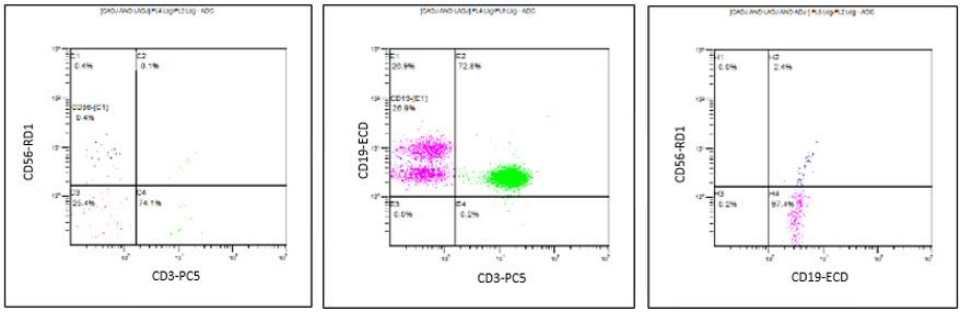


- This is an example of the data plots from a tetraCXP test with the signal loss on the FL2 channel, from the current protocols.

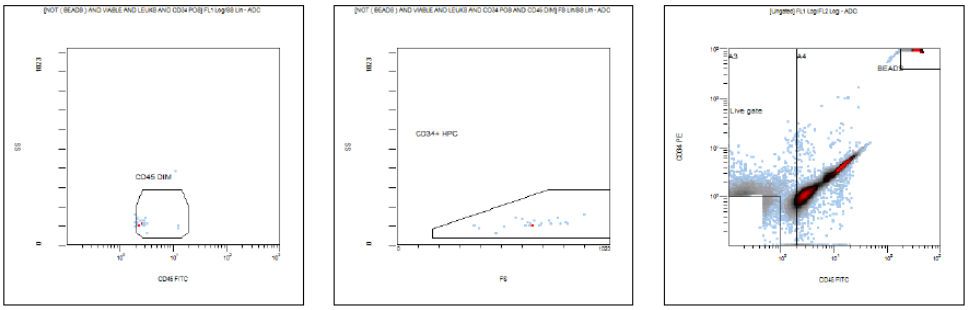
tetraCXP 45-4-8-3



tetraCXP 45-56-19-3



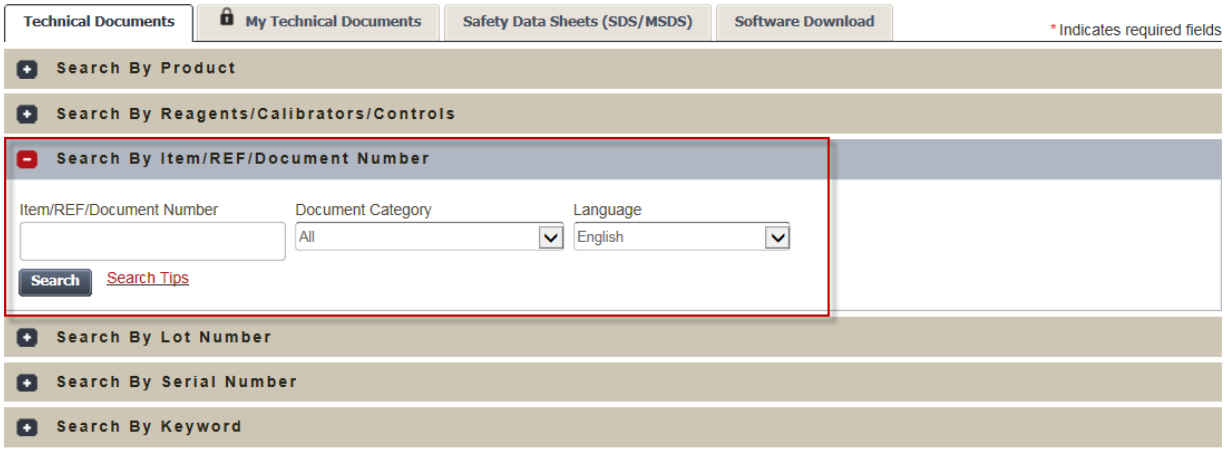
- This is an example from a stemCXP test with the FL1 signal loss

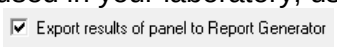


Attachment 3

Instructions for tetraCXP and stemCXP Locked Protocols
Manual IVD Protocol Creation

1. Locate the indicated product instructions for use at www.beckmancoulter.com/ifu.
2. Scroll down to the option to search by Item/REF/Document Number



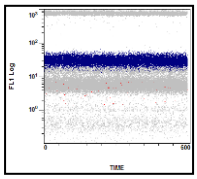
3. Enter the following information to locate the indicated IFUs:
    a. B90108 – CYTOSTAT tetraCHROME IFU
    b. B60229 – Stem-Kit Reagent IFU
4. Follow the applicable IVD reagent IFU for instructions on creating unlocked manual protocols:
    a. CYTOSTAT tetraCHROME IFU, PN B90108
    b. Stem-Kit Reagent, PN B60229 (or use the stemCXP 7HPCM protocols)
5. Select Time as a parameter for data collection.
6. In addition to the plots indicated in the respective reagent IFUs, create a Time versus Parameter Density plot (FS/Time, SS/Time, FL1/Time, etc.) for each signal collected, and save each protocol.
7. Add these plots to the FlowPAGE for the test for ease of data review.
8. Create the associated panel if desired.
    a. Use the Panel Wizard to create a Panel. Refer to the ***Creating Panels*** section in the System Overview chapter in the CXP Instructions For Use manual, PN 624923.
    b. If Panel Reports are used in your laboratory, use the Panel Wizard to create a Panel ensuring the 

is selected when saving the export panel. Refer to the ***Creating Panels*** section in the System Overview chapter in the CXP Instructions For Use manual, PN 624923.
        1) Create the Panel Report template.
            a) For the tetraCHROME Panel Report Template, refer to the ***Creating a New Panel Report Template*** section in the CXP Reference manual, PN 175570.
            b) For the stem-KIT or 7HPCM Panel Report Template, refer to the ***Panel Report Setup*** section of the stemCXP System Guide, PN 627260.

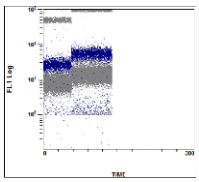
Data Review Instructions

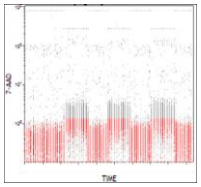
9. Data review must include a review of all Time plots, in addition to those used for result reporting.
10. Monitor consistent Forward Scatter, Side Scatter and all fluorescence data over time as shown below.

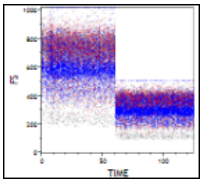
Example: Stable Acquisition

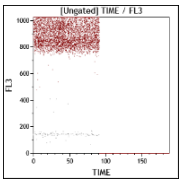


Examples: Compromised Acquisition

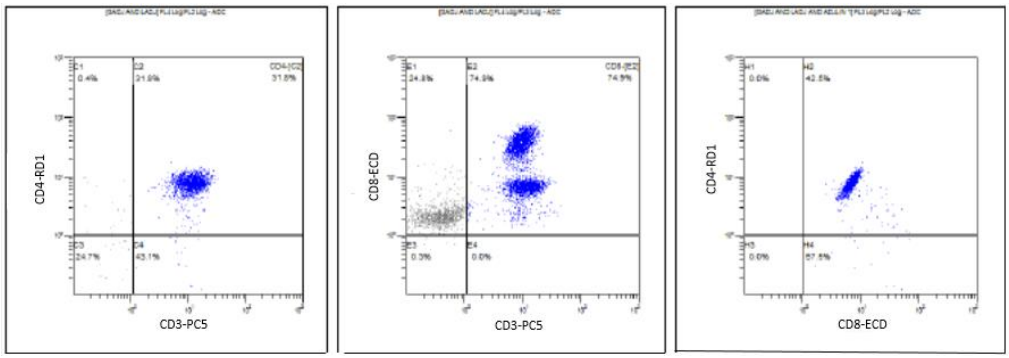




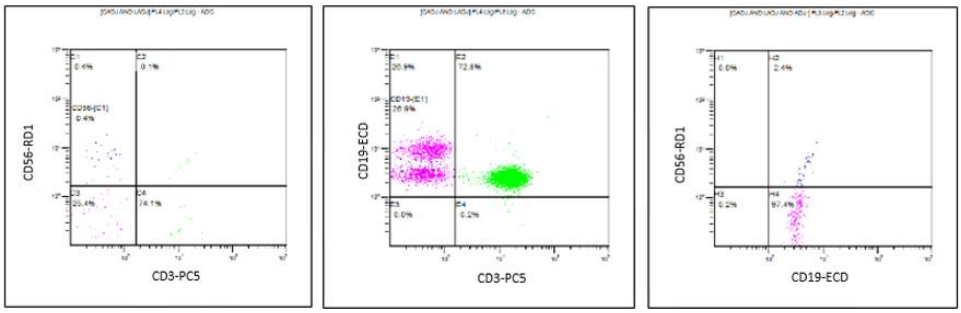




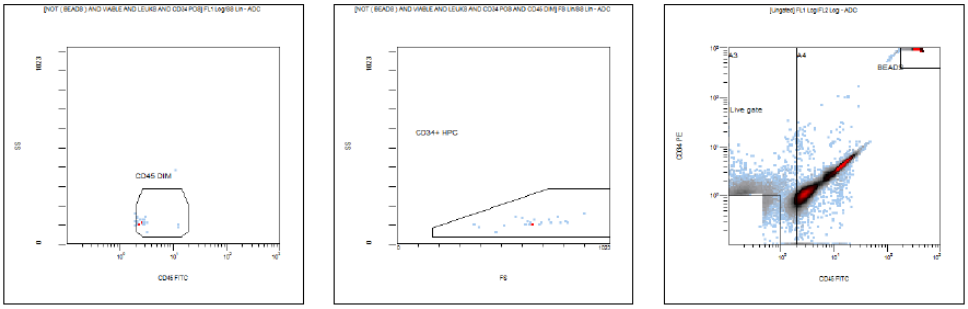
- This is an example of the data plots from a tetraCXP test with the signal loss on the FL2 channel, from the current protocols.
- tetraCXP 45-4-8-3



- tetraCXP 45-56-19-3



- This is an example from a stemCXP test with the FL1 signal loss



11. Unexpected fluctuations in the events over time may indicate compromised data acquisition conditions (see Special Procedures and Troubleshooting Manuals for the FC 500 with CXP (PN 175572) or FC 500 MPL (PN 177580)) for instructions on handling compromised fluidics or optics conditions).
12. Follow the Data Review instructions in the respective IFU(s) and System Guides, as well as the instructions included in this notification.

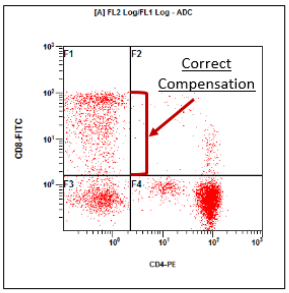
Note:

- Replay of a previously collected listmode file (without Time plots) in the new protocol with Time Plots **may overwrite the new protocol with the old run time protocol, resulting in loss of the time plots**. This applies to both locked and unlocked protocols. Ensure to replay the listmode data in the correct protocol.
- When adding time as a new parameter, the **original parameter names for all signals in the protocol are replaced by signal names**.

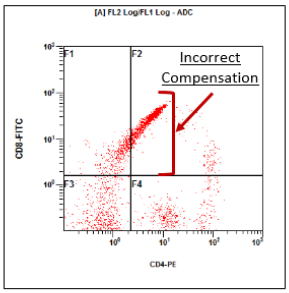
Attachment 4

Additional Information for ClearLLab Reagents, CytoDiff Reagents and Laboratory Developed Tests

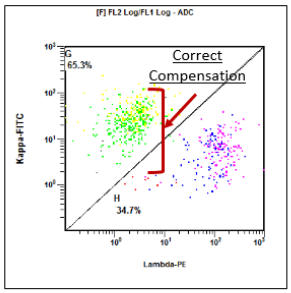
- <u>In certain applications, the implementation of the Time vs Parameter plots may not always result in detection of the failure</u> therefore, ensure that the appearance of the data patterns are reviewed, look for suboptimal compensation and ensure that the pattern appearance matches the statistical data reported. These applications include:
  - ClearLLab Reagents 5 Color Panels *(ClearLLab T1 – B66807; ClearLLab T2 – B66808; ClearLLab B1 – B66809; ClearLLab B2 – B66810; ClearLLab M – B66812)*
  - Laboratory Developed Tests (LDT)
  - CytoDiff (*PN A84341*)
- The following are examples of suboptimal compensation:



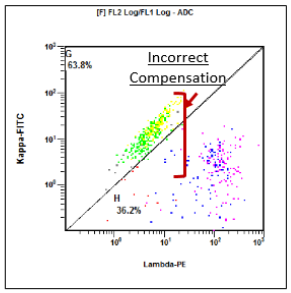
No Failure



Failure in FL1

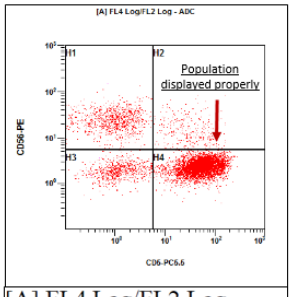


No Failure



Failure in FL1

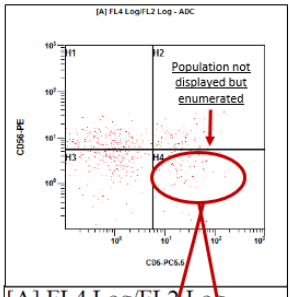
- The following are examples of data where the pattern appearance does not match the statistical data reported below the plots:



[A] FL4 Log/FL2 Log

Region	Number	%Gated
ALL	8056	100.00
H1	1381	17.14
H2	315	3.91
H3	792	9.83
H4	5568	69.12

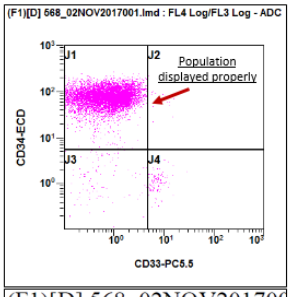
No Failure



[A] FL4 Log/FL2 Log

Region	Number	%Gated
ALL	8058	100.00
H1	839	10.41
H2	66	0.82
H3	1347	16.72
H4	5806	72.05

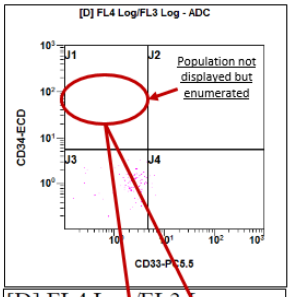
Failure in FL2



(F1)[D] 568_02NOV201700

Region	Number	%Gated
ALL	24890	100.00
J1	24642	99.00
J2	17	0.07
J3	133	0.53
J4	98	0.39

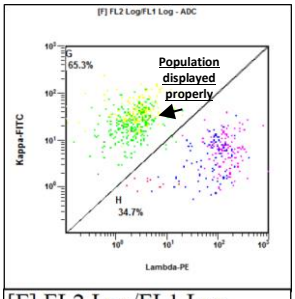
No Failure



[D] FL4 Log/FL3 Log

Region	Number	%Gated
ALL	25015	100.00
J1	24785	99.08
J2	0	0.00
J3	224	0.90
J4	6	0.02

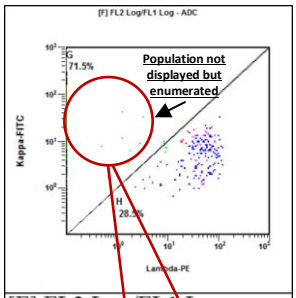
Failure in FL4



[F] FL2 Log/FL1 Log

Region	Number	%Gated
ALL	597	100.00
G	390	65.33
H	207	34.67

No Signal Failure

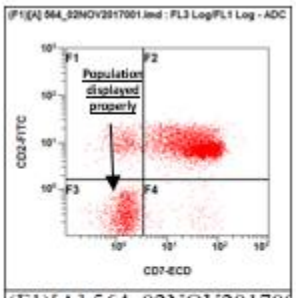


[F] FL2 Log/FL1 Log

Region	Number	%Gated
ALL	579	100.00
G	414	71.50
H	165	28.50

Failure in FL2

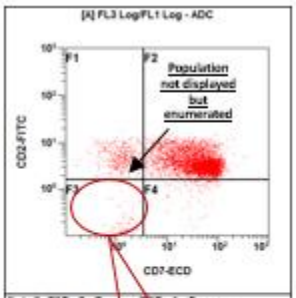
- In some instances the finding may be especially subtle as illustrated in the example below. In this particular instance case a similar pattern could be due to a small compensation error. Consider the possibility that this may be an Amplifier board failure.



(F1)[A] 564_02NOV20170

Region	Number	%Gated
ALL	8098	100.00
F1	556	6.87
F2	5705	70.45
F3	1679	20.73
F4	158	1.95

No Signal Failure



[A] FL3 Log/FL1 Log

Region	Number	%Gated
ALL	8098	100.00
F1	552	6.82
F2	5586	68.98
F3	1692	20.89
F4	268	3.31

Subtle Failure in FL1