Understanding Quality Control for Infectious Disease Testing

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ASLM Quality Control Workshop

Abuja, Nigeria

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NRL Science of Quality

Disclosure

- Attendance at ASLM part-sponsored by CDC
- No personal financial gain

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Acknowledgements

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- Katy Yao – CDC
- Anna Murphy

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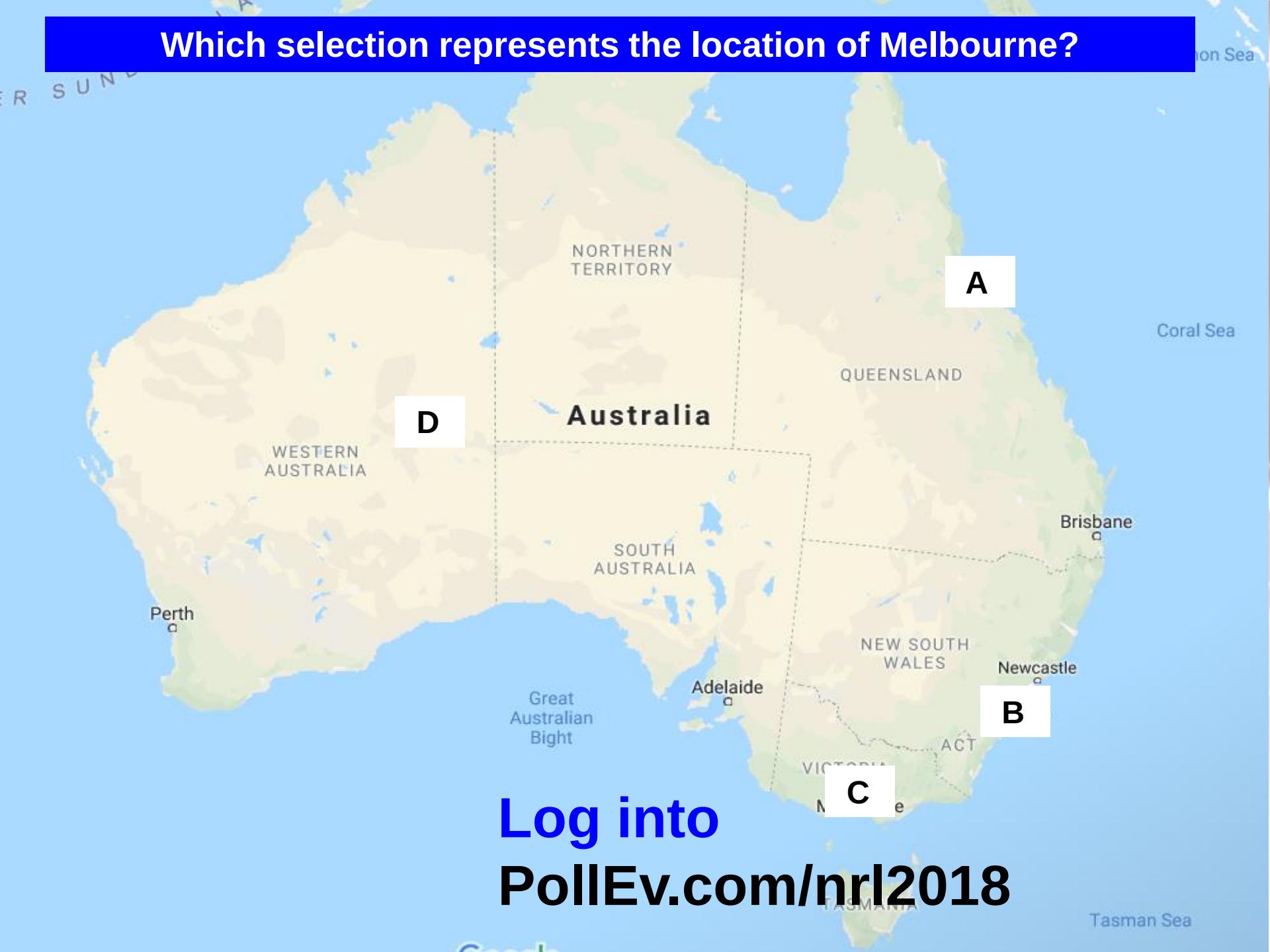
Which selection represents the location of Melbourne?



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Which selection represents the location of Melbourne?

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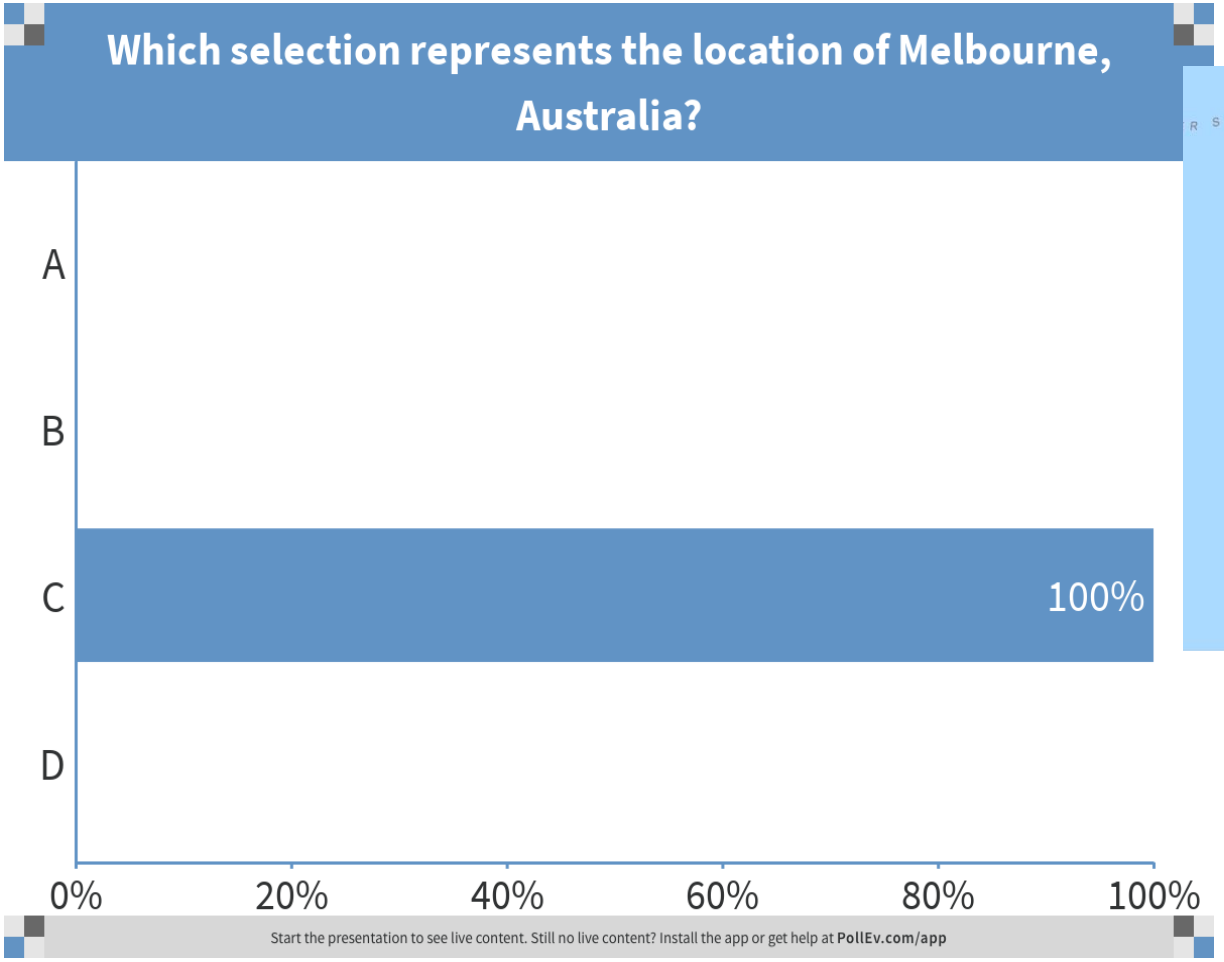

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NRL

- Established in 1985
- Not-for-profit organisation that exists to support laboratories that perform testing for the diagnosis and management of human infectious disease
- Funded partially by the Australian Government
- Mission

  To promote the quality of tests and testing for infectious diseases globally.

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NRL

- Our objectives are achieved by providing:
  - comprehensive and innovative quality assurance services;
  - evaluations of tests and test algorithms;
  - specialised laboratory testing services;
  - training with sustainable outcomes;
  - consultation and advice on policy relating to laboratory testing.

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- Major Stakeholders:
  - Australian Government (DoH, DFAT, TGA)
  - WHO, US CDC, Global Fund, UNDP
  - Australian Red Cross Blood Service
  - Test kit manufacturers
  - Laboratories (blood screening and clinical)

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- Credentials:
  - WHO Collaborating Centre
  - Certified to Management Standard AS/NZS ISO 9001:2008
  - Accreditation as a Medical Testing Laboratory; Compliant with ISO/IEC 15189: 2007
  - Accredited as EQAS Provider to ISO 17043:2010
  - Licensed by TGA under the *Code of Good Manufacturing Practice - Human Blood and Tissue:2000*

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Major Activities

- NRL Evaluations
- NRL Training
- NRL Testing
- NRL Workshop
- Quality Assurance
  - EQAS
  - QC

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Who am I?

- Medical scientist
  - Fellow AIMS
  - Fellow RCPA (faculty of science)
  - MBA
- Microbiology scientist
- Laboratory auditor
- WHO consultant
- Standards Australia committee member
- Reviewer of NRL's QC program results

What I am not

- Clinician
- Clinical biochemist
- Statistician
- Salesman
- Solver of all things QC

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History of Quality Control

- Walter A. Shewhart of the Bell Telephone Laboratories (1924) introduced the first control chart
- W. Edwards Deming of US Bureau of the Census (1940s) used statistical sampling techniques
- Post WWII emergence in Japanese manufacturing
- Deming Cycle of quality control in 1950s
- Adoption of control charts by Levey and Jennings (1950) in clinical chemistry

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History of Quality Control

- Invention of control rules by Westgard et al (1981)
- Six Sigma was pioneered by Motorola in 1980s
- Operational Process Specifications charts (OPSpecs) in 1994 by Westgard
- Six Sigma as applied to clinical chemistry introduced by Westgard in 2001
- CLSI Guidelines 3rd ed. Vol. C24-A3 (2006)
- CLSI Guidelines 4th ed. Vol. C24 (2016)

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History of Quality Control

- Since 1990s only three non-NRL published papers on QC applied to infectious disease serology
  - One on HBsAg testing
  - Two reviewing antibody testing – limited reagent lot changes
- No systematic studies on QC for viral load testing

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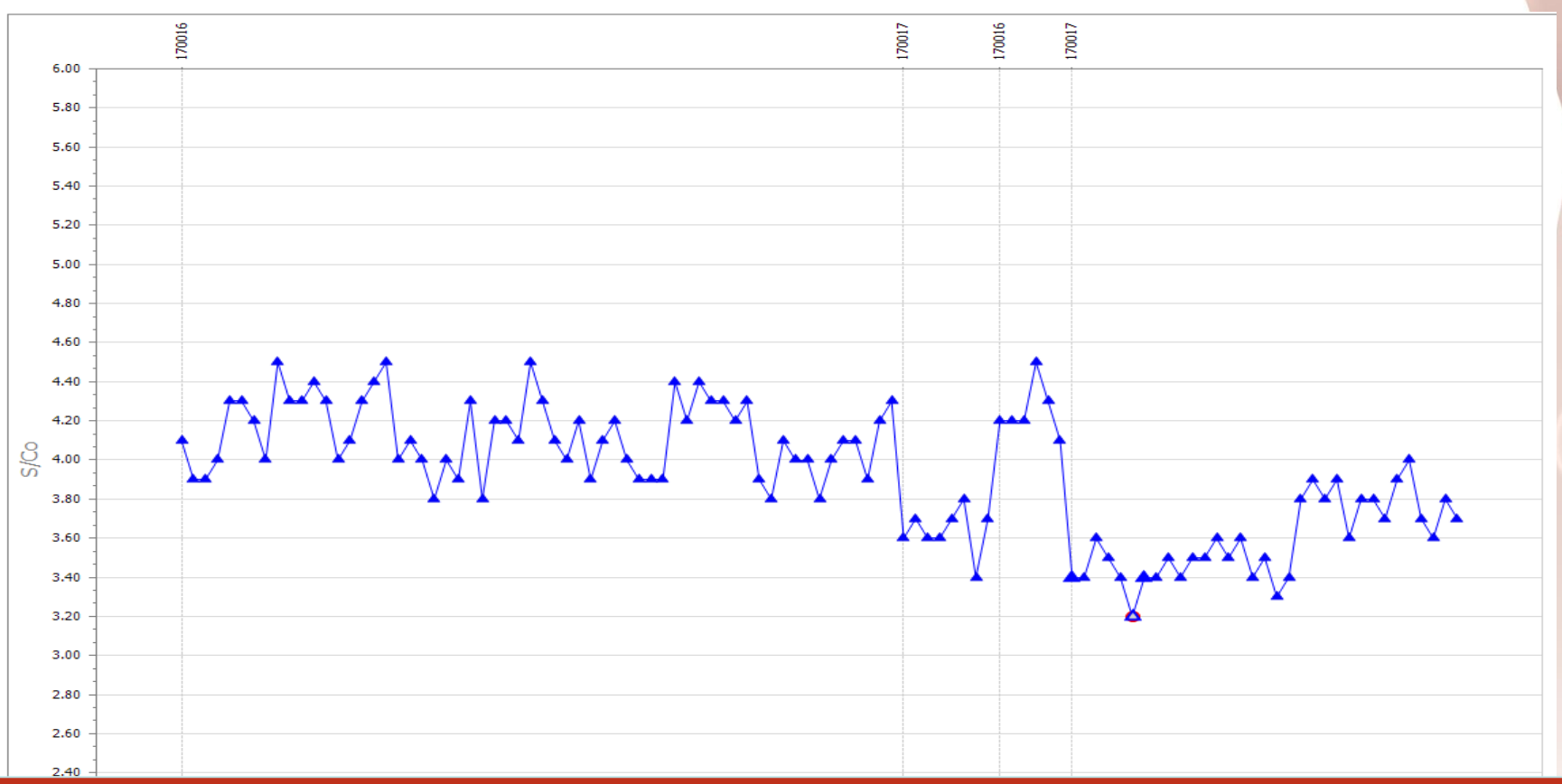
Point 1:

Measuring systems must be fit for purpose

Variation



Point 2:

Measurement systems have *normal* variation

Titanic

- Captain Smith ignored seven iceberg warnings from his crew and other ships
- Speeding to make crossing in 6 days
- Rivets made of sub-standard iron
- Water-tight compartments compromised to allow more 1st class room
- There were too few lifeboats
- Captain of ***SS Californian*** took no action

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- People
- Processes
- Components
- Equipment

Variation

- Reagent lots
- Instrument and equipment
- Calibrations and maintenance
- Operators
- Storage and transport conditions
- Environmental conditions

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Why Run Quality Control?

To monitor

- People
- Processes
- Components
- Equipment

Point 3:

Variation is derived from people, process, components and equipment

Common terms

- Accuracy
  - the ability to measure the true value correctly on average
- Precision
  - a measure of inherent variability in the measurement (the repeatability of a result)
- Bias
  - the difference between the observed value and the expected/target value

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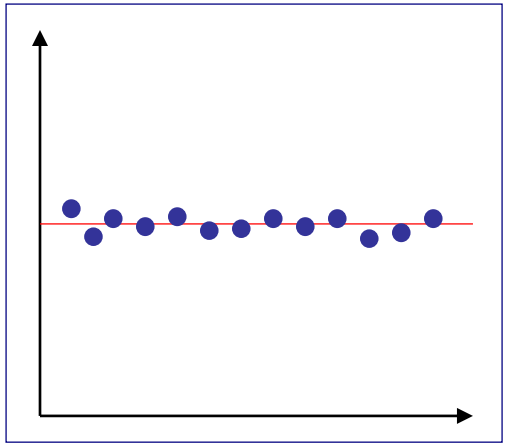
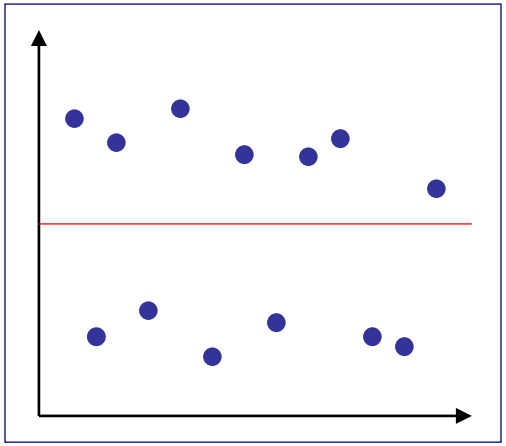
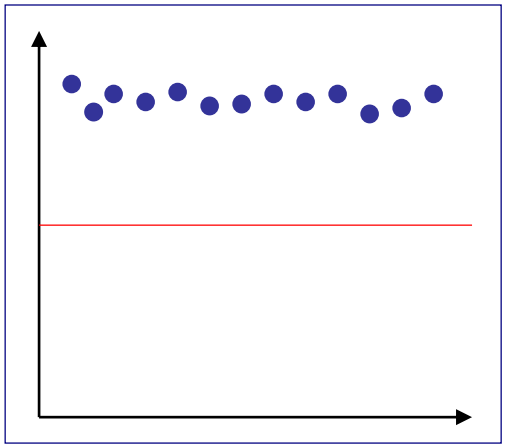
Common terms



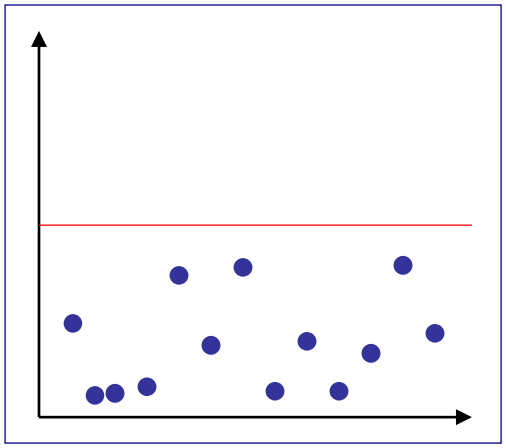
A. Accurate and Precise



B. Accurate (on average) but not Precise



C. Precise but not Accurate

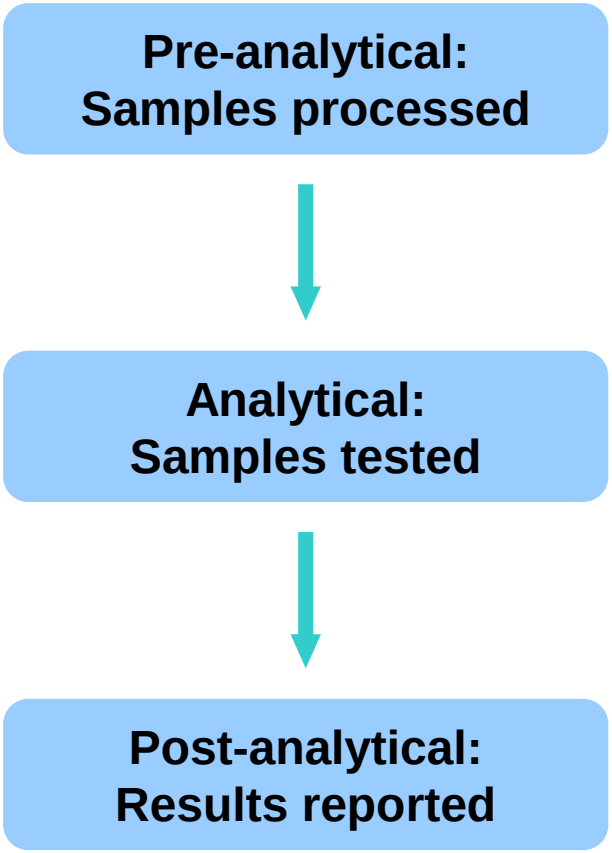


D. Neither Precise nor Accurate

Quality Control

EQAS

- Monitors integrity of entire testing process
- Snapshot in time
- Identifies systematic and random errors
- Inter-lab comparisons identify assay and/or lab problems



QC

- **Monitors analytical process only**
- **On-going**
- **Identifies systematic and random errors**
- **Estimates precision within lab**
- **Inter-lab comparisons for estimation of accuracy**
- **Uncertainty of Measurement**

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Caveat – This talk is about:

Quality control for

infectious disease testing

Quality control means

Run control (IQC or EQC)

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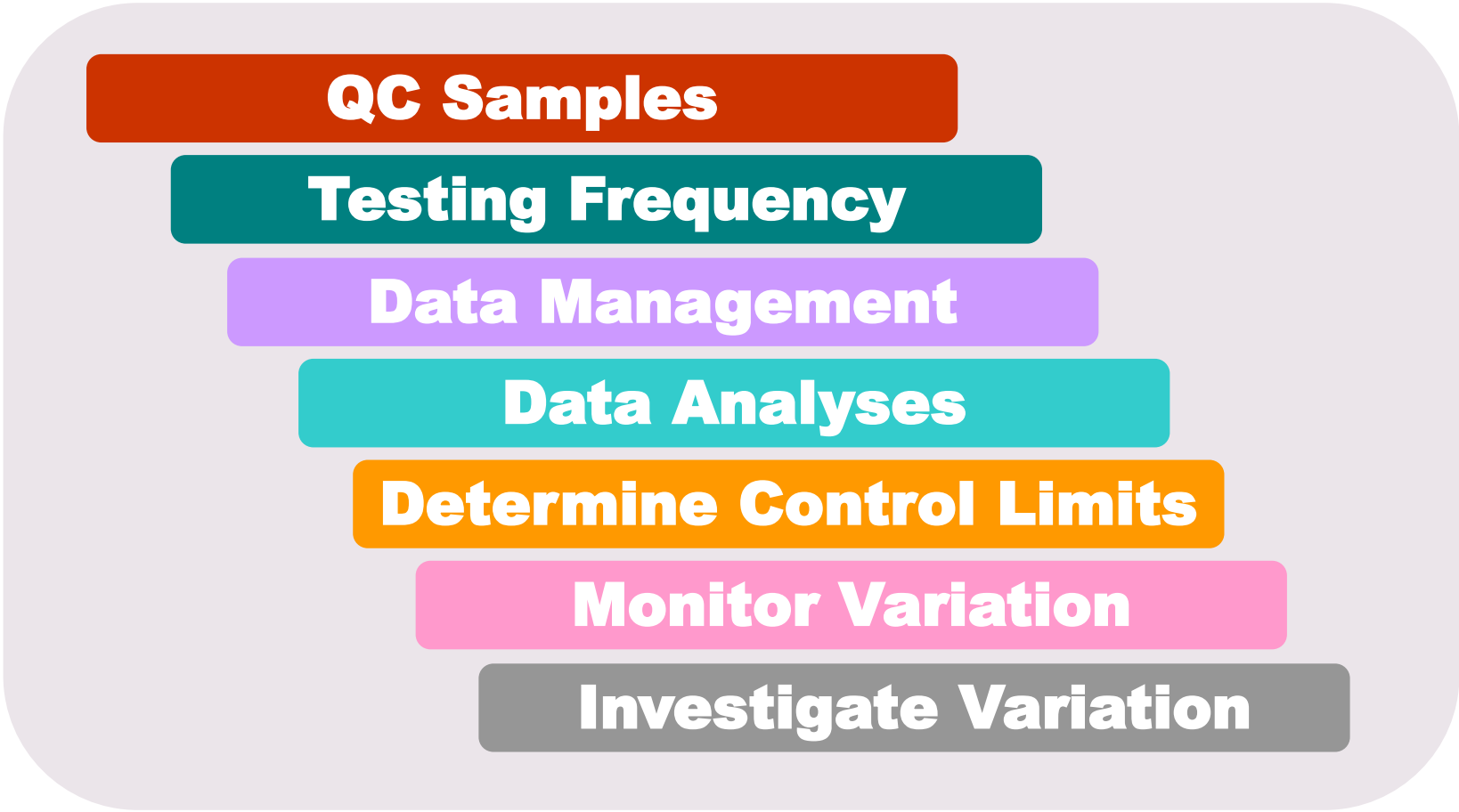
The Quality Control Process



Always test the manufacturer's kit controls as these are used to validate the assay

QC Samples

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Quality Control Sample

- Sufficient volume for extended use
- Stable over a long period
- Minimal lot-to-lot variation
- Composition similar to patient sample
- Results within the clinically significant range
- Must not “saturate” the assay
- Must be on the linear part of the curve
- Colour coded; Bar coded
- Liquid stable - no reconstitution

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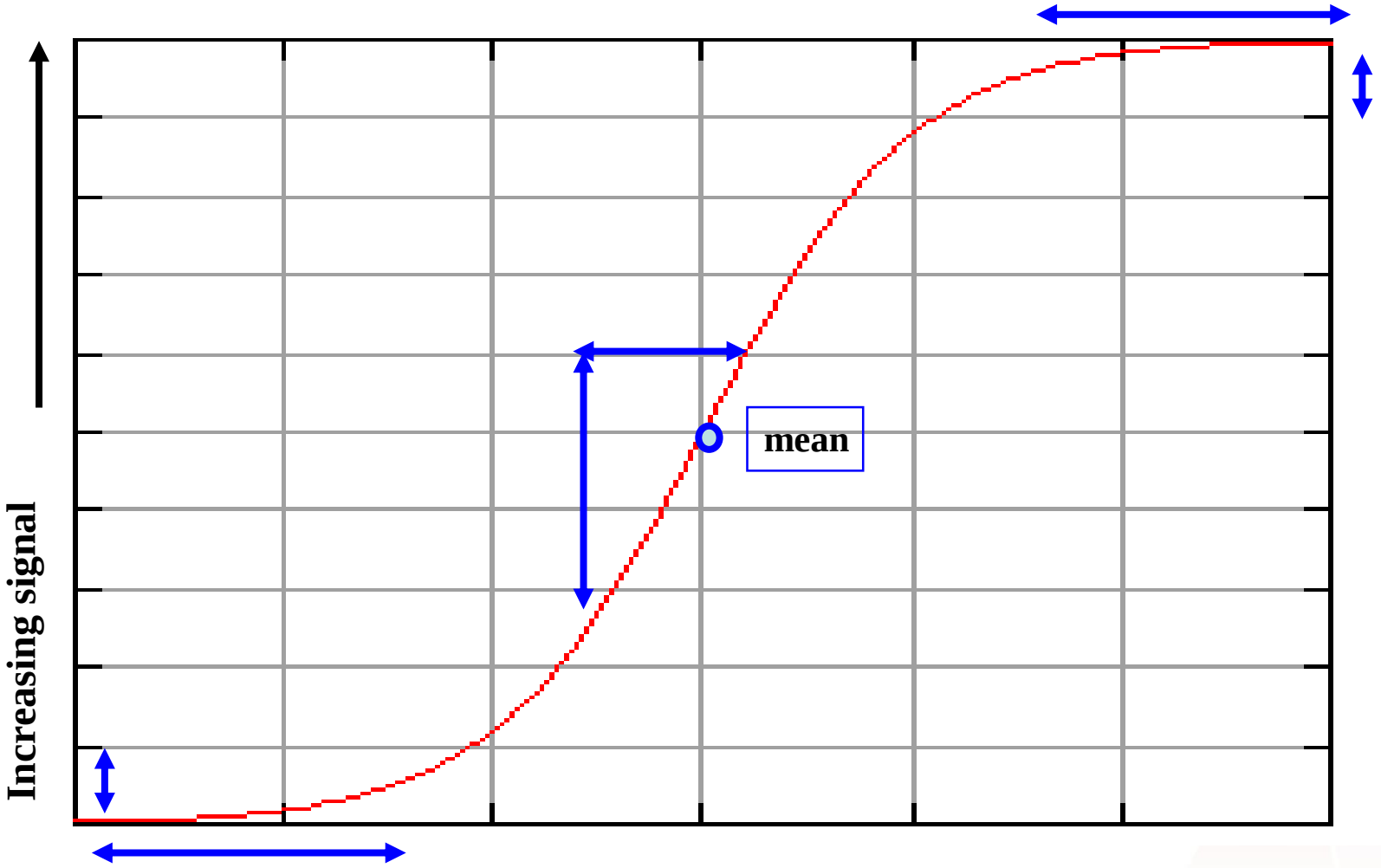
Ideal QC/Assay Combination

Serology Dose Response

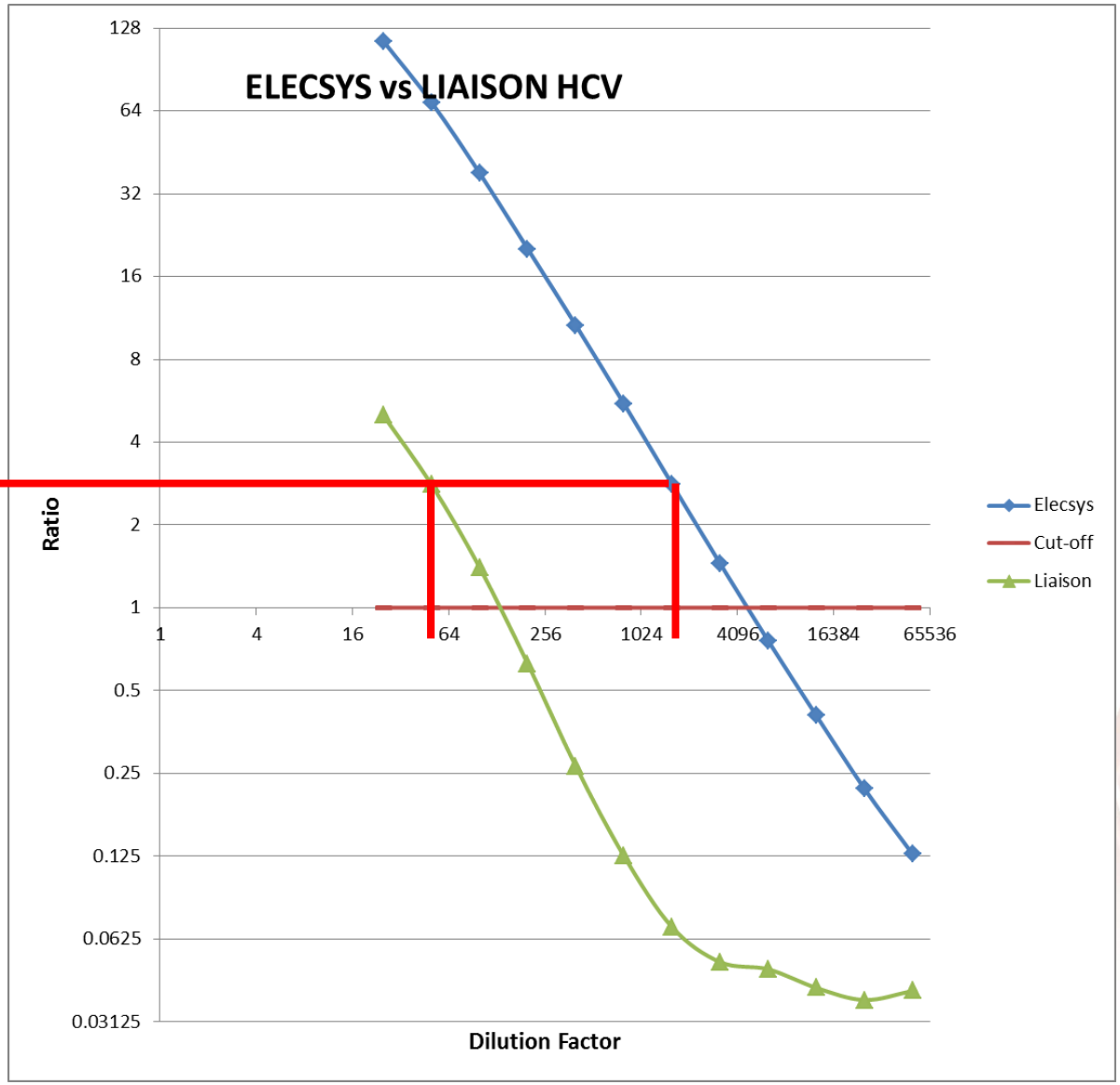


Serology Dose Response

Traditional "obsession" with 2-3x cut-off

Ideal ratio?

Appearances can be deceptive!!



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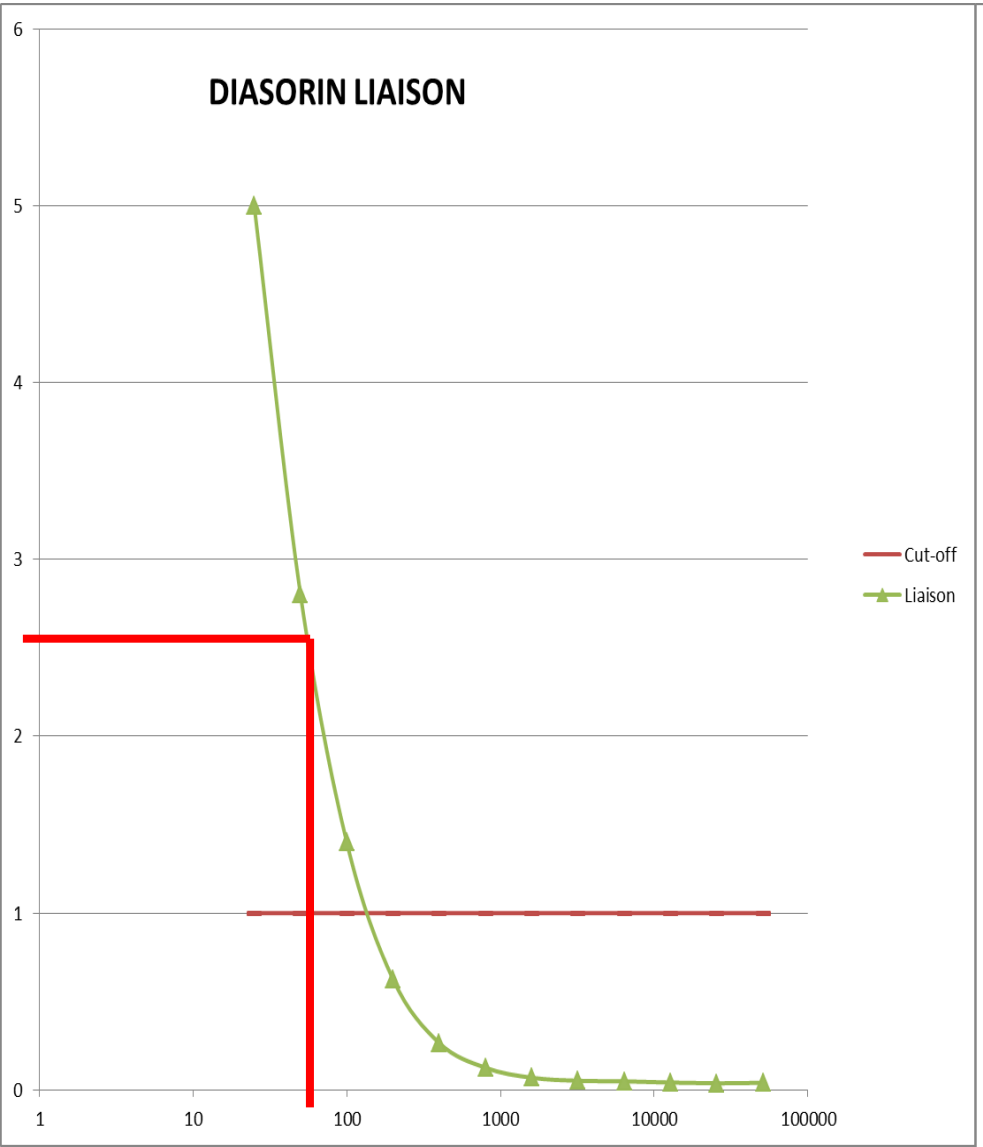
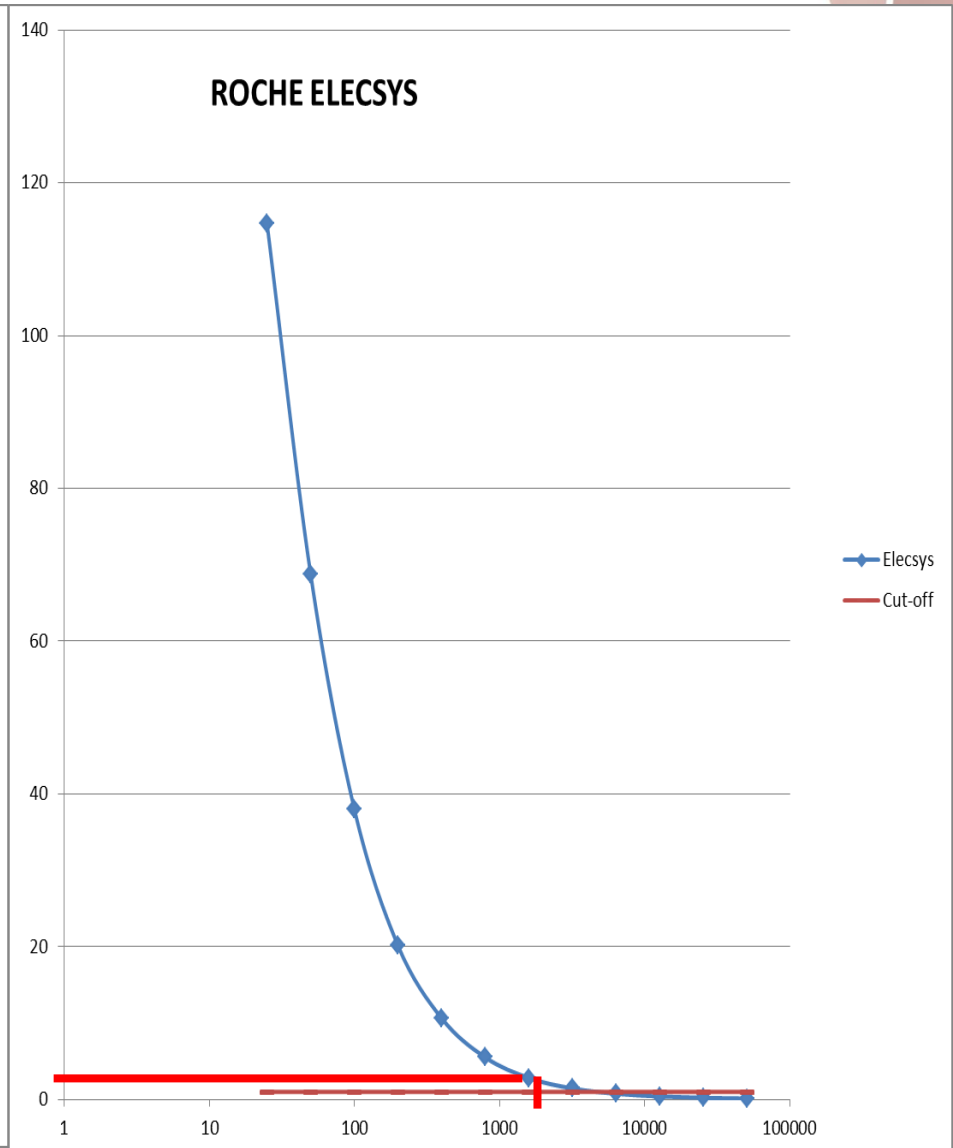
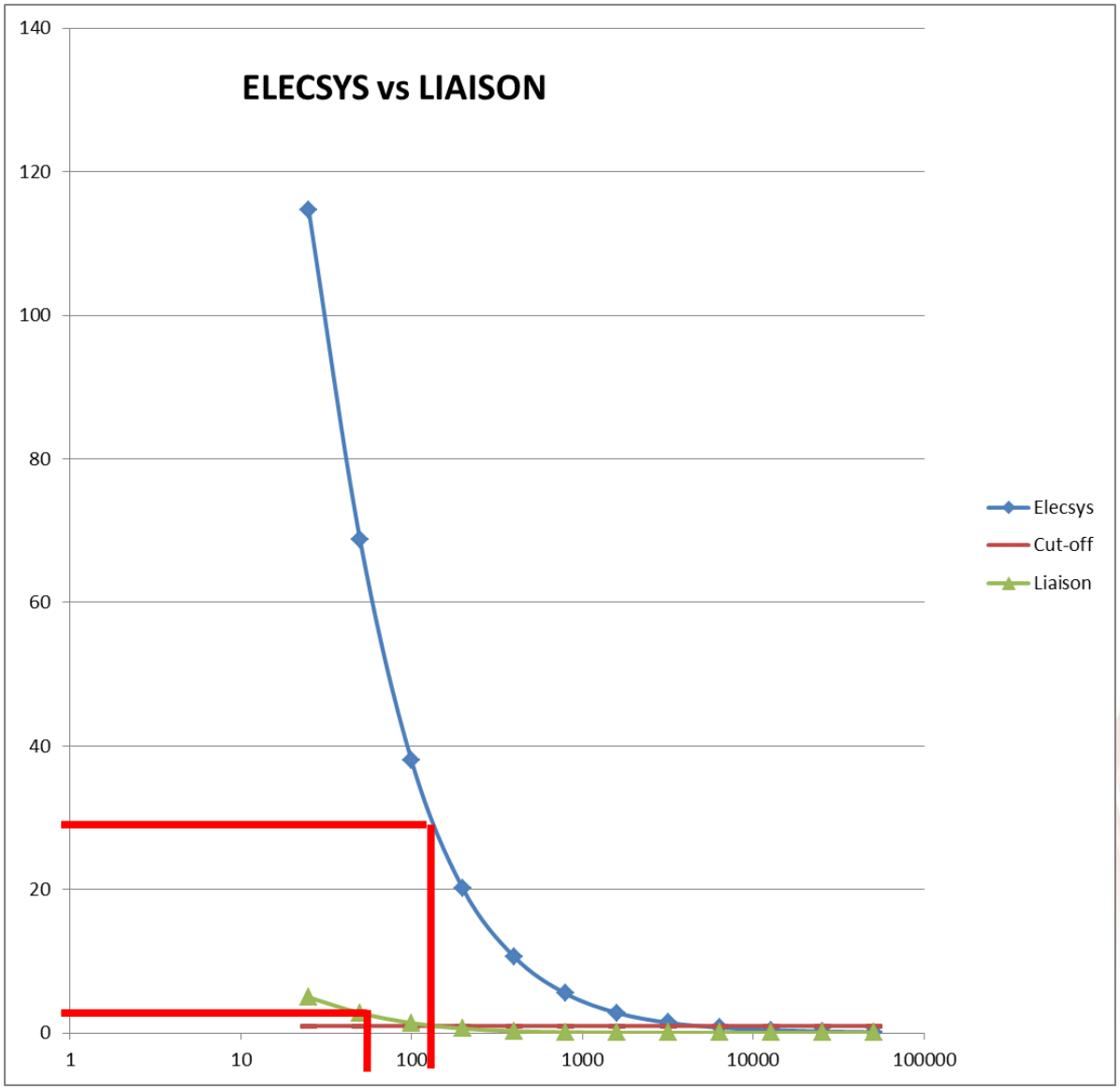
Serology Dose Response





Examples of Dilution Series



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Point 4:

Dynamic range of serology assays is not always linear

Point 5:

Choose QC sample that reacts at the linear portion of the dilution curve

Differences between Clinical Chemistry and ID Assays

Clinical Chemistry	Infectious Disease Serology
Linear	Non-linear
Inert analyte	Functional biological analyte
Quantitative	Qualitative
Adjust for bias	No adjustment for bias
Lower level of regulation	Highly regulated
Several medical decision points	Single decision point
Adjust for lots variation	No adjustment for lot variation

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Differences between Clinical Chemistry and ID Assays

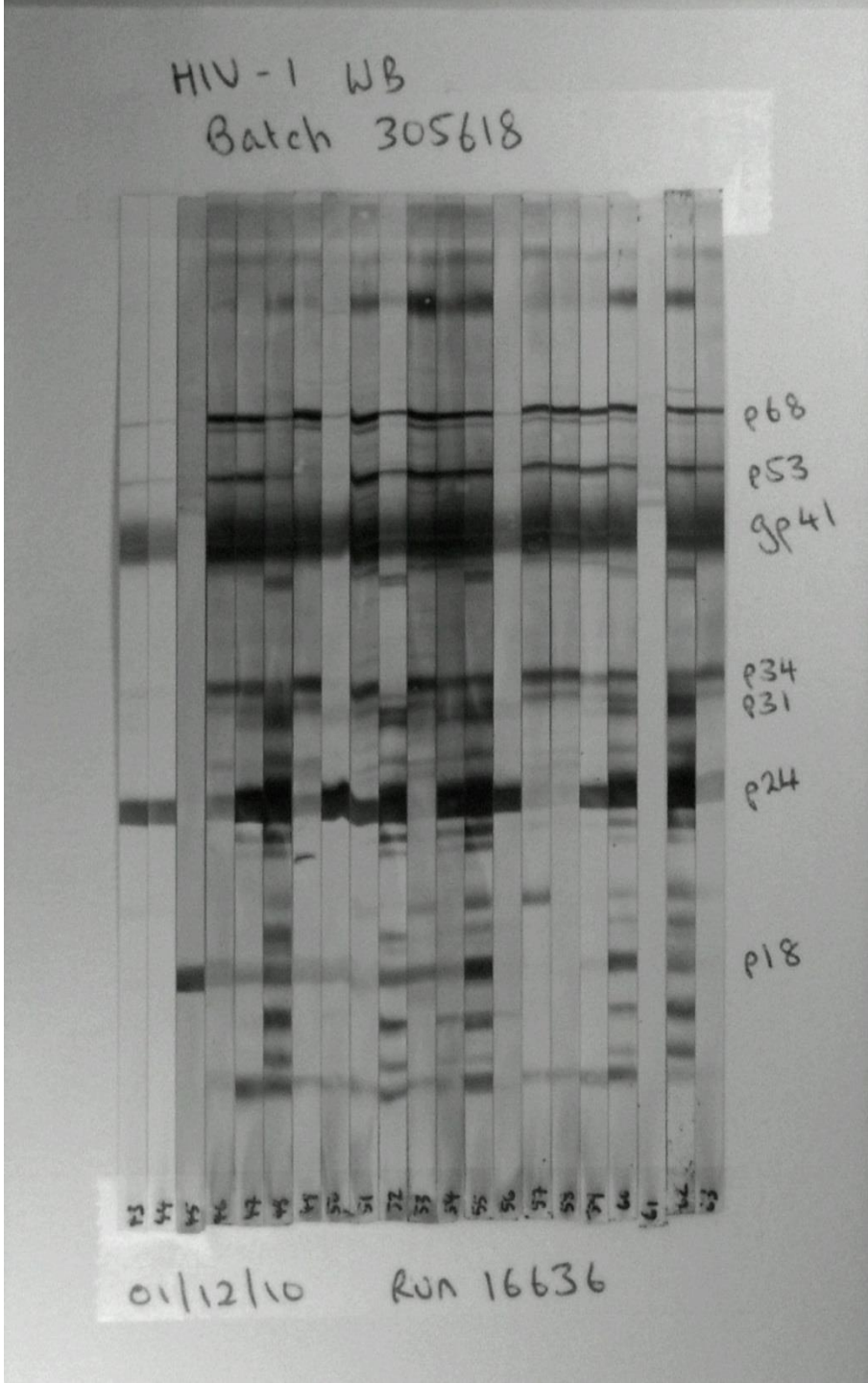
Clinical Chemistry	Infectious Disease Serology
International standards	Poor or no standards
Certified reference methods	No CRMs
Available in a pure form	Different forms
Single target	Multiple and varying targets
TEa	?? TEa

Point 6:

There are fundamental differences between testing for an inert chemical and a functional, biological analyte

HIV western blot

- Different Ab responses in different people
- Assay response depends on what the manufacturer has used in design



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Testing Frequency

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Testing Frequency

- No correct answer
- Cost vs risk
- Knowledge of assay
- Local and international regulation
- Minimum vs optimum

Point 7: Recommendation

Daily at start of day for automated platforms and or every microtiter plate

Data Management

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Data Management

- QC samples are a tool, not the end point
- Results collected after each test run
- Displayed graphically
- Have acceptance rules
- React immediately if unexpected results are detected

Point 8:

Monitoring QC results without reference to a peer-group only monitors precision

What We (Think) We Know About Quality Control

Interpretation of QC Results

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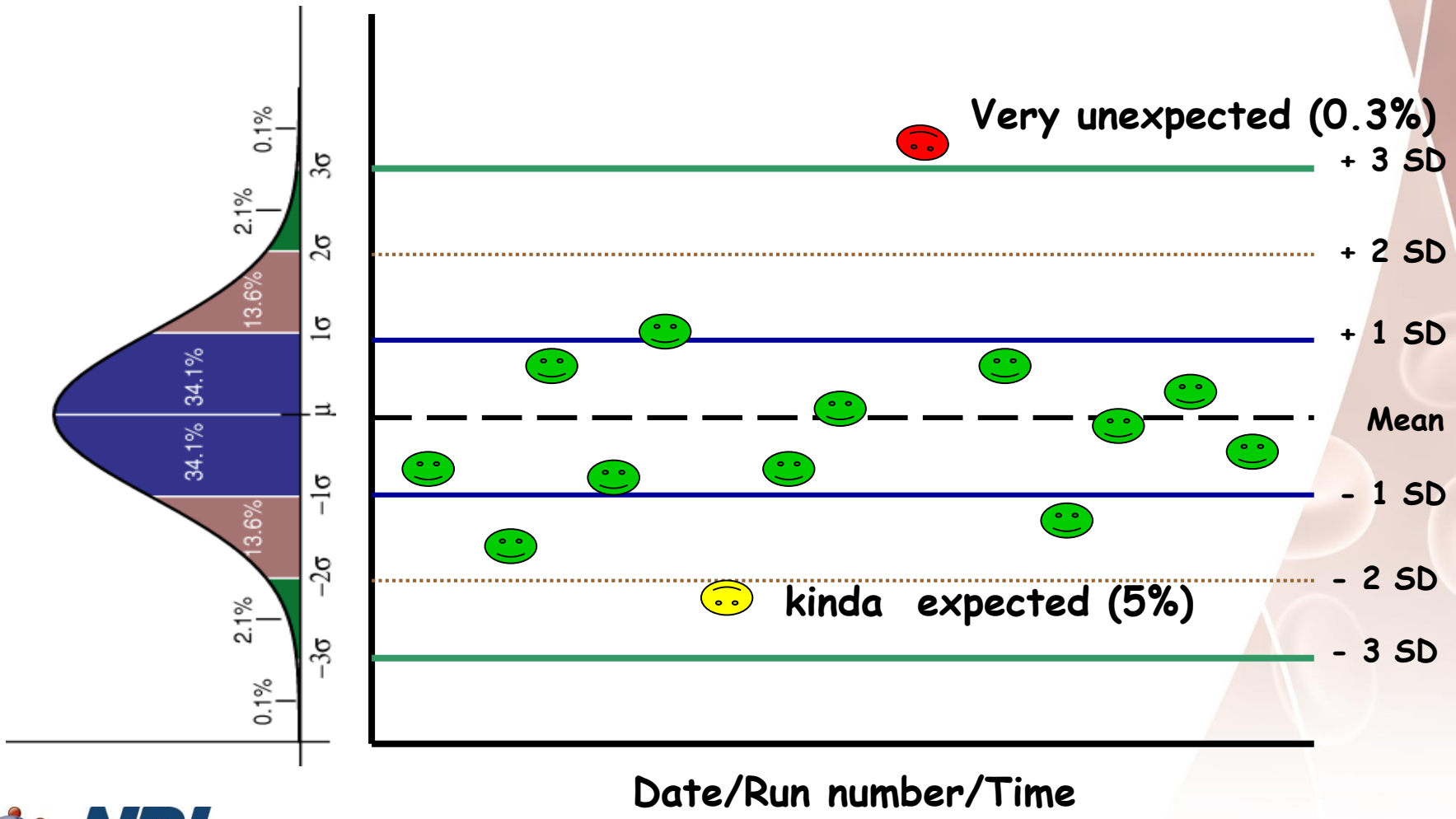
Control Limits



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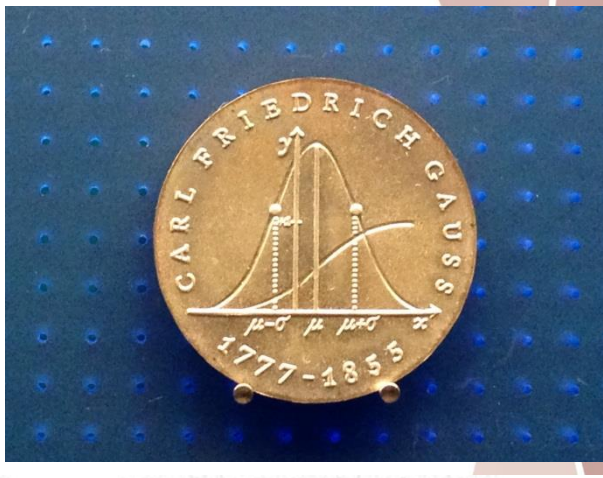
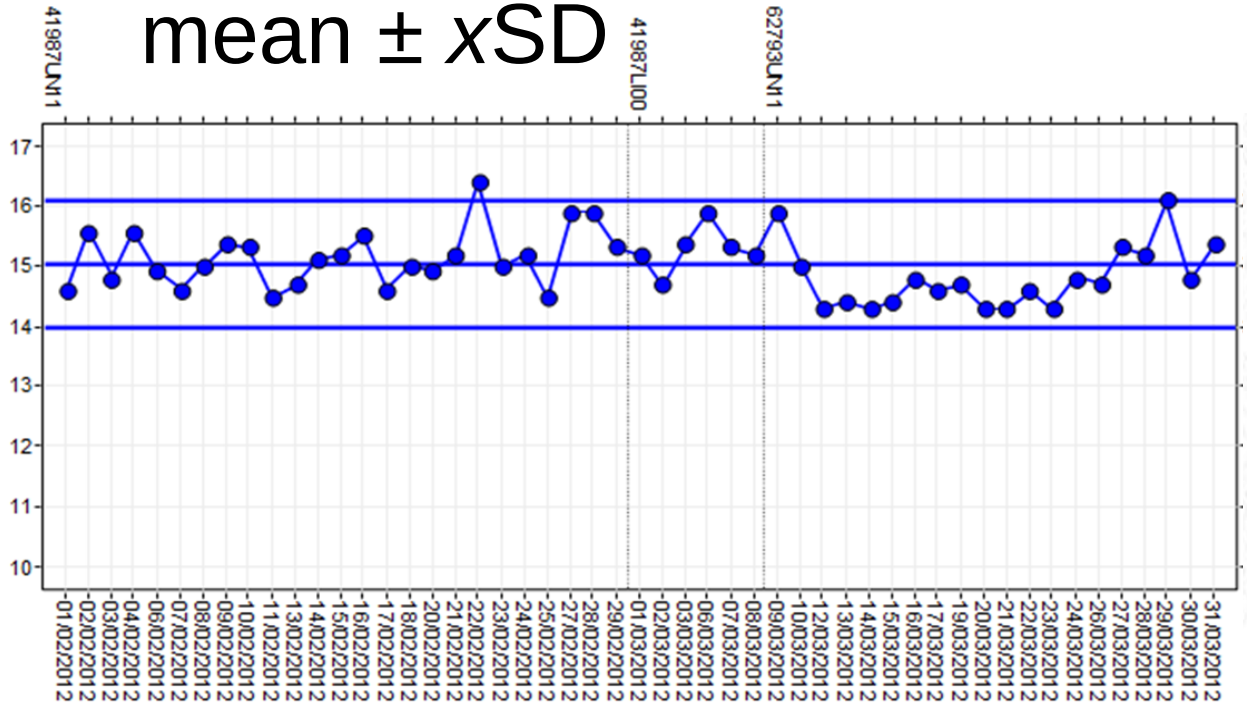
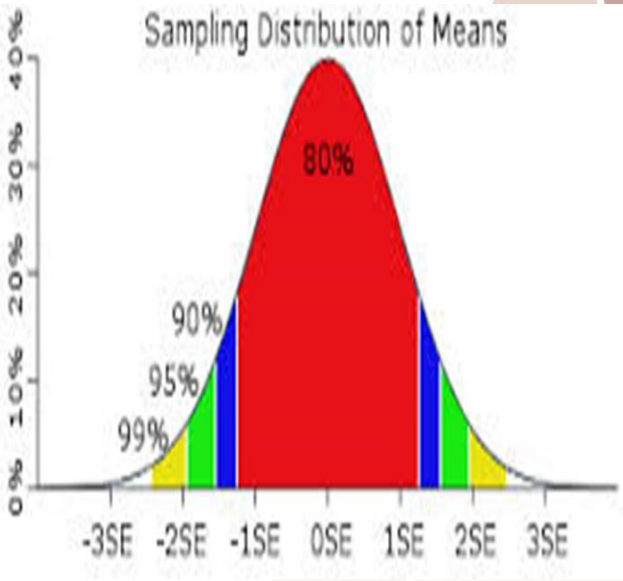
Control Limits

- Traditional methods for setting QC limits rely on mean ± *x*SD







…of what data set?

Control Limits

- RiliBÄK standard (2015)
  15
- Public Health England (2015)
  20
- CLSI Guideline third edition C24-A3 (2006)
  20
- CLSI Guideline fourth edition C24 (2016)
  20 (recalculate periodically)

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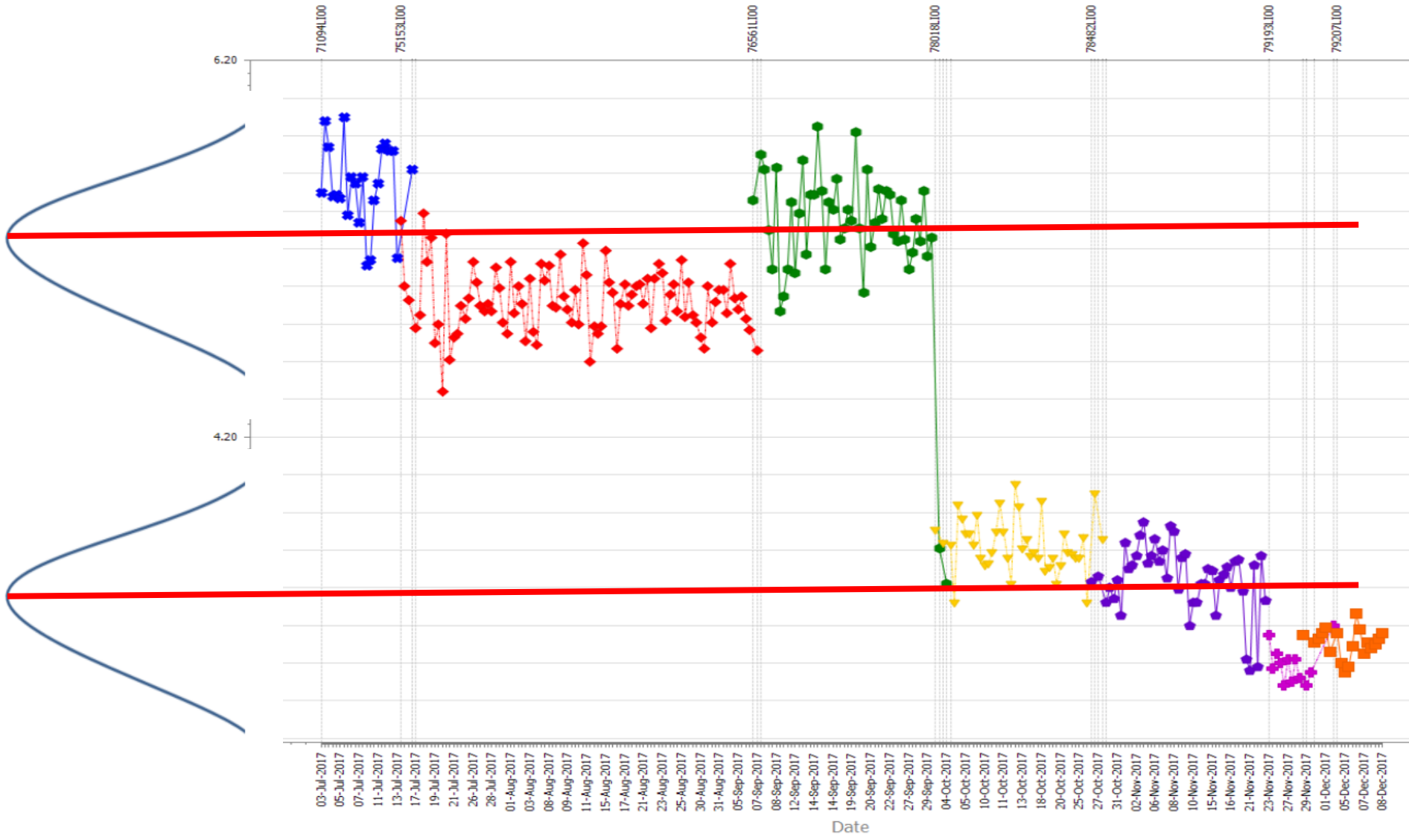
Traditional Approaches to QC

- Assumes normal distribution of QC results
- Patient and QC sample results change proportionally (Commutability)
- Data set used to establish limits are representative of future results

Point 9:

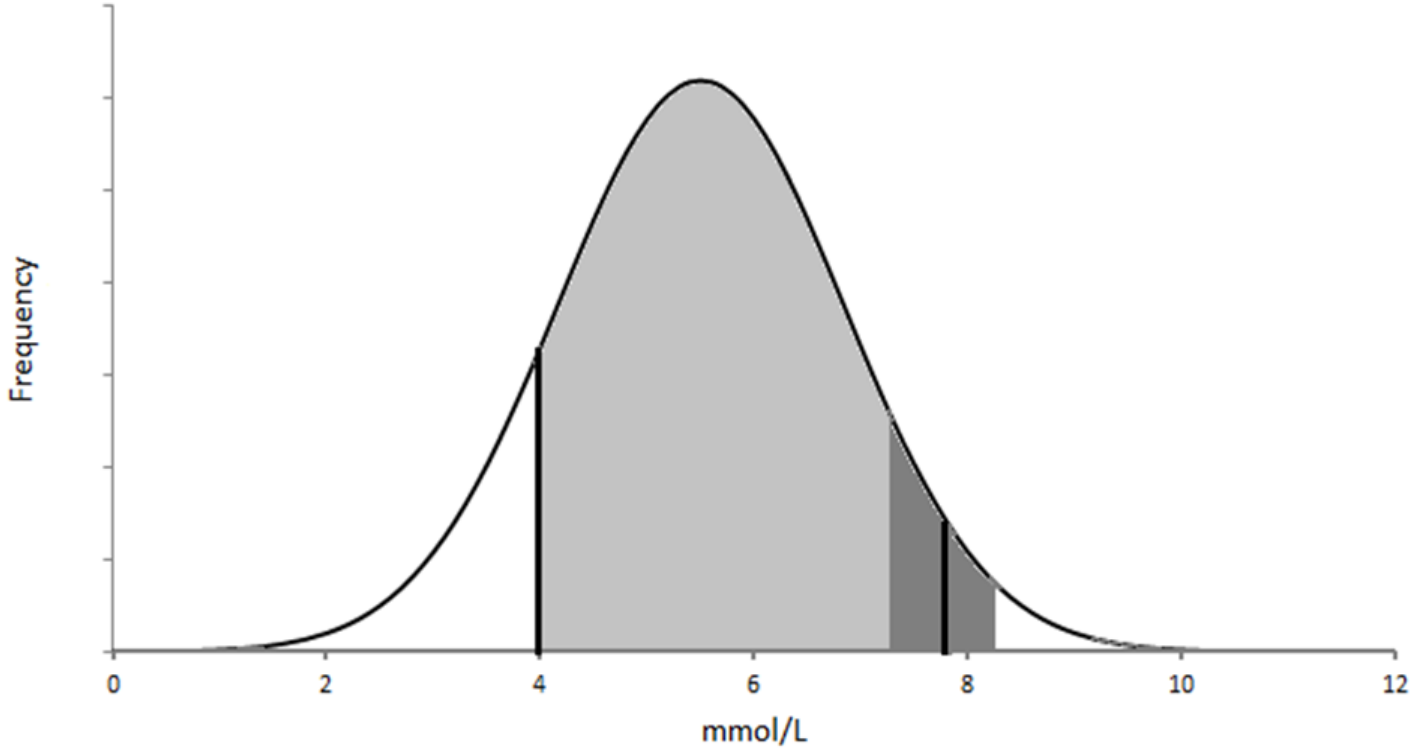
These assumptions are not true for infectious disease serology

Data are Normally Distributed



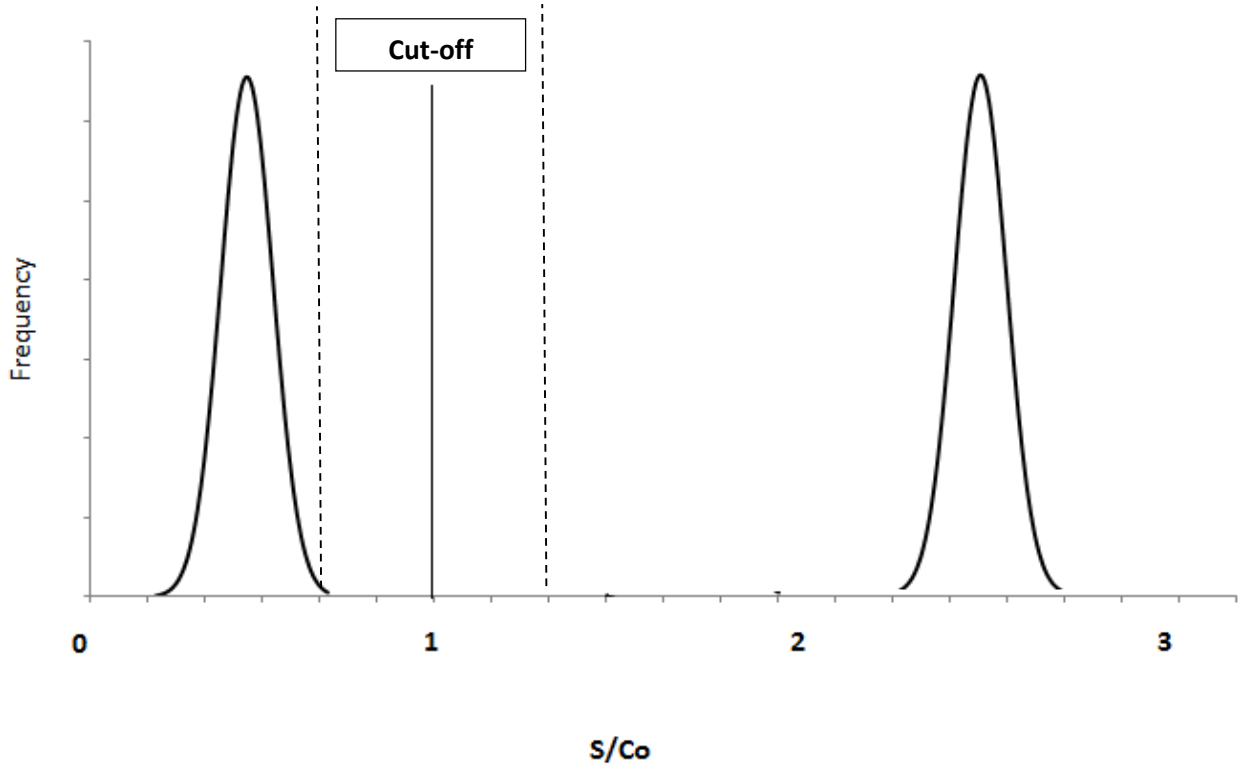
QC Commutability

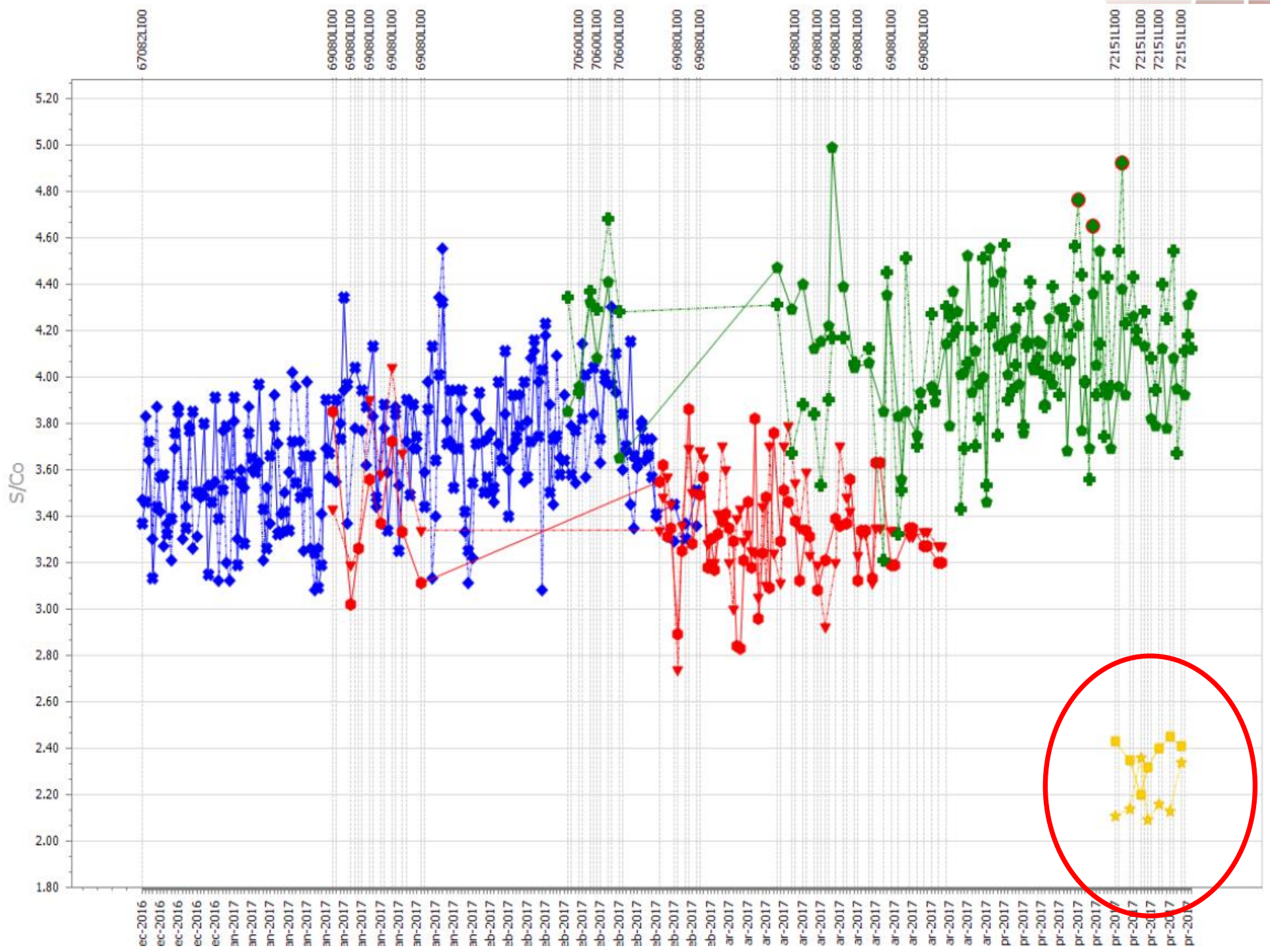
- Assuming QC commutability, percentage misinterpretation of chemistry results can be determined



QC Commutability

- However, in serology, very few results will be misinterpreted
- How do you estimate TEa for serology?

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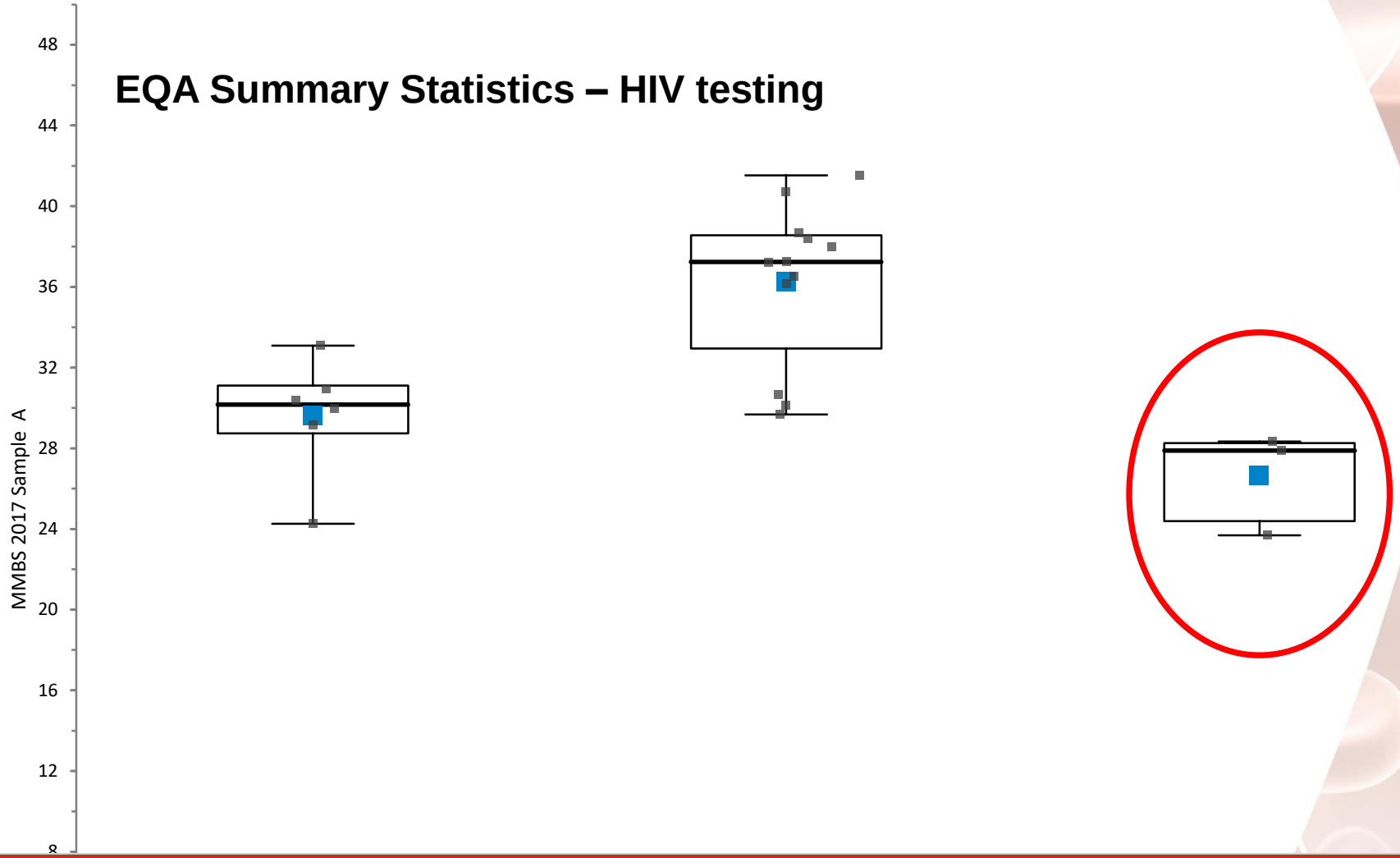


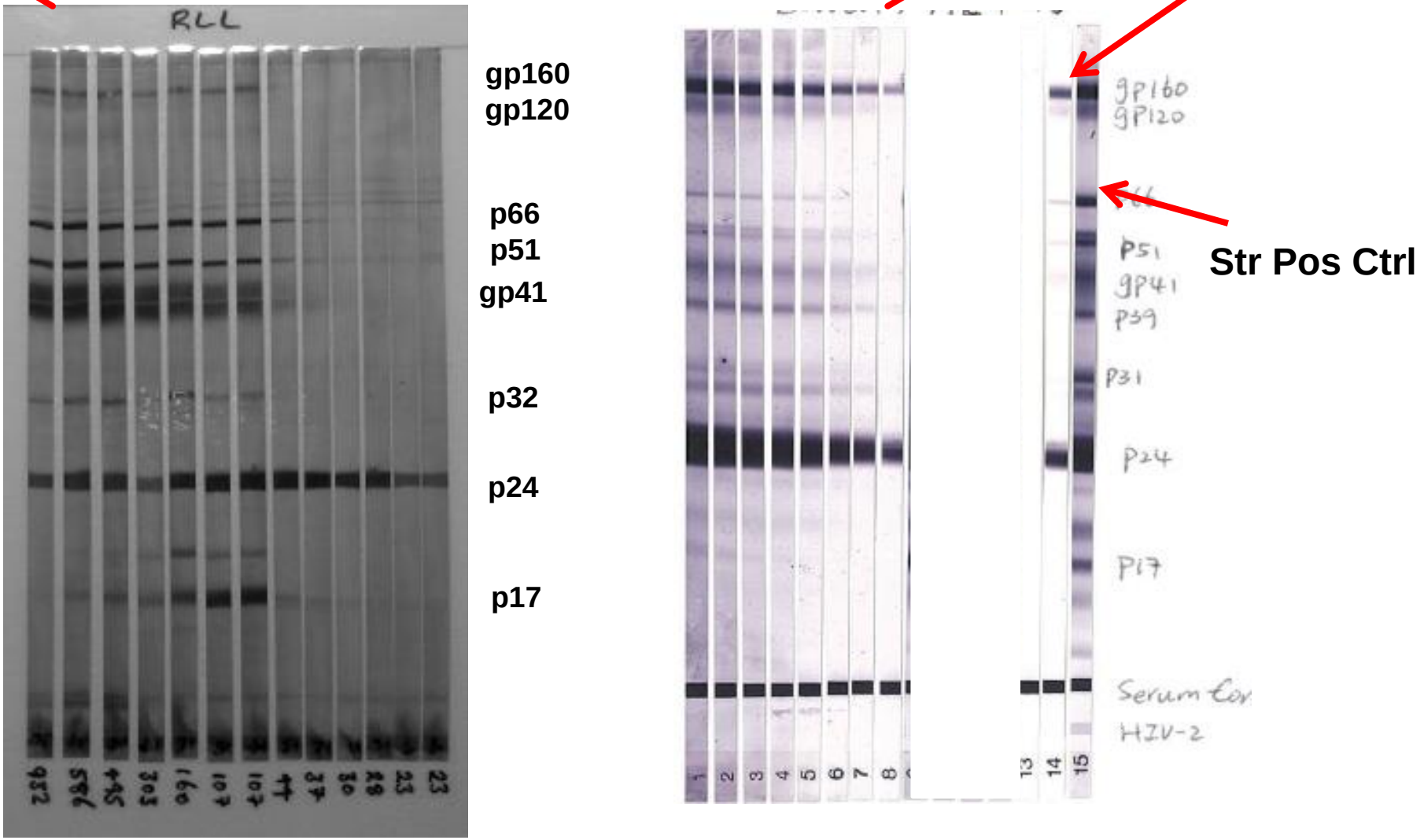
Point 10:
Commutability of QC samples and patient samples should not be assumed

Low levels QC mimics seroconversion

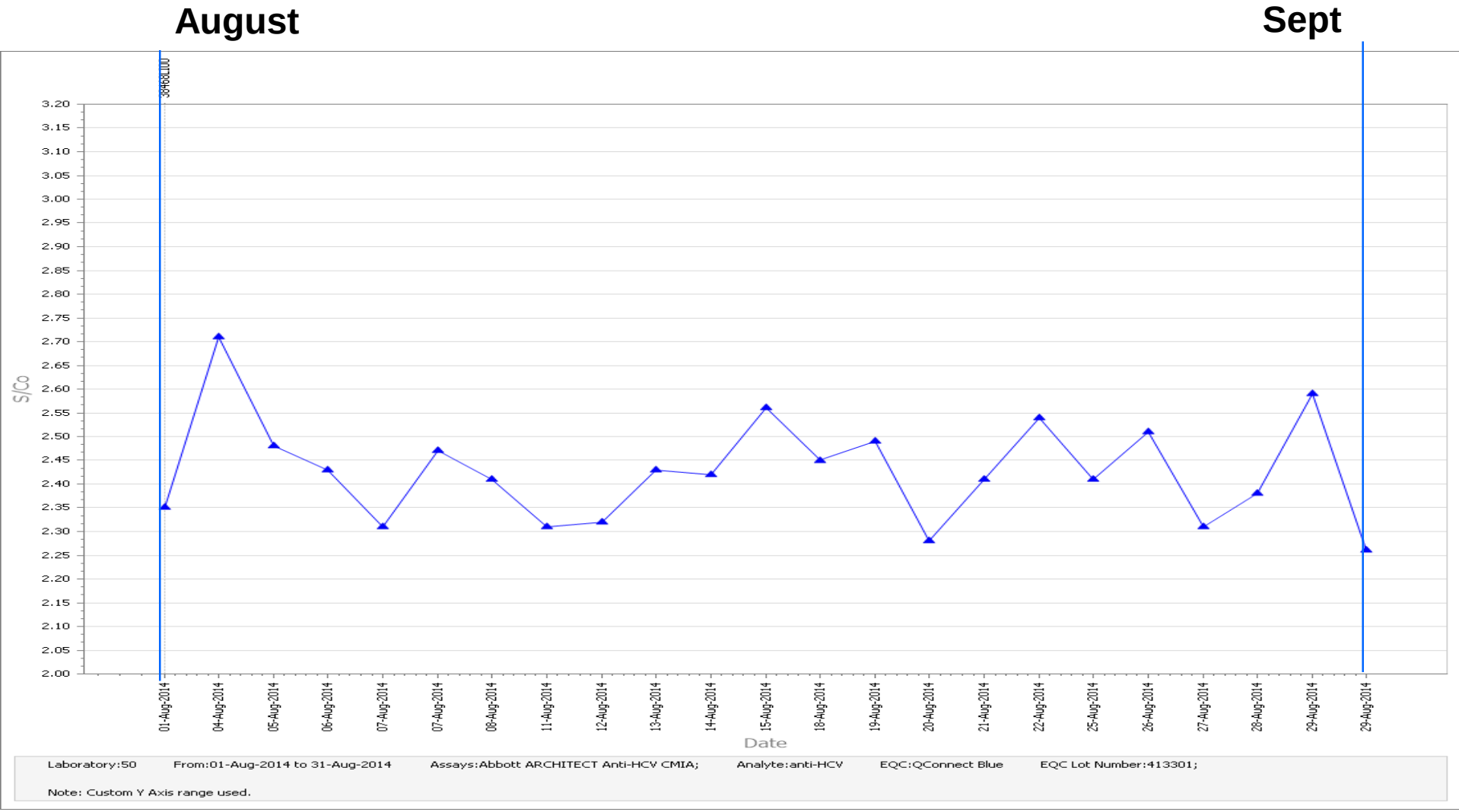
- Low positive, diluted QC mimics a seroconverter
- Diluted samples ≠ early infection
- Antibodies ramp up very quickly
- Antibody profiles different to early infection (seroconversion)

Point 11:
Using a diluted sample to mimic early infection is a flawed concept

WB Seroconversion vs Dilution



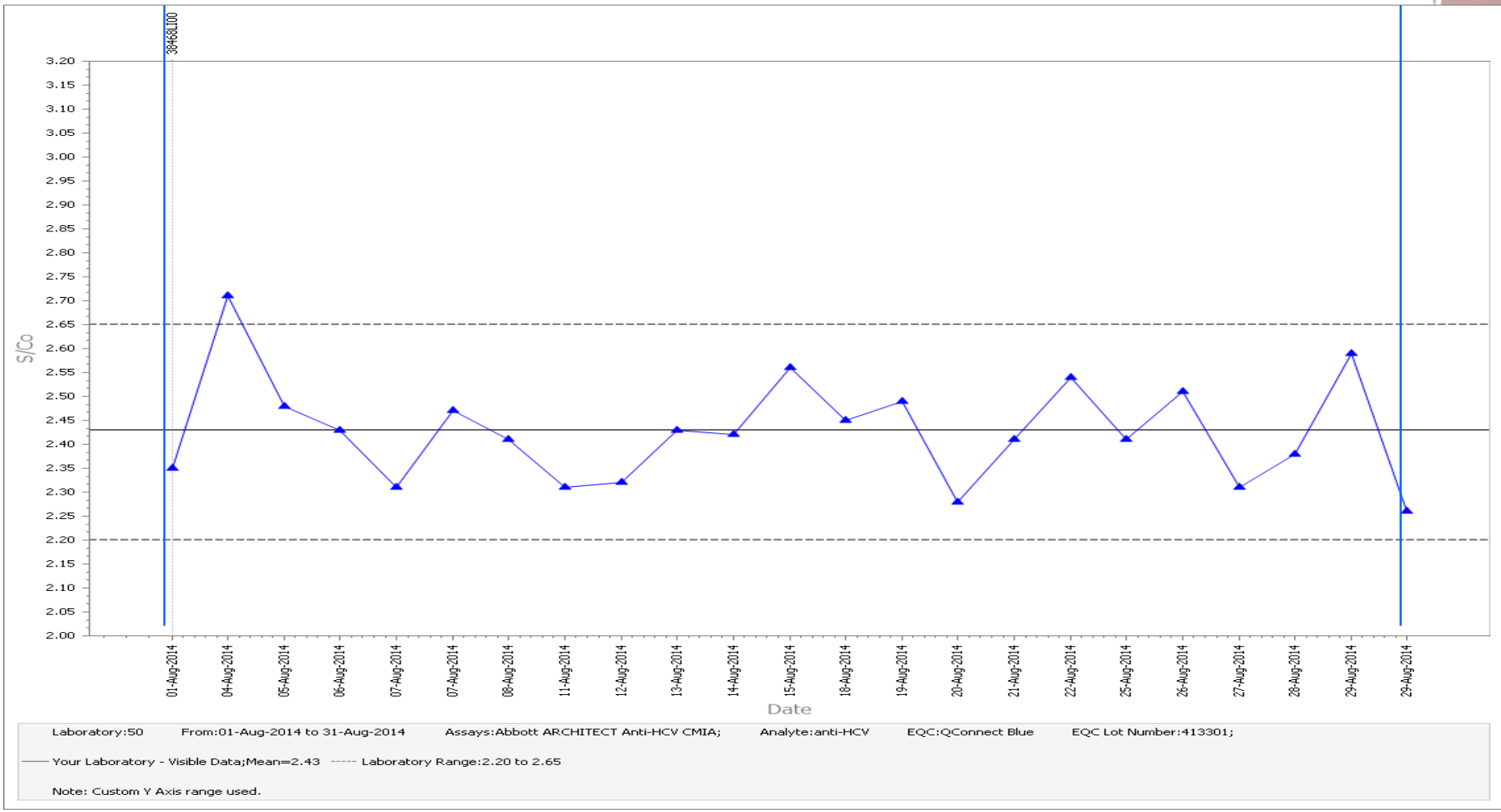
Data are Representative



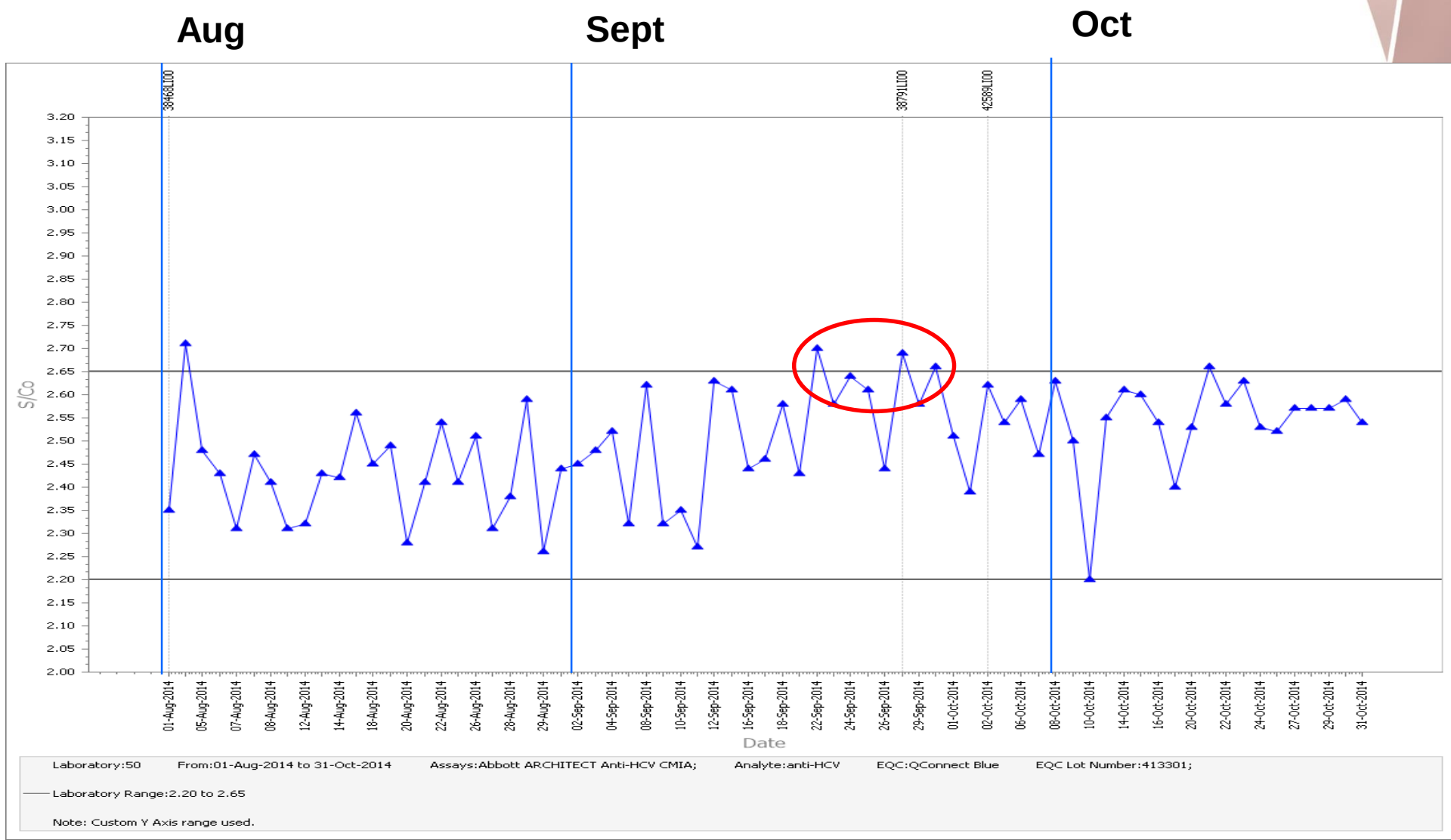
Data are representative

August

Sept



Data are representative



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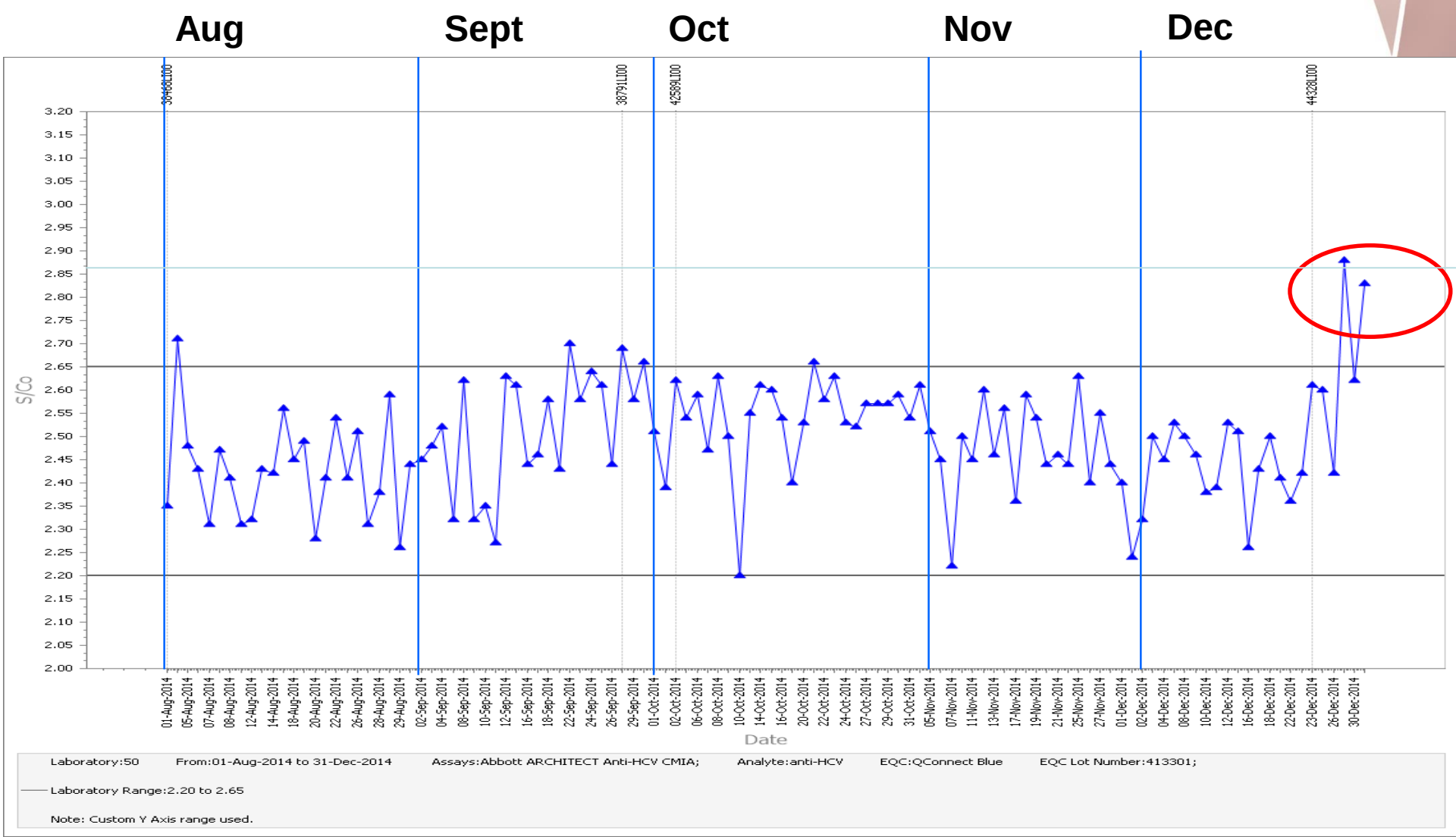

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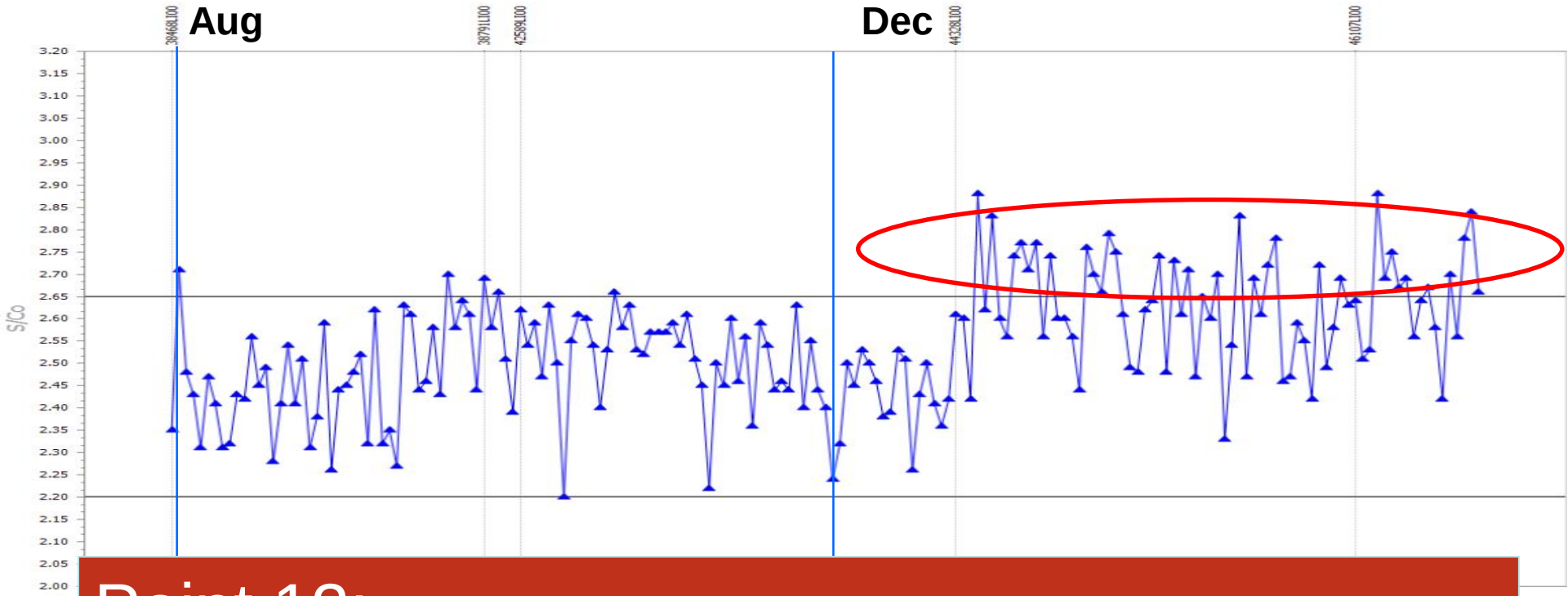
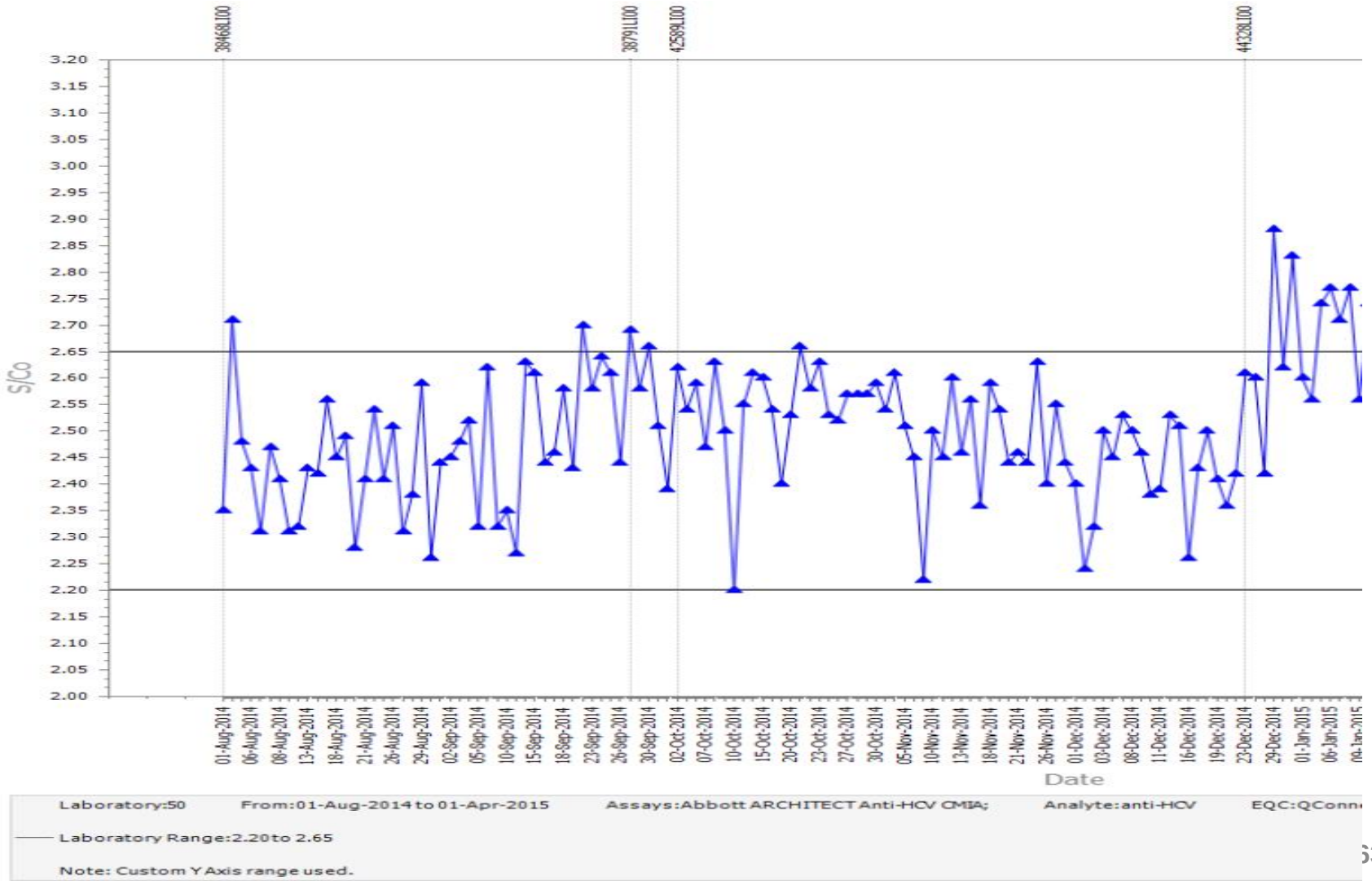


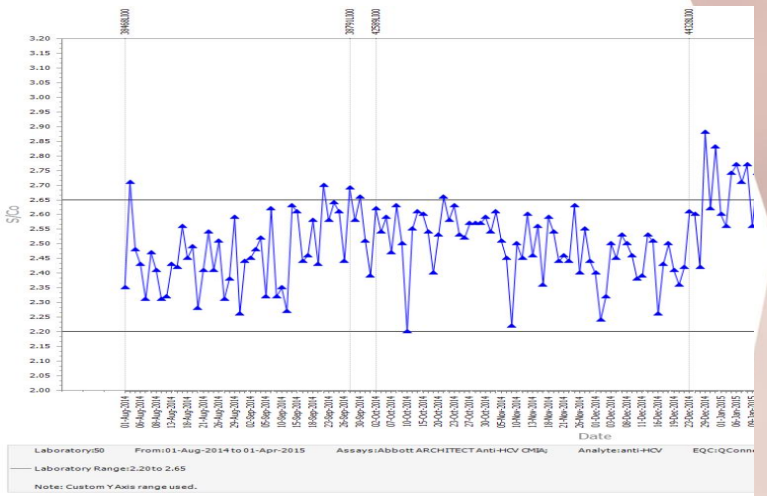
Point 12:

Reagent lot variation is the major contributor to normal variation of serology assays

What would you do?



Possible actions when reagent lot changes



A - Ignore

B - Re-test QC

C - Re-calibrate instrument

D - Re-set limits

E – Contact manufacturer

F – Reject reagent lot

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What do you do?

A - Ignore

B - Re-test QC

C - Re-calibrate instrument

D - Re-set limits

E - Contact manufacturer

F - Reject reagent lot

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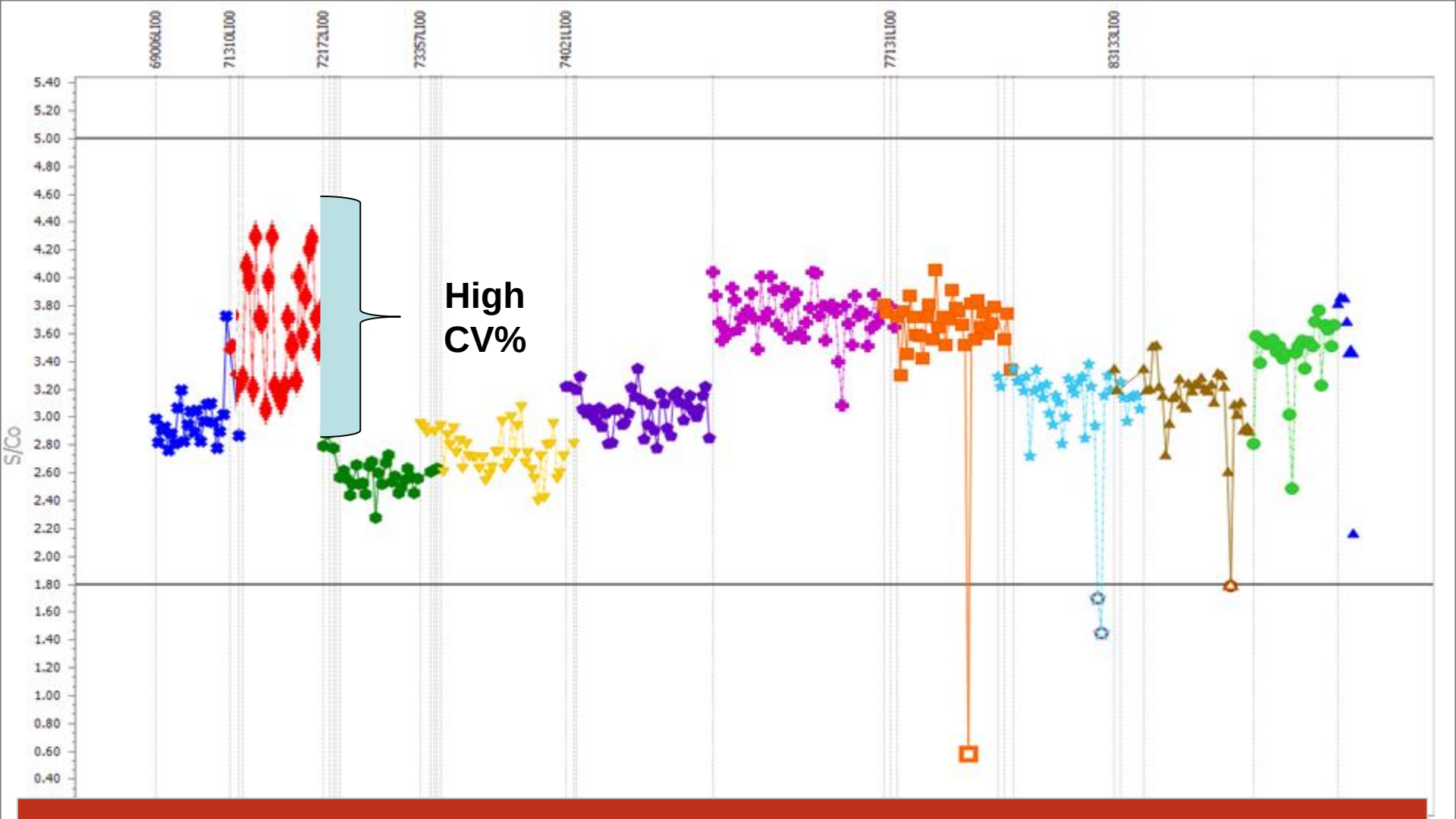
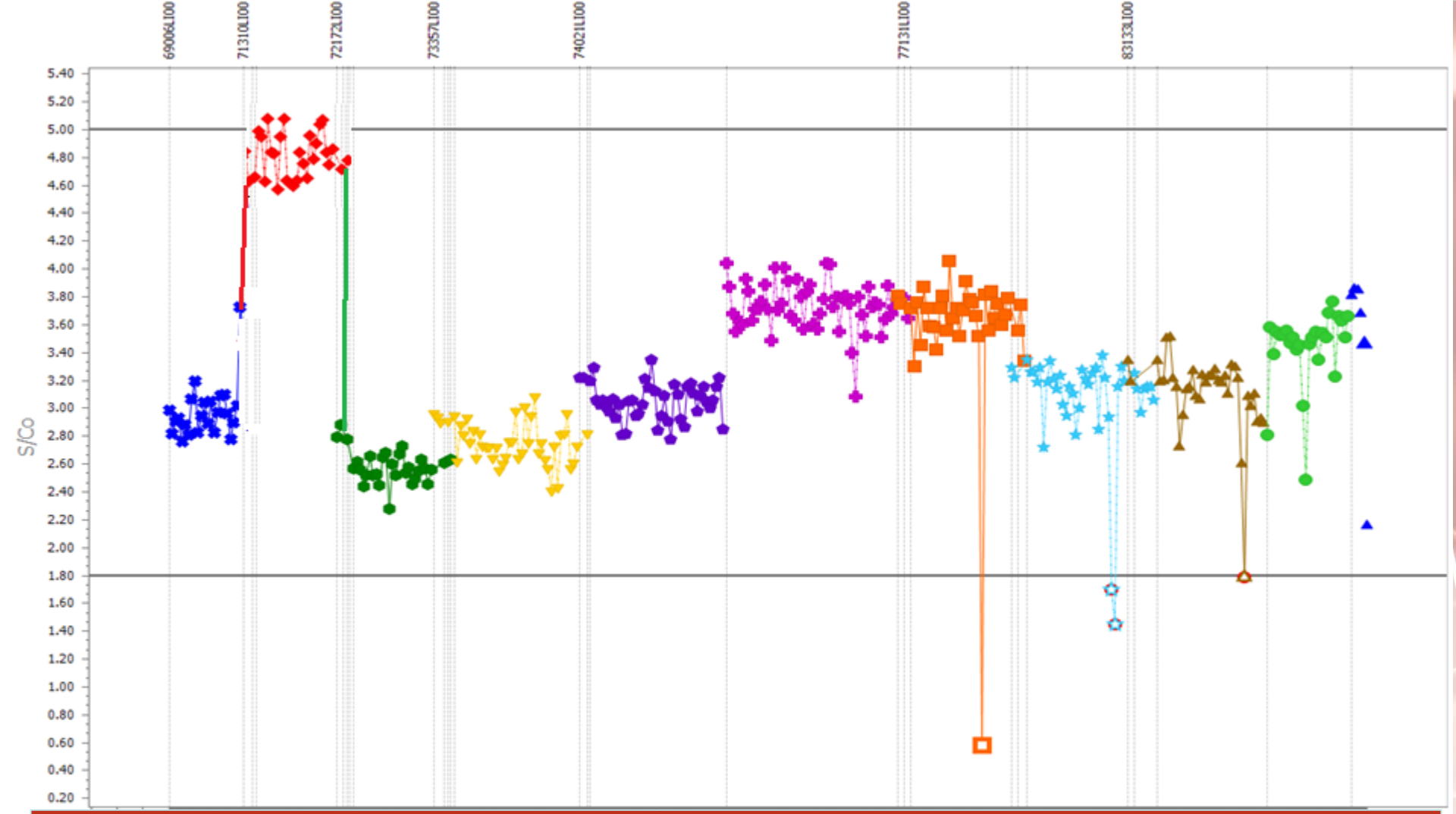


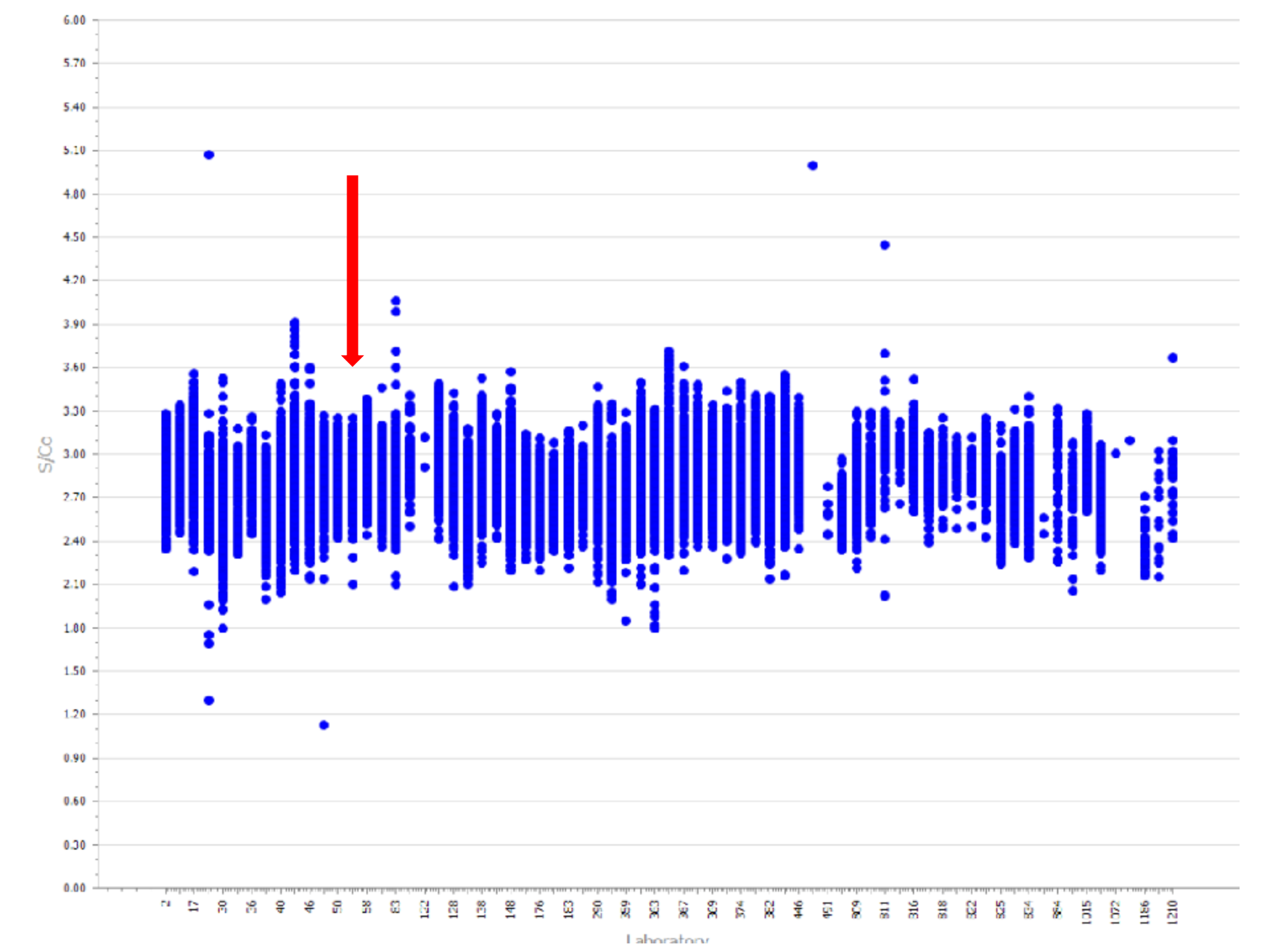
Point 13:

Usually there are insufficient runs to re-set limits before reagent lot is exhausted



Point 14:

By re-setting limits, you are accepting that the variation is normal


S/Cc
6.00
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122
128
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183
250
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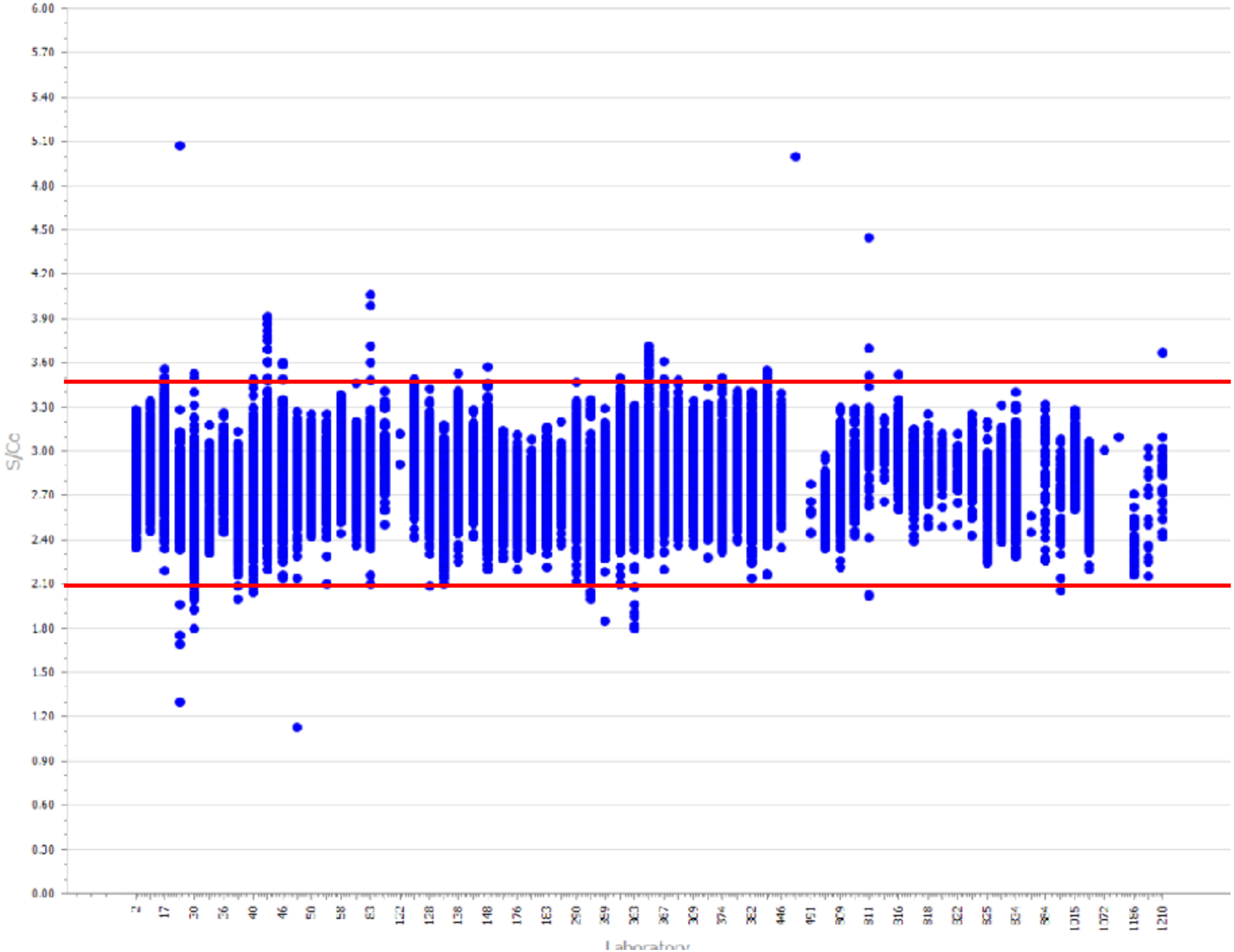
303
307
309
374
382
446
451
809
811
816
818
832
835
854
864
1015
1072
1186
1210
Laboratory

Normal Assay Variation

- One years results for Abbott Architect HCV
- 71 laboratories
- 94 instruments
- 77 reagent lot numbers
- 7 QC lot numbers
- 18,234 results
- CV% range: 3.74 to 10.86%
- CV% average 7.24%
- NRL Range: 2.1 to 3.5 (S/Co)


S/Cc
6.00
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0.30
0.00
2
17
30
36
40
46
50
58
83
122
128
138
148
176
183
250
259
303
307
309
374
382
446
451
809
811
816
818
832
835
854
864
1015
1072
1186
1210
Laboratory

Setting Acceptance Limits for Serology

- 20 data points is not representative
- Should include all normal variation
- QConnect limits uses historical data
- Laboratories can use their own data over time
- Determine acceptable range and acceptable CV%

NRL Science of Quality

Quality Control for Viral Load Testing

- Three processes
  - Extraction
  - Amplification
  - Detection
- Possibly use different reagents and instruments for each process

Differences between Clinical Chemistry and Viral Load Testing

Clinical Chemistry	Serology	Viral Load
Linear	Non-linear	Linear
Inert analyte	Functional biological analyte	Biological, not functional
Quantitative	Qualitative	Quantitative
Adjust for bias	No adjustment for bias	No adjustment for bias
Lower level of regulation	Highly regulated	Highly regulated
Several medical decision points	Single decision point	Several medical decision points
Adjust for lots variation	No adjustment for lot variation	No adjustment for lot variation
International standards	Poor or no standards	International standards
Certified reference methods	No CRMs	Certified reference methods
Available in a pure form	Different forms	Some mutations or variation
Single target	Multiple and varying targets	Single target
TEa	?? TEa	?? TEa

Hepatitis B DNA

Assay	No Labs	No QC Lots	n	Mean (log^{10})	SD	CV(%)
Abbott RealTime HBV (0.5 mL)	**2**	**3**	**186**	**2.4**	**0.12**	**4.99**
Abbott RealTime HBV (0.2 mL)	**4**	**3**	**385**	**2.5**	**0.23**	**8.88**
Roche COBAS AmpliPrep/TaqMan HBV Test v2	**16**	**3**	**604**	**2.3**	**0.10**	**4.40**
Roche COBAS 4800 HBV	**1**	**2**	**73**	**2.3**	**0.08**	**3.52**
Roche cobas HBV Quantitative (6800/8800)	**6**	**2**	**208**	**2.3**	**0.16**	**6.83**

NRL Science of Quality

Hepatitis C RNA

Assay	No Labs	No QC Lots	n	Mean (log^{10})	SD	CV(%)
Abbott RealTime HCV (0.2 mL)	2	2	79	2.3	0.25	10.56
Abbott RealTime HCV (0.5 mL)	4	2	196	2.4	0.24	9.52
Roche COBAS AmpliPrep/COBAS TaqMan HCV v2	16	2	724	2.7	0.25	8.94
Roche cobas 4800 HCV	2	2	92	2.5	0.18	7.24
Roche cobas HCV Quantitative (6800/8800)	6	2	299	2.4	0.19	7.78

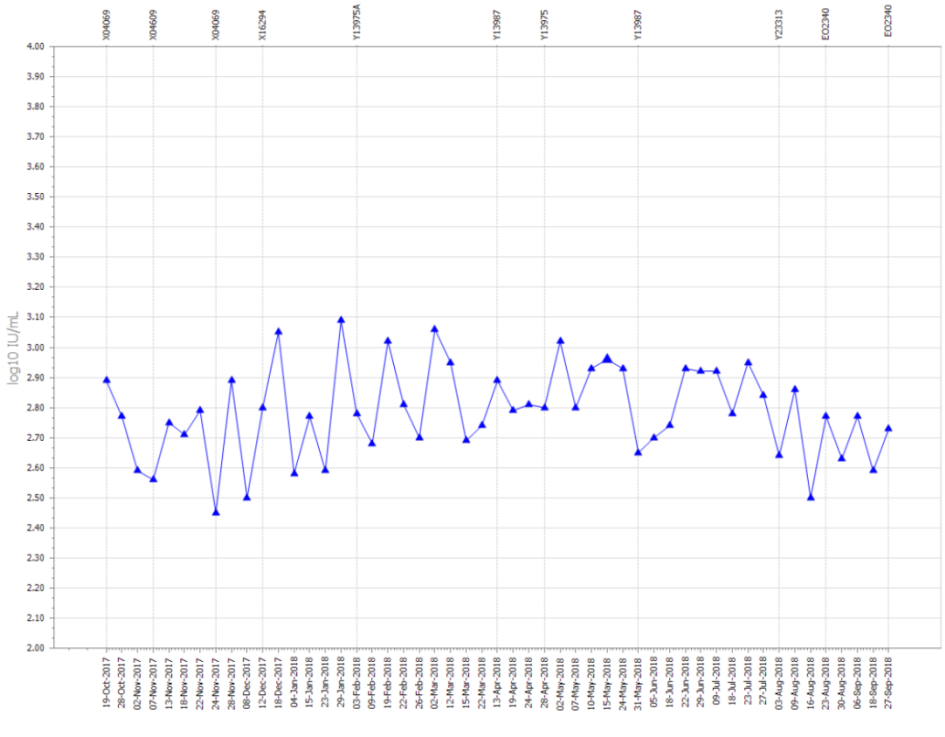
NRL Science of Quality

HIV RNA

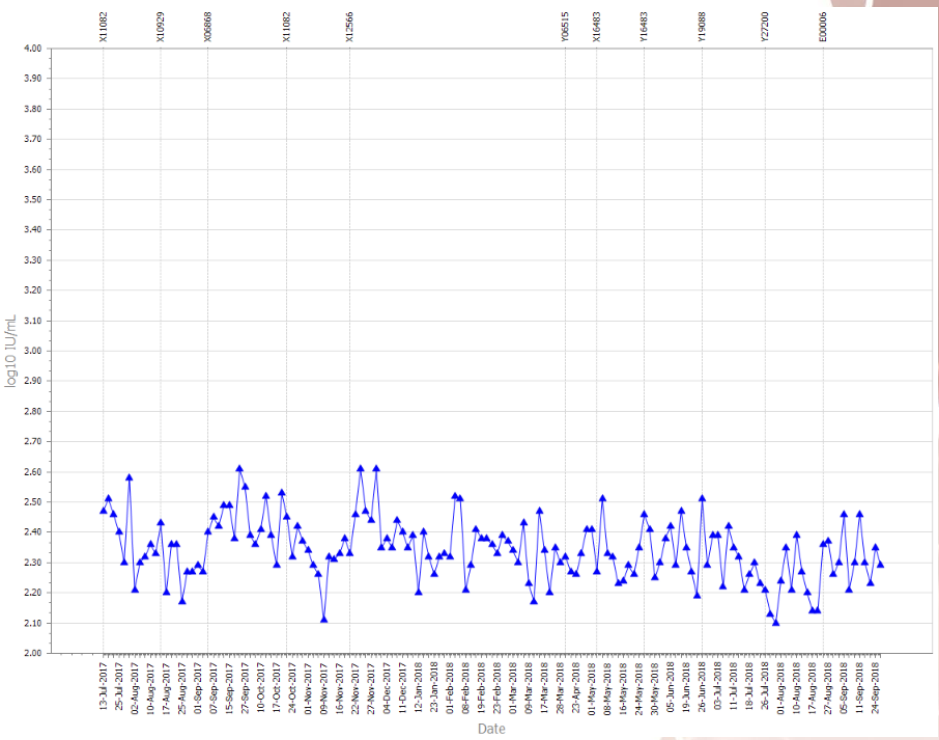
Assay	No Labs	No QC Lots	n	Mean (log^{10})	SD	CV(%)
Abbott RealTime HIV-1 (0.2 mL)	1	2	22	2.3	0.16	6.85
Abbott RealTime HIV-1 (0.6 mL)	4	2	217	2.2	0.16	6.91
Cepheid Xpert HIV-1 Viral Load	1	2	13	2.1	0.10	4.57
Roche cobas 4800 HIV-1	1	2	33	2.2	0.13	5.63
Roche cobas HIV-1 Quantitative (6800/8800)	3	2	139	2.2	0.14	6.28
Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test v2	16	2	902	2.4	0.15	6.10

NRL Science of Quality

LJ Chart for Selected Laboratory

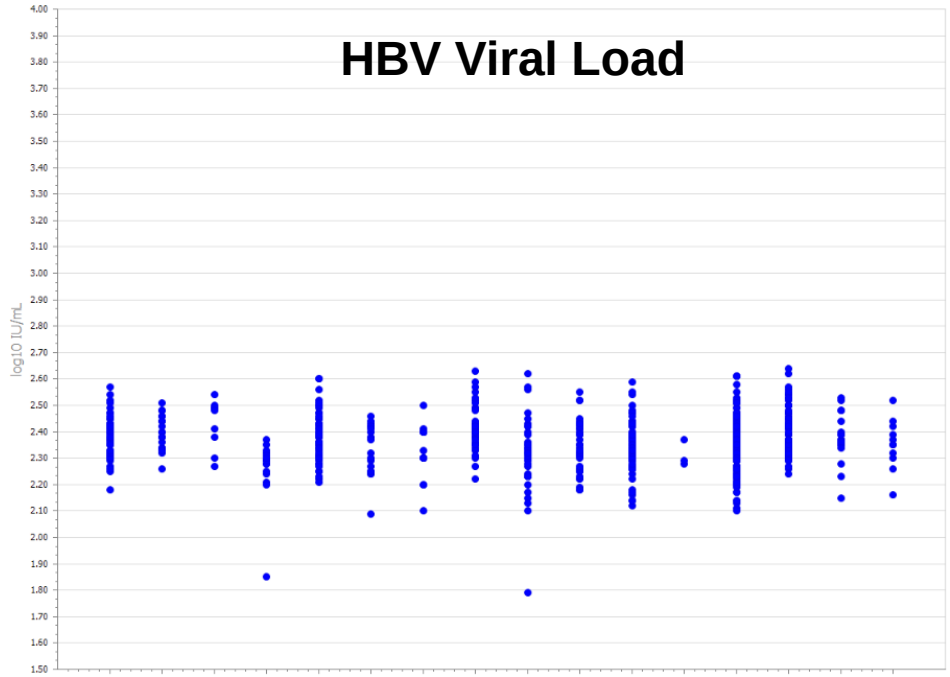


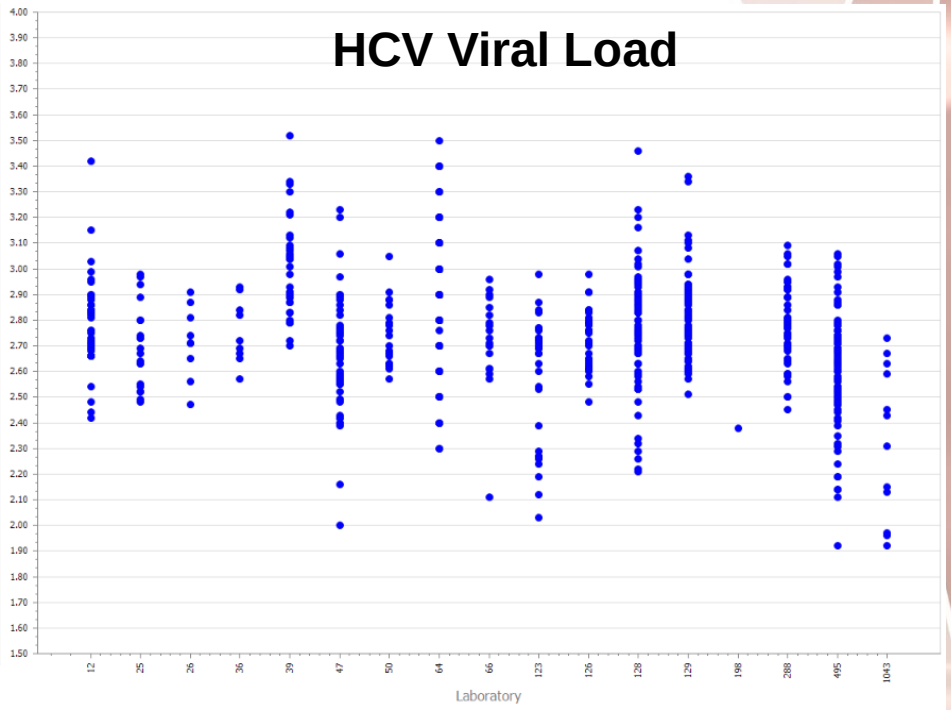
HCV Viral Load

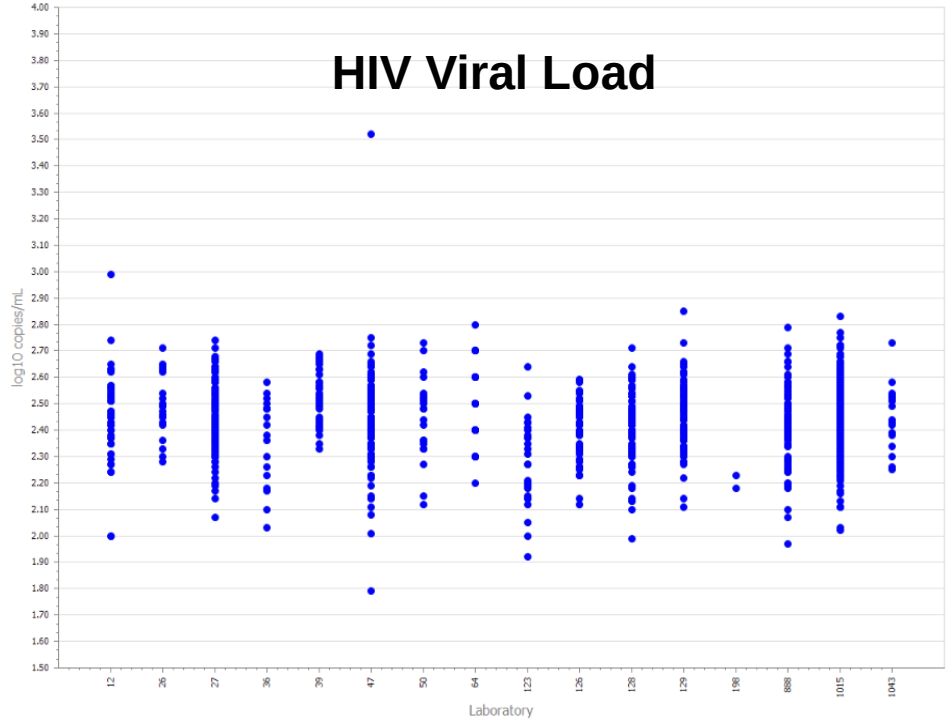


HBV Viral Load

NRL Science of Quality

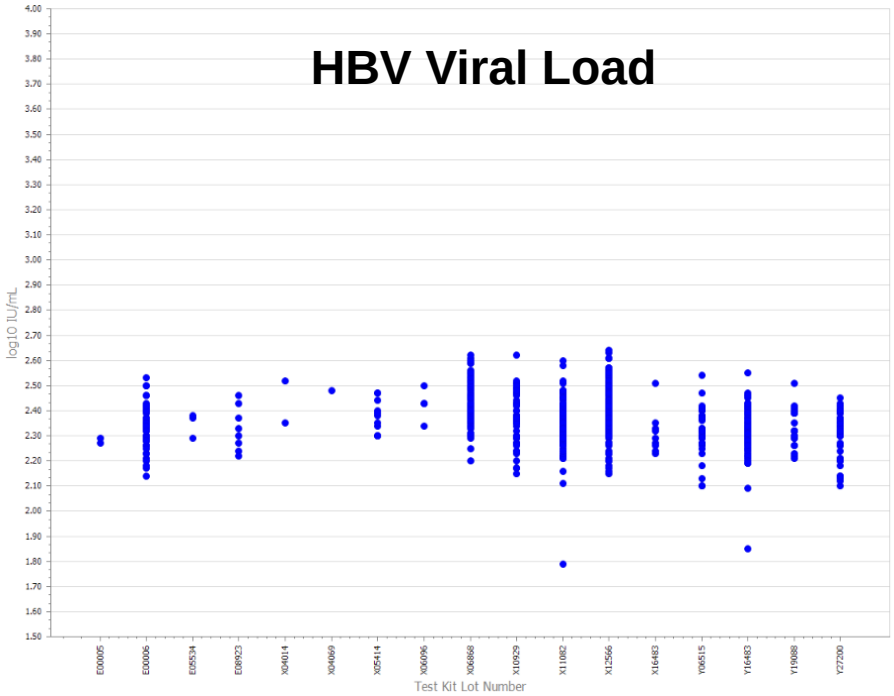


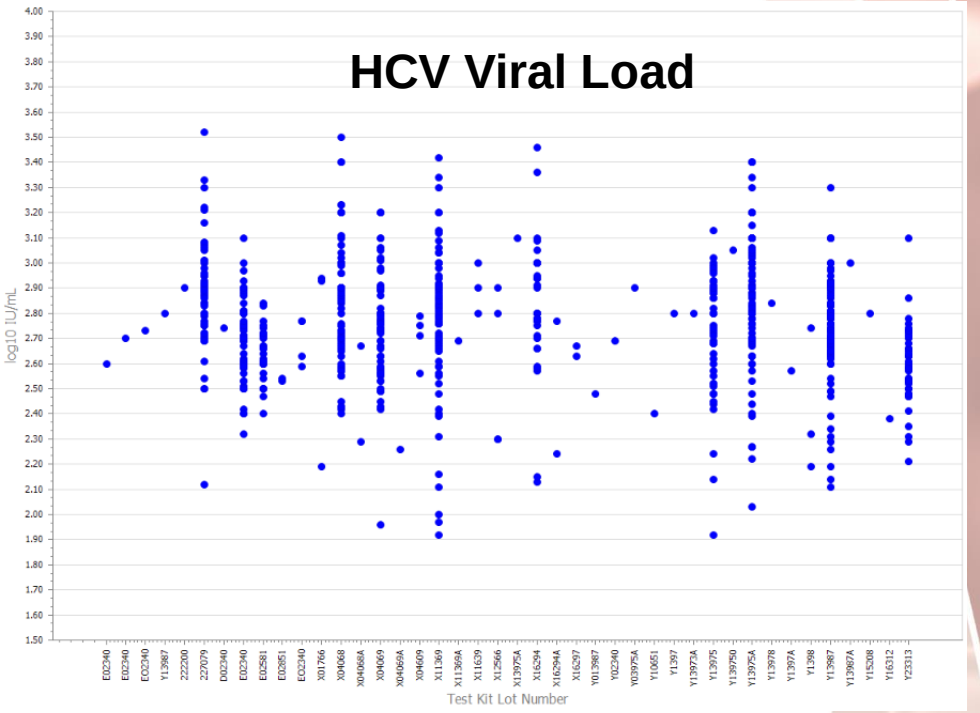


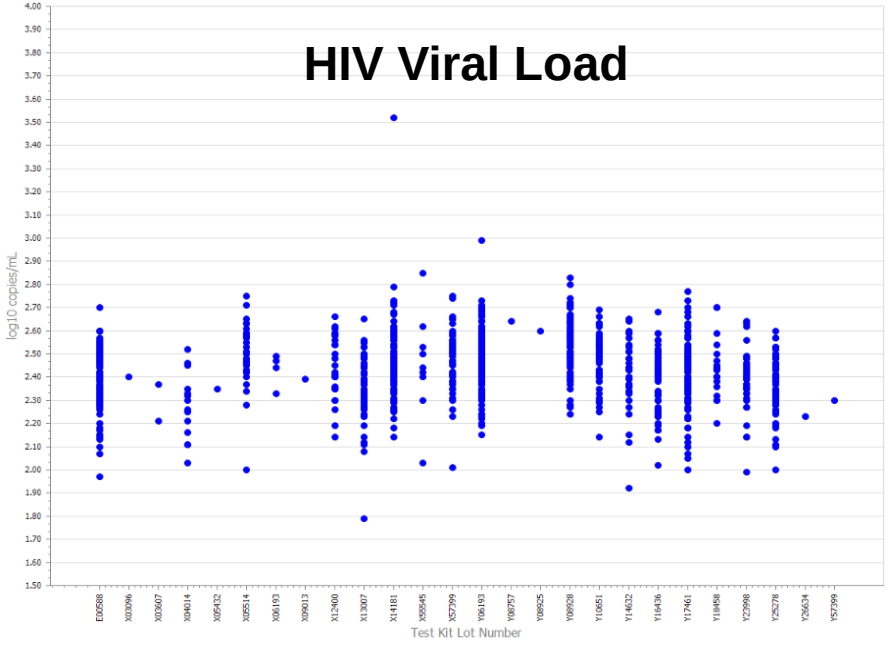


Roche COBAS AmpliPrep/COBAS TaqMan Assays

(Laboratory Results)







Roche COBAS AmpliPrep/COBAS TaqMan Assays

(Reagent Lot Number Results)

Quality Control for Viral Load Testing

- Similarities with clinical chemistry and serology
- Dose response is linear
- Reagent lot variation not as great as serology
- Standardisation between assays is good
- Clinically significant change is acknowledged
- Precision is predictable

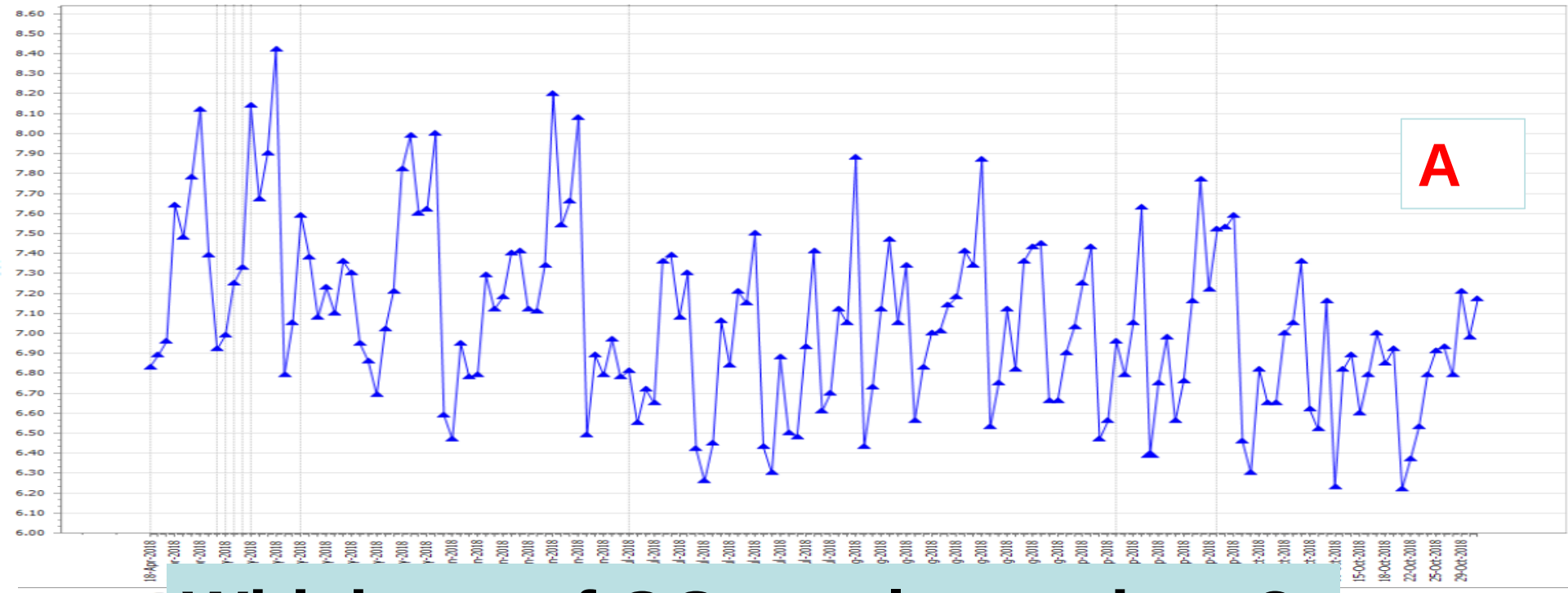
Setting Acceptance Limits for Viral Load Testing

- Traditional Methods?
- QConnect Limits?
- Alternative based on:
  - clinical significant change (TEa)
  - expected variation (QC and EQA)
  - Assay specific or general rules
- Cannot assume VL is similar to chemistry or serology
- Requires investigation using true QC results; not modelling

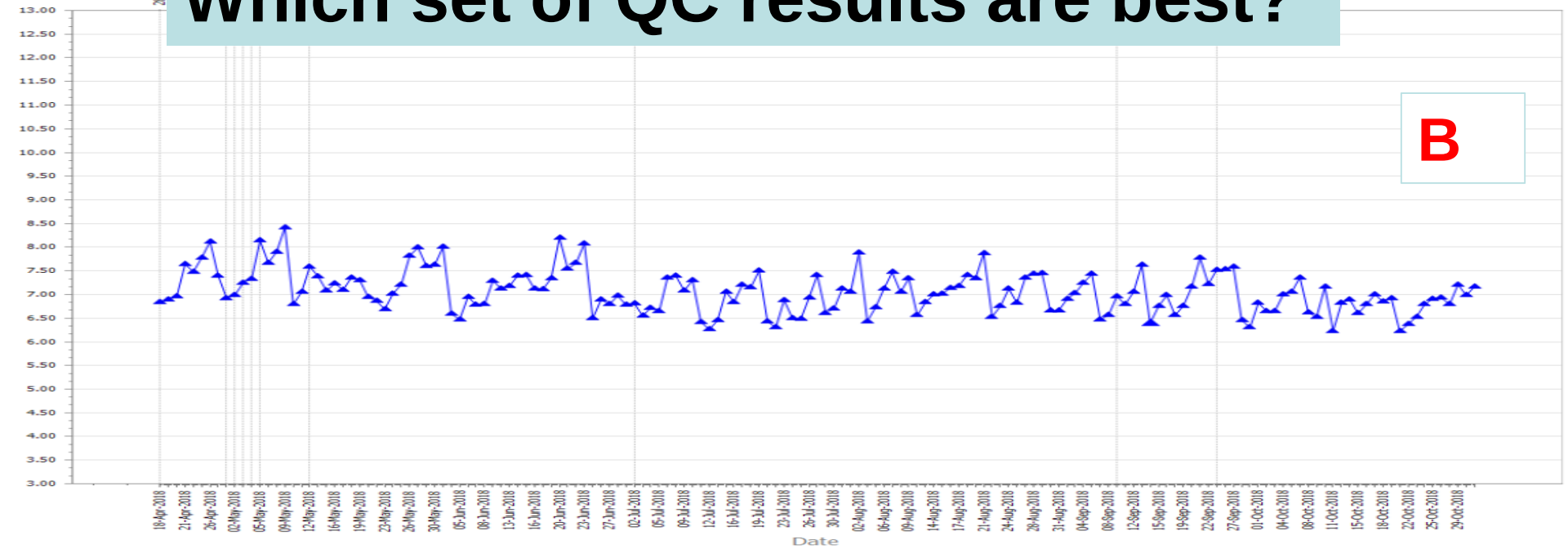
Quiz Time

Let's have some fun!

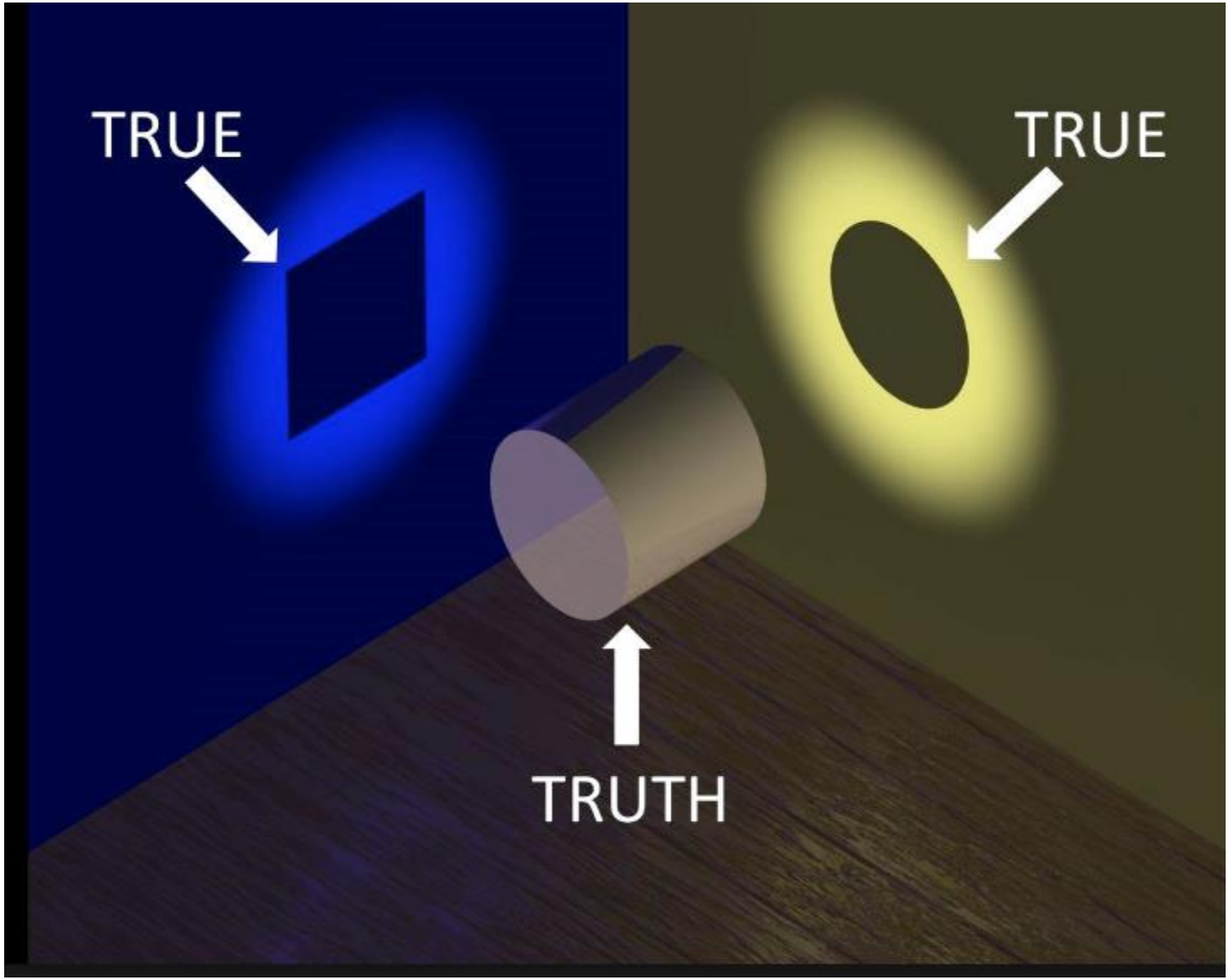
NRL Science of Quality



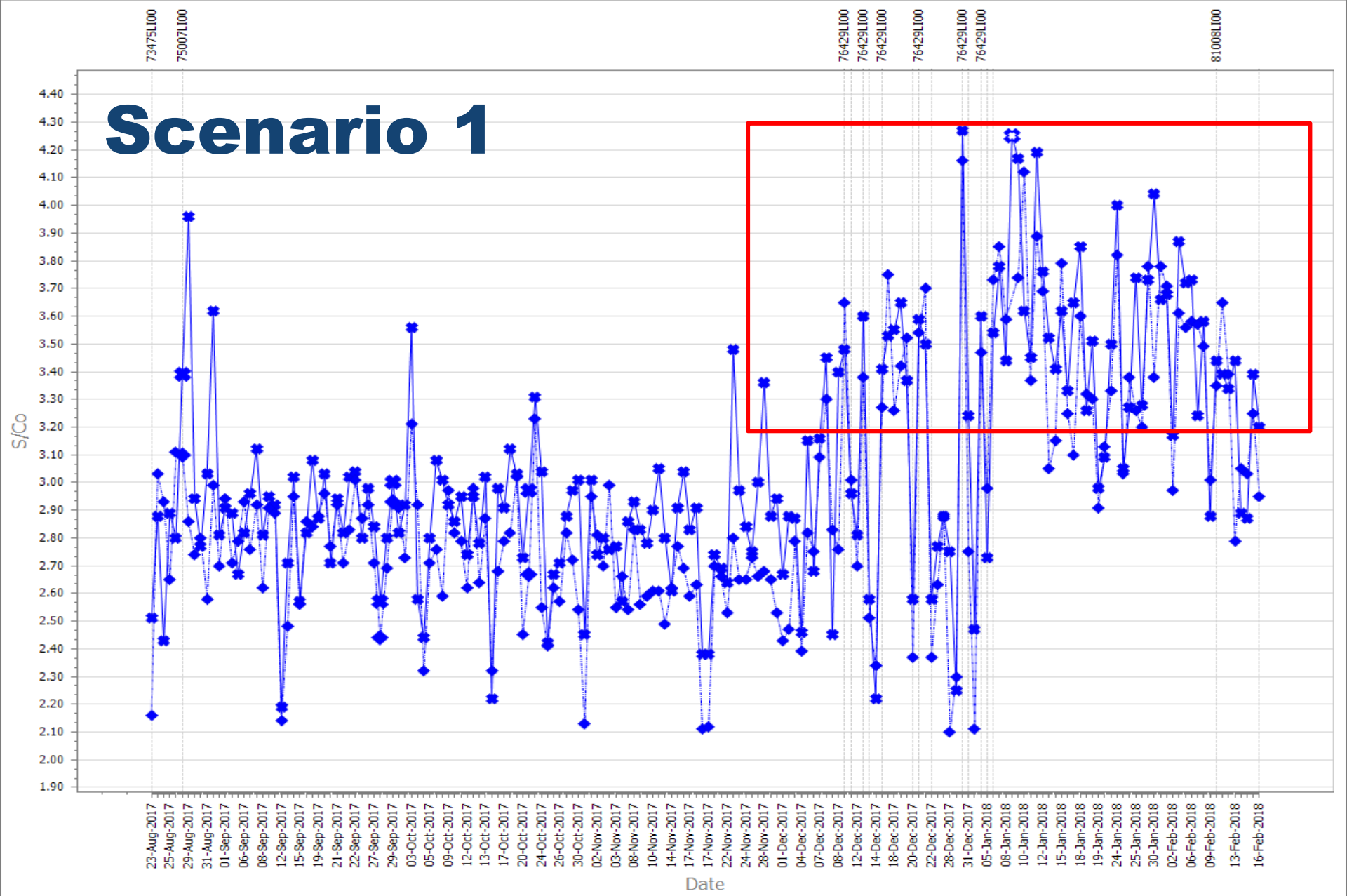
Which set of QC results are best?



Which set of QC results are bst?


TRUE
TRUE
TRUTH

Scenario 1


Scenario 1
73475LI00
75007LI00
76429LI00
76429LI00
76429LI00
76429LI00
76429LI00
76429LI00
81008LI00
S/Co
4.40
4.30
4.20
4.10
4.00
3.90
3.80
3.70
3.60
3.50
3.40
3.30
3.20
3.10
3.00
2.90
2.80
2.70
2.60
2.50
2.40
2.30
2.20
2.10
2.00
1.90
23-Aug-2017
25-Aug-2017
29-Aug-2017
31-Aug-2017
01-Sep-2017
06-Sep-2017
08-Sep-2017
12-Sep-2017
15-Sep-2017
19-Sep-2017
21-Sep-2017
22-Sep-2017
27-Sep-2017
29-Sep-2017
03-Oct-2017
05-Oct-2017
09-Oct-2017
12-Oct-2017
13-Oct-2017
17-Oct-2017
20-Oct-2017
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26-Oct-2017
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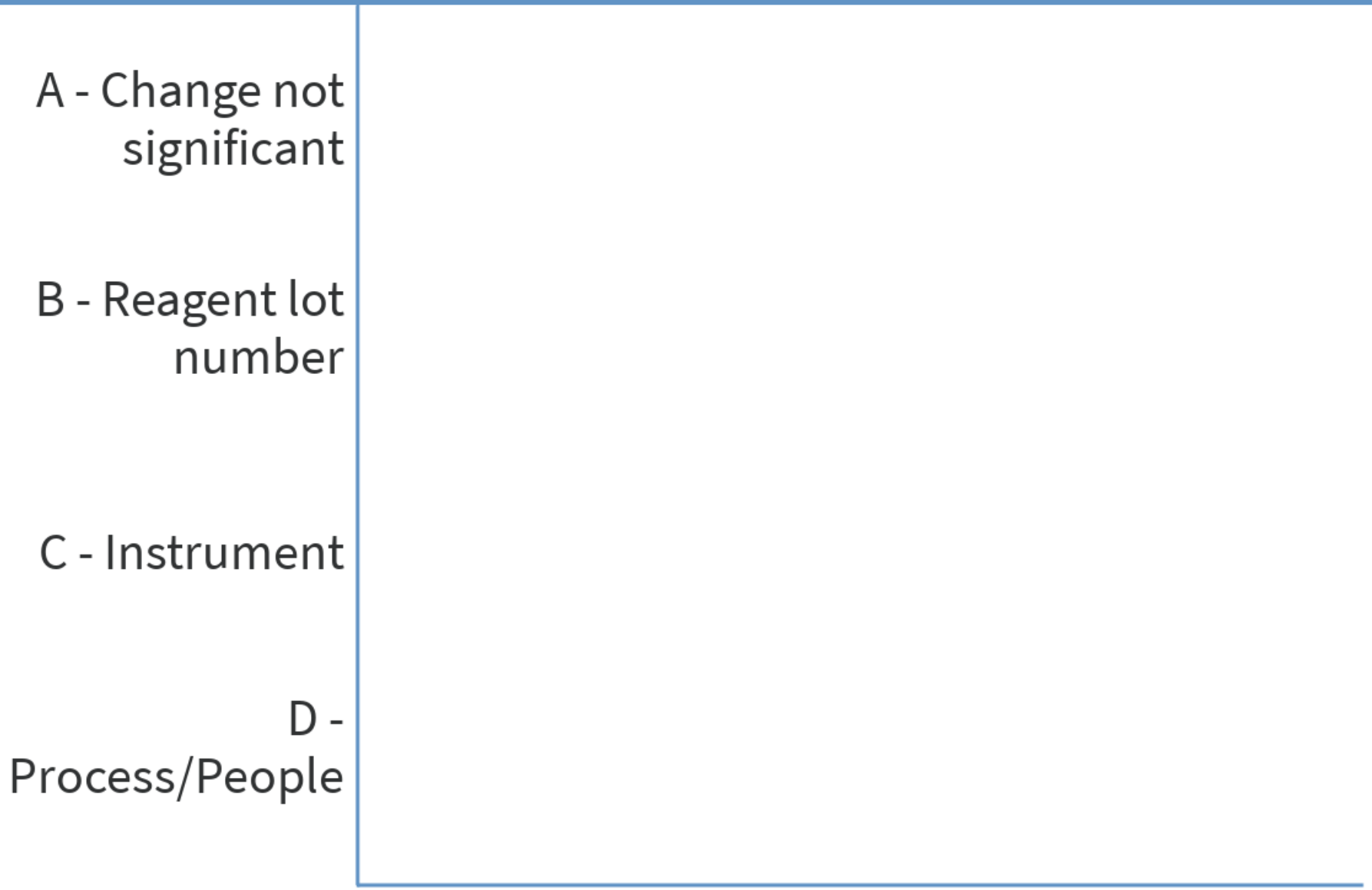
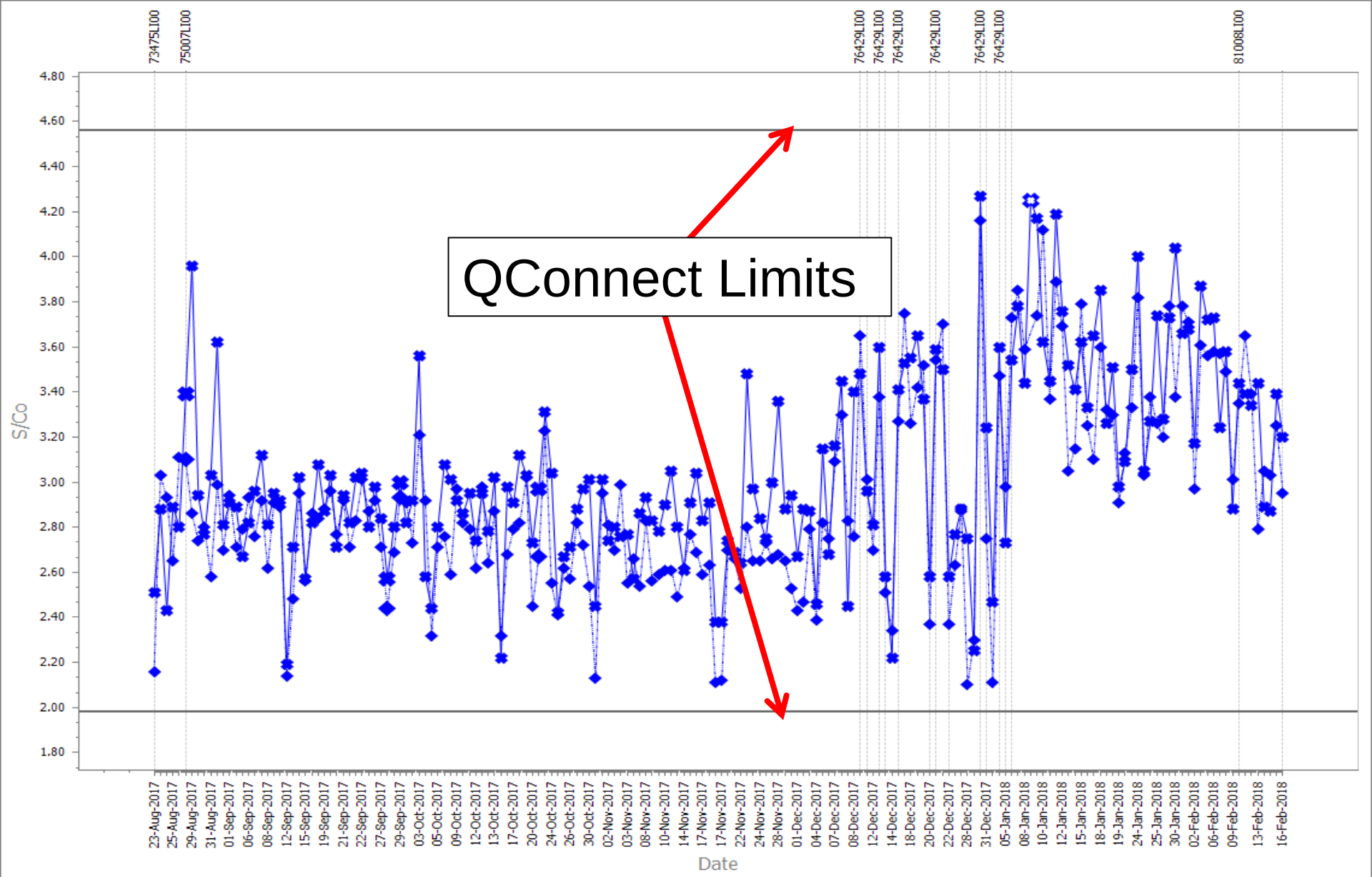
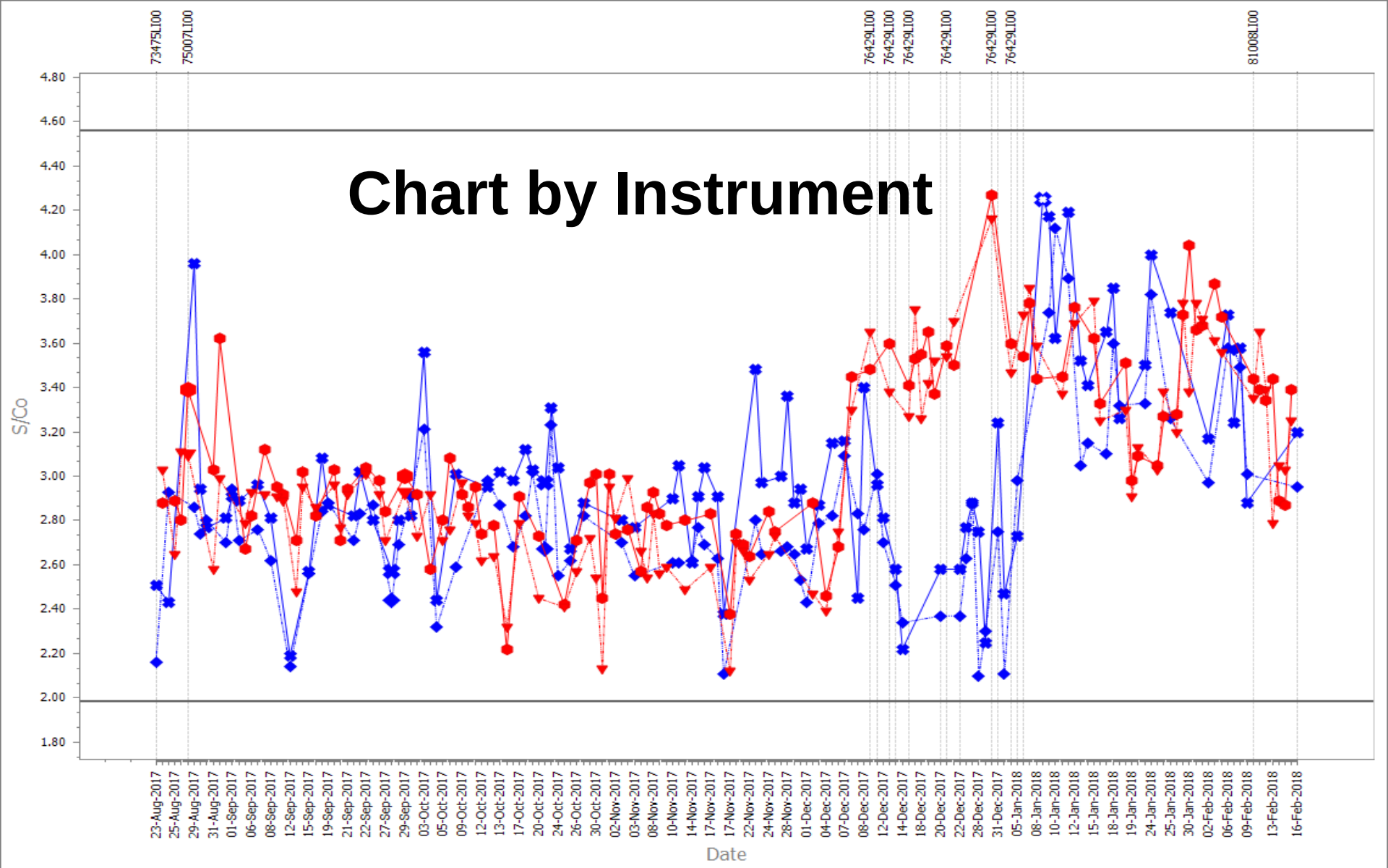
14-Nov-2017
17-Nov-2017
17-Nov-2017
22-Nov-2017
24-Nov-2017
28-Nov-2017
01-Dec-2017
04-Dec-2017
07-Dec-2017
08-Dec-2017
12-Dec-2017
14-Dec-2017
18-Dec-2017
20-Dec-2017
22-Dec-2017
28-Dec-2017
31-Dec-2017
05-Jan-2018
08-Jan-2018
10-Jan-2018
12-Jan-2018
15-Jan-2018
18-Jan-2018
19-Jan-2018
24-Jan-2018
25-Jan-2018
30-Jan-2018
02-Feb-2018
06-Feb-2018
09-Feb-2018
13-Feb-2018
16-Feb-2018
Date
Laboratory:3
From:01-Feb-2017 to 20-Feb-2018
Assays:Abbott PRISM HIV Ag/Ab Combo ChLIA;
Analyte:HIV p24 Ag/Anti-HIV
EQC:QConnect Purple
EQC Lot Number:DM17076;
Subchannel A
Subchannel B
Trend: Assay
Abbott PRISM HIV Ag/Ab Combo ChLIA/Subchannel A
Abbott PRISM HIV Ag/Ab Combo ChLIA/Subchannel B

What is the cause of the change




QConnect Limits
S/Co
Date
Laboratory:3
From:01-Feb-2017 to 20-Feb-2018
Assays:Abbott PRISM HIV Ag/Ab Combo ChLIA;
Analyte:HIV p24 Ag/Anti-HIV
EQC:QConnect Purple
EQC Lot Number:DM17076;
Subchannel A
Subchannel B
Trend: Assay
Abbott PRISM HIV Ag/Ab Combo ChLIA/Subchannel A
Abbott PRISM HIV Ag/Ab Combo ChLIA/Subchannel B
NRL Range:1.98 to 4.56



Laboratory:3 From:01-Feb-2017 to 20-Feb-2018 Assays:Abbott PRISM HIV Ag/Ab Combo ChLIA; Analyte:HIV p24 Ag/Anti-HIV EQC:QConnect Purple EQC Lot Number:DM17076;

Subchannel A Subchannel B

Trend: Instrument; Test Process: Detection PRISM/Channel 3 (1045)/Subchannel A PRISM/Channel 3 (1045)/Subchannel B PRISM/Channel 3 (1528)/Subchannel A PRISM/Channel 3 (1528)/Subchannel B

NRL Range:1.98 to 4.56

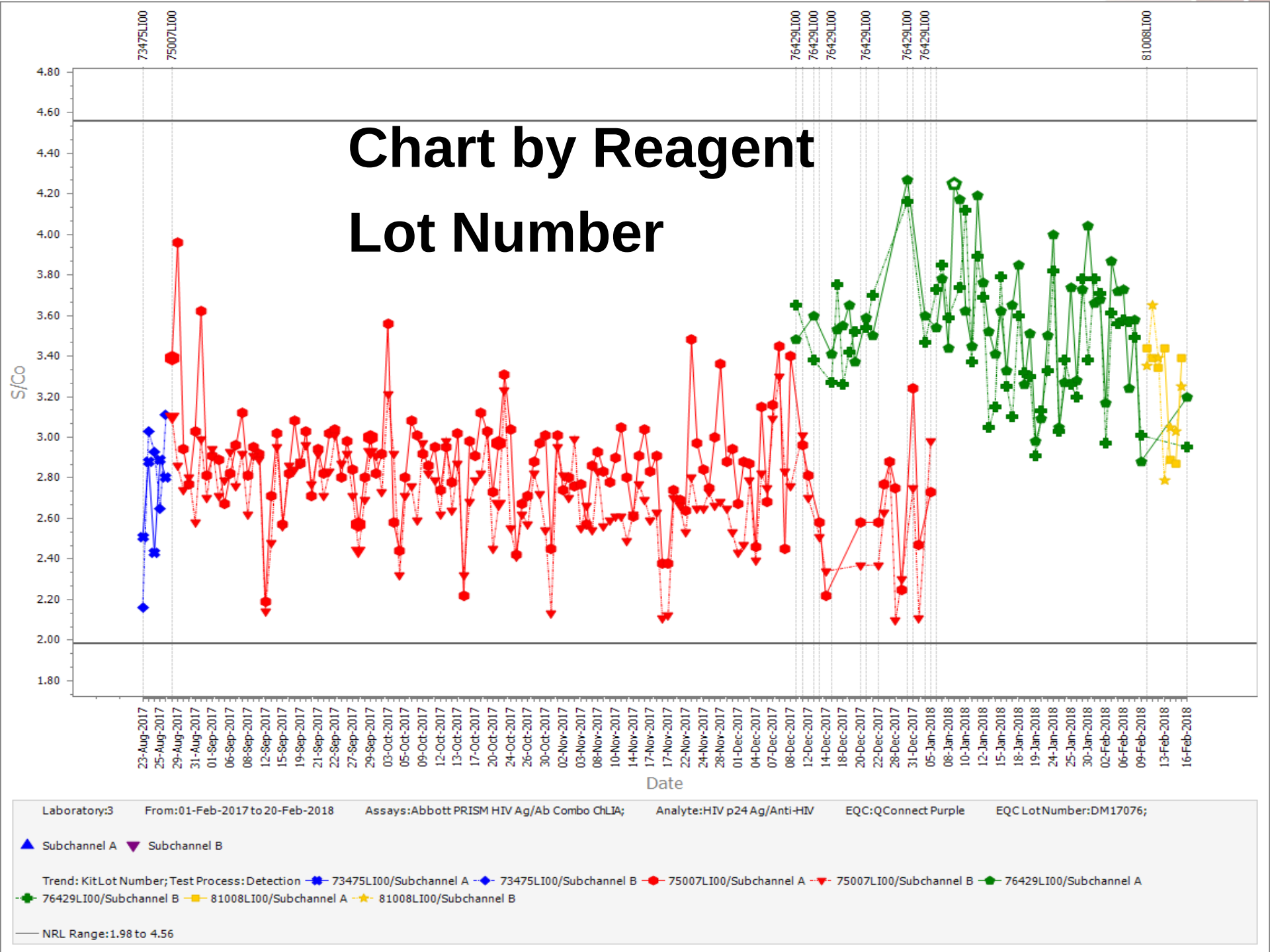
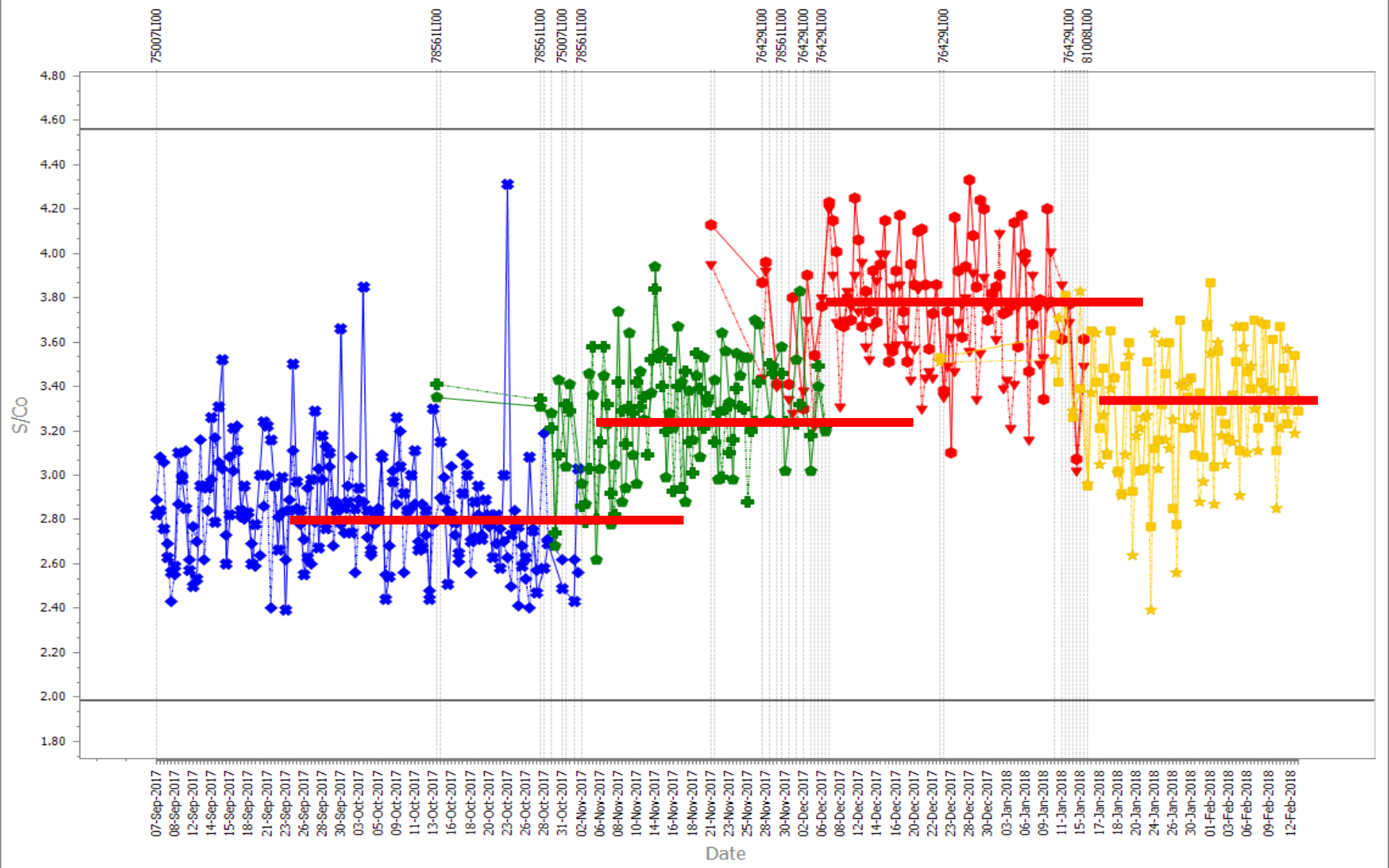


Chart by Reagent Lot Number
73475LI00
75007LI00
76429LI00
81008LI00
S/Co
Date
Laboratory:3
From:01-Feb-2017 to 20-Feb-2018
Assays:Abbott PRISM HIV Ag/Ab Combo ChLIA;
Analyte:HIV p24 Ag/Anti-HIV
EQC:QConnect Purple
EQC Lot Number:DM17076;
Subchannel A
Subchannel B
Trend: Kit Lot Number; Test Process: Detection
73475LI00/Subchannel A
73475LI00/Subchannel B
75007LI00/Subchannel A
75007LI00/Subchannel B
76429LI00/Subchannel A
76429LI00/Subchannel B
81008LI00/Subchannel A
81008LI00/Subchannel B
NRL Range:1.98 to 4.56



Laboratory:11 From:01-Feb-2017 to 20-Feb-2018 Assays:Abbott PRISM HIV Ag/Ab Combo ChLIA; Analyte:HIV p24 Ag/Anti-HIV EQC:QConnect Purple EQC Lot Number:DM17076;

Subchannel A Subchannel B

Trend: Kit Lot Number; Test Process: Detection 75007LI00/Subchannel A 75007LI00/Subchannel B 76429LI00/Subchannel A 76429LI00/Subchannel B 78561LI00/Subchannel A 78561LI00/Subchannel B 81008LI00/Subchannel A 81008LI00/Subchannel B

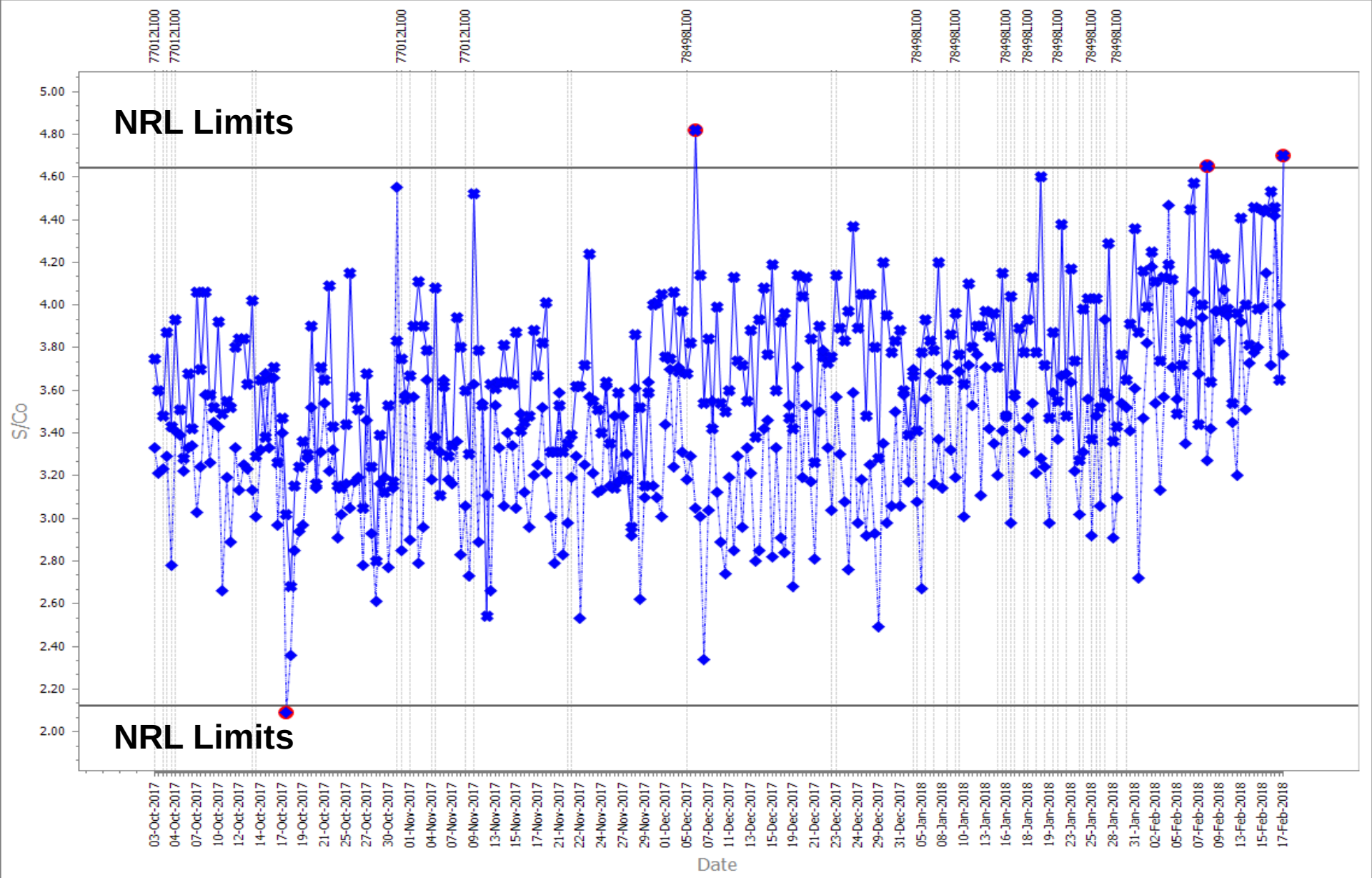
NRL Range:1.98 to 4.56

Scenario 1

Answer:

Classic reagent lot variation

Scenario 2



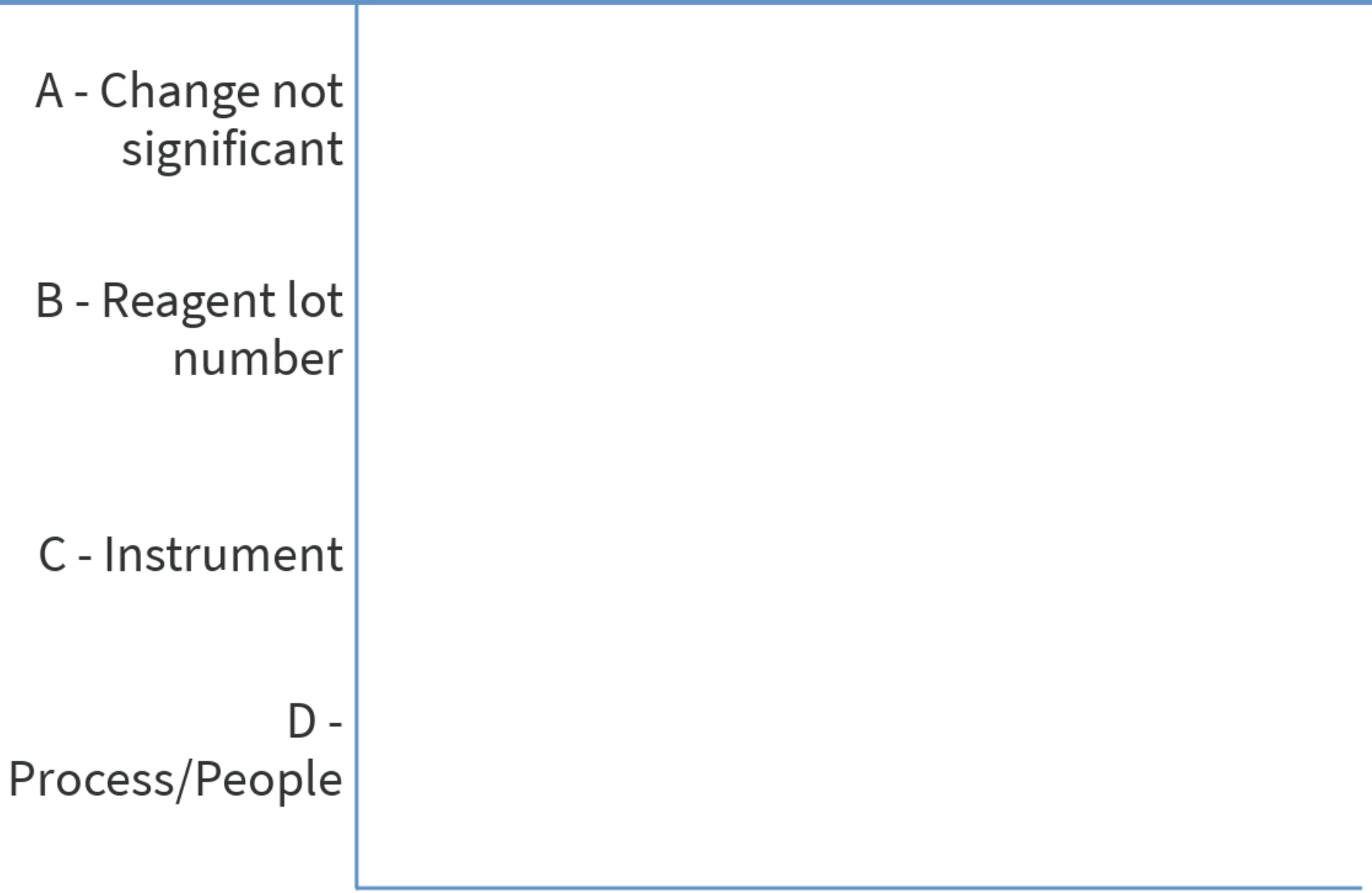
Laboratory:11 From:03-Oct-2017 to 22-Feb-2018 Assays:Abbott PRISM HCV ChLIA; Analyte:anti-HCV EQC:QConnect Purple EQC Lot Number:DM17076;

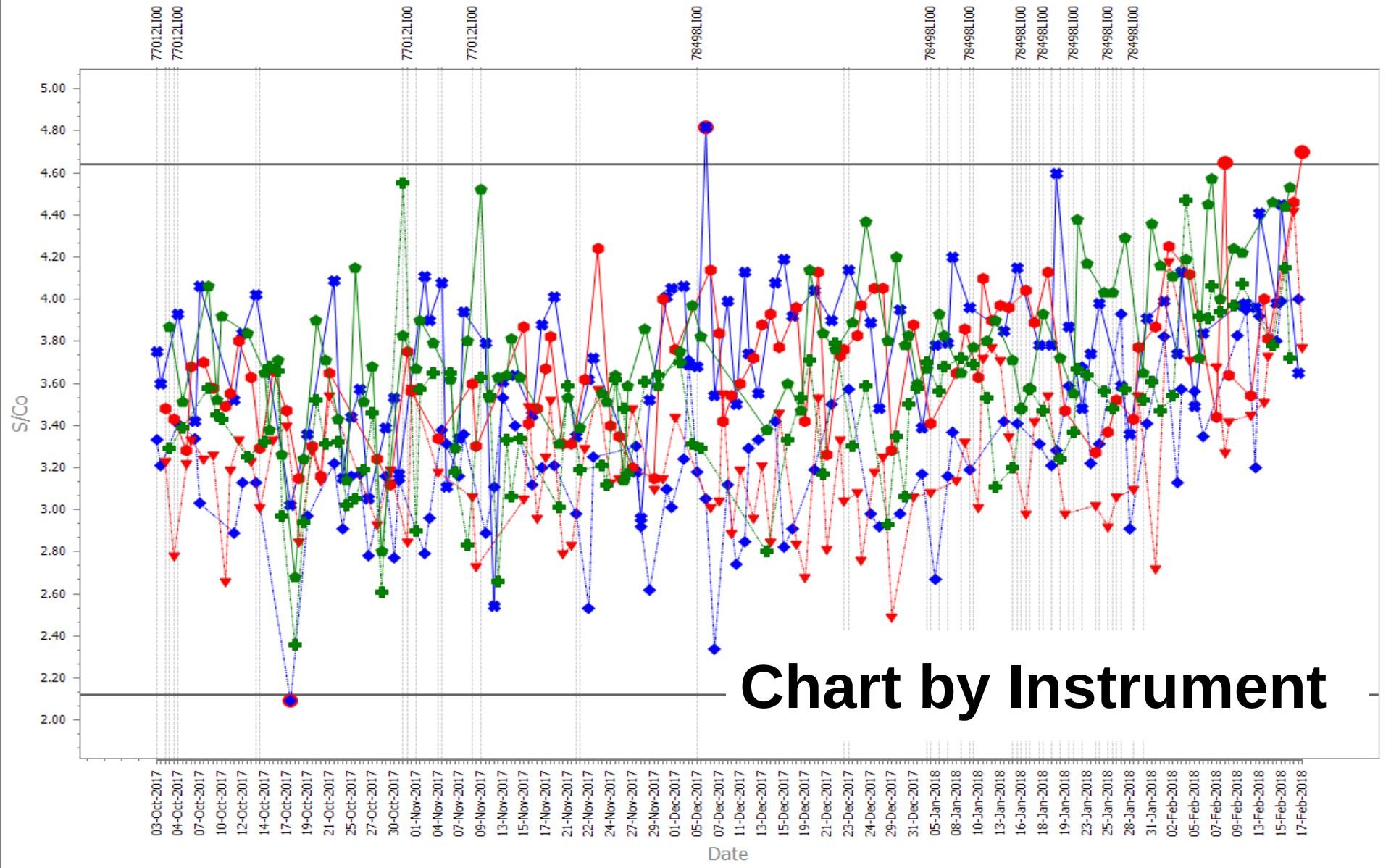
Subchannel A Subchannel B

Trend: Assay Abbott PRISM HCV ChLIA/Subchannel A Abbott PRISM HCV ChLIA/Subchannel B

NRL Range:2.12 to 4.64

What is the cause of the change



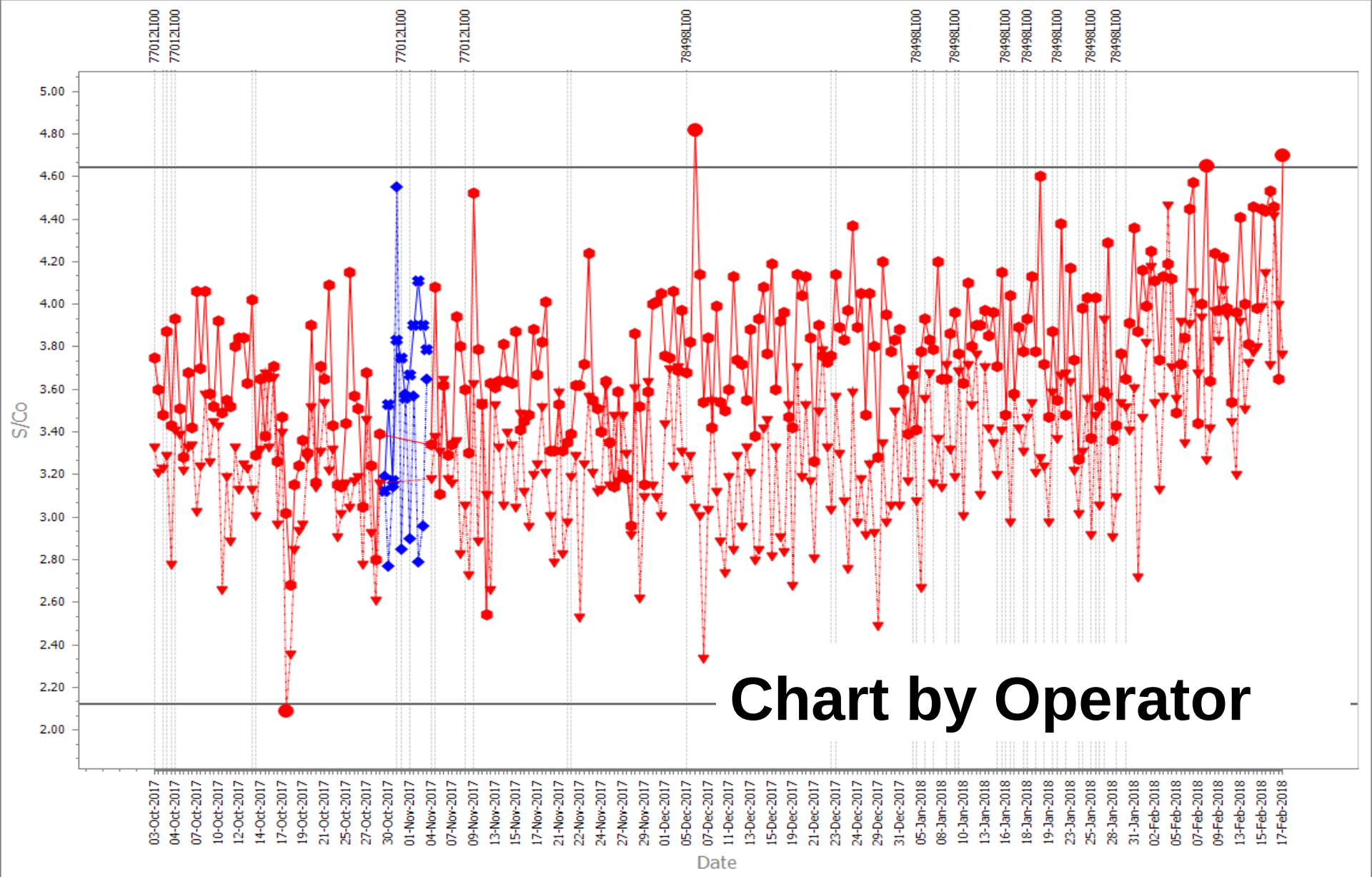


Laboratory:11 From:03-Oct-2017 to 22-Feb-2018 Assays:Abbott PRISM HCV ChLIA; Analyte:anti-HCV EQC:QConnect Purple EQC Lot Number:DM17076;

Subchannel A Subchannel B

Trend: Instrument; Test Process: Detection PRISM/Channel 2 (1048)/Subchannel A PRISM/Channel 2 (1048)/Subchannel B PRISM/Channel 2 (1092)/Subchannel A PRISM/Channel 2 (1092)/Subchannel B PRISM/Channel 2 (1118)/Subchannel A PRISM/Channel 2 (1118)/Subchannel B

NRL Range:2.12 to 4.64


77012L100
77012L100
77012L100
77012L100
78498L100
78498L100
78498L100
78498L100
78498L100
78498L100
78498L100
78498L100
5.00
4.80
4.60
4.40
4.20
4.00
3.80
3.60
3.40
3.20
3.00
2.80
2.60
2.40
2.20
2.00
S/Co
03-Oct-2017
04-Oct-2017
07-Oct-2017
10-Oct-2017
12-Oct-2017
14-Oct-2017
17-Oct-2017
19-Oct-2017
21-Oct-2017
25-Oct-2017
27-Oct-2017
30-Oct-2017
01-Nov-2017
04-Nov-2017
07-Nov-2017
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24-Dec-2017
29-Dec-2017
31-Dec-2017
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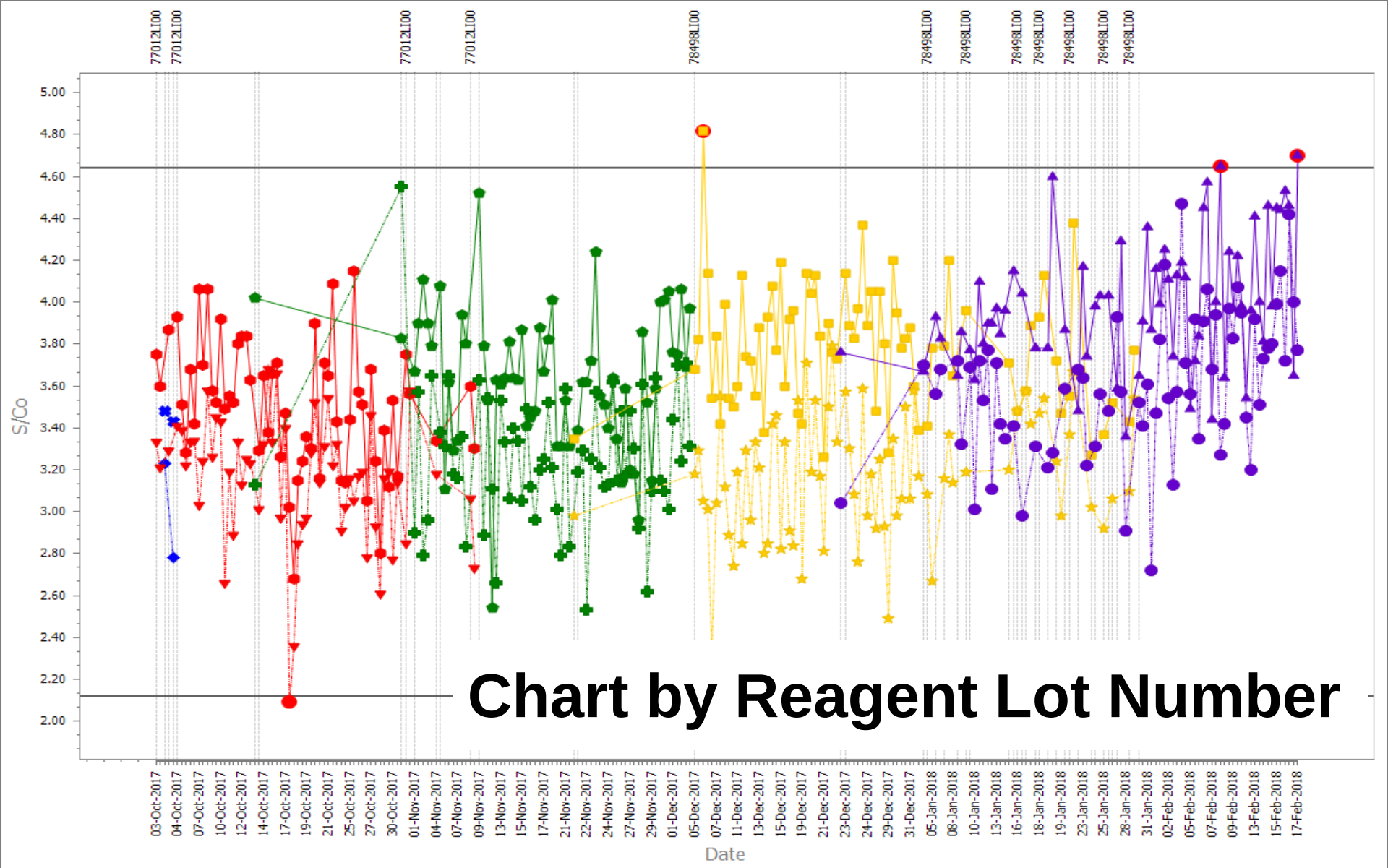
08-Jan-2018
10-Jan-2018
13-Jan-2018
16-Jan-2018
18-Jan-2018
19-Jan-2018
23-Jan-2018
25-Jan-2018
28-Jan-2018
31-Jan-2018
02-Feb-2018
05-Feb-2018
07-Feb-2018
09-Feb-2018
13-Feb-2018
15-Feb-2018
17-Feb-2018
Date
Chart by Operator
Laboratory:11
From:03-Oct-2017 to 22-Feb-2018
Assays:Abbott PRISM HCV ChLIA;
Analyte:anti-HCV
EQC:QConnect Purple
EQC Lot Number:DM17076;
Subchannel A
Subchannel B
Trend: Operator; Test Process: Detection
DV/Subchannel A
DV/Subchannel B
SH/Subchannel A
SH/Subchannel B
NRL Range:2.12 to 4.64

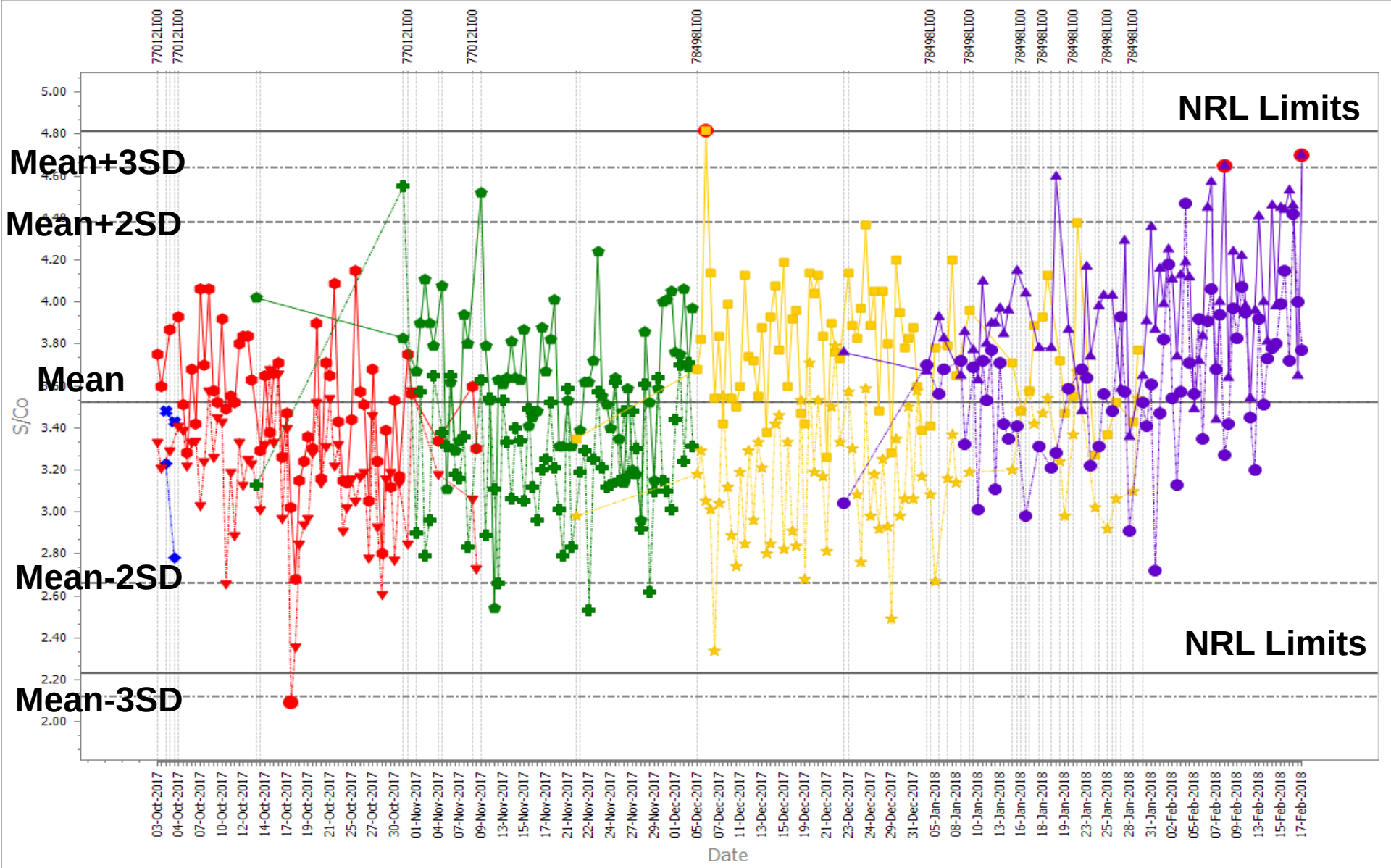


Laboratory:11 From:03-Oct-2017 to 22-Feb-2018 Assays:Abbott PRISM HCV ChLIA; Analyte:anti-HCV EQC:QConnect Purple EQC Lot Number:DM17076;

Subchannel A Subchannel B

Trend: Kit Lot Number; Test Process: Detection 75017LI00/Subchannel A 75017LI00/Subchannel B 77012LI00/Subchannel A 77012LI00/Subchannel B 77308LI00/Subchannel A 77308LI00/Subchannel B 78498LI00/Subchannel A 78498LI00/Subchannel B 79546LI00/Subchannel A 79546LI00/Subchannel B

NRL Range:2.12 to 4.64


NRL Limits
Mean+3SD
Mean+2SD
Mean
Mean-2SD
Mean-3SD
NRL Limits
S/Co
Date
77012LI00
78498LI00
Laboratory:11
From:03-Oct-2017 to 22-Feb-2018
Assays:Abbott PRISM HCV ChLIA;
Analyte:anti-HCV
EQC:QConnect Purple
EQC Lot Number:DM17076;
Subchannel A
Subchannel B
Trend: Kit Lot Number; Test Process: Detection
75017LI00/Subchannel A
75017LI00/Subchannel B
77012LI00/Subchannel A
77012LI00/Subchannel B
77308LI00/Subchannel A
77308LI00/Subchannel B
78498LI00/Subchannel A
78498LI00/Subchannel B
79546LI00/Subchannel A
79546LI00/Subchannel B
Your Laboratory - Visible Data;Mean=3.52;+3SD=4.81;-3SD=2.23
Your Laboratory - Visible Data;Mean=3.52;+2SD=4.38;-2SD=2.66
NRL Range:2.12 to 4.64

Scenario 2

- **Normal QC performance**
- n = 593
- Data within NRL Limits = 99.3% (n=589)
- Number of points within
  ±2SD (n=569) and ±3SD (n=591)
- Compare this with statistical likelihood
  ±2SD = 95% (actual 95.95%)
  ±3SD = 99.7% (actual 99.66%)

NRL Science of Quality

Scenario 2

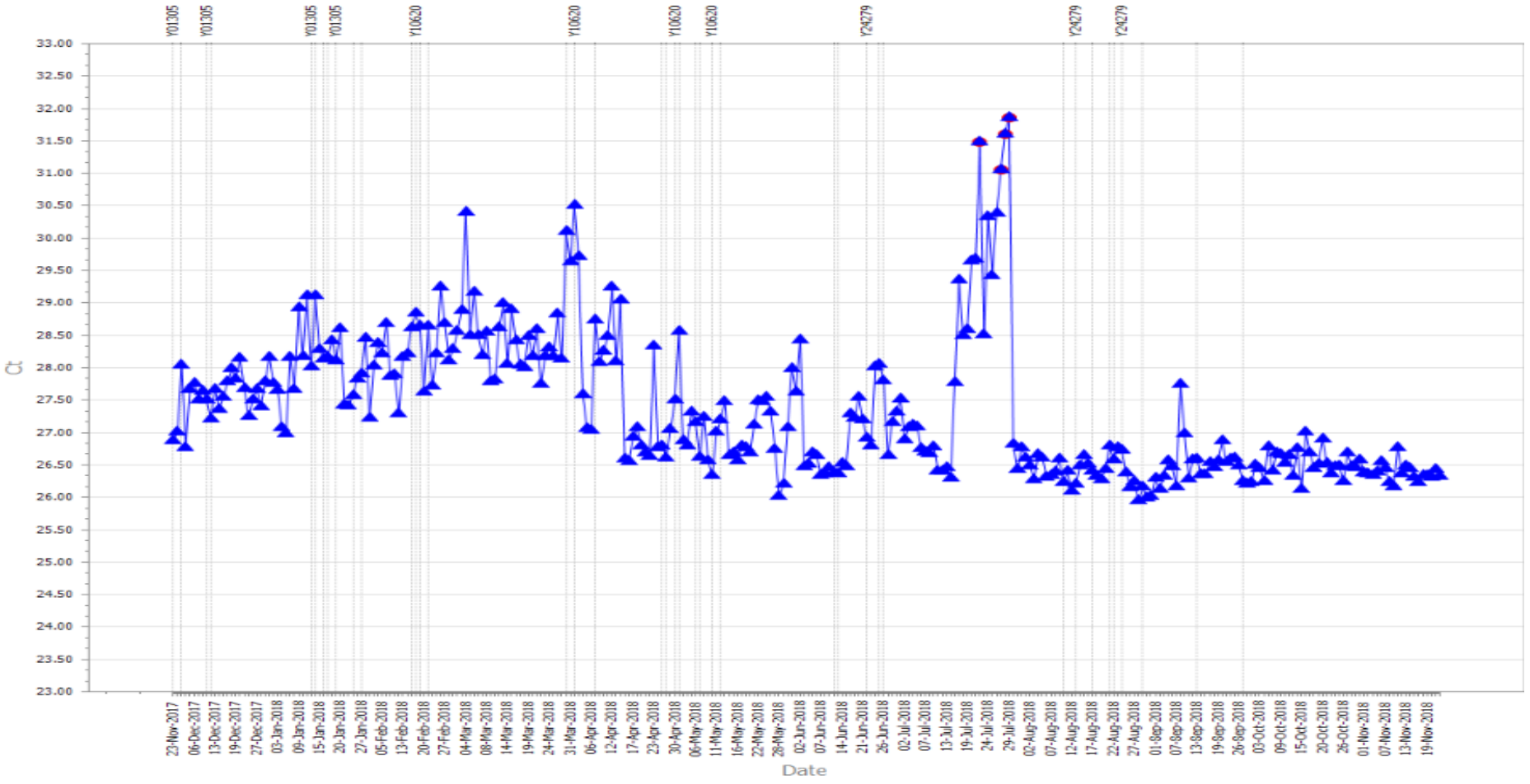
Answer:

Nothing to see here folks

NRL
Science of Quality

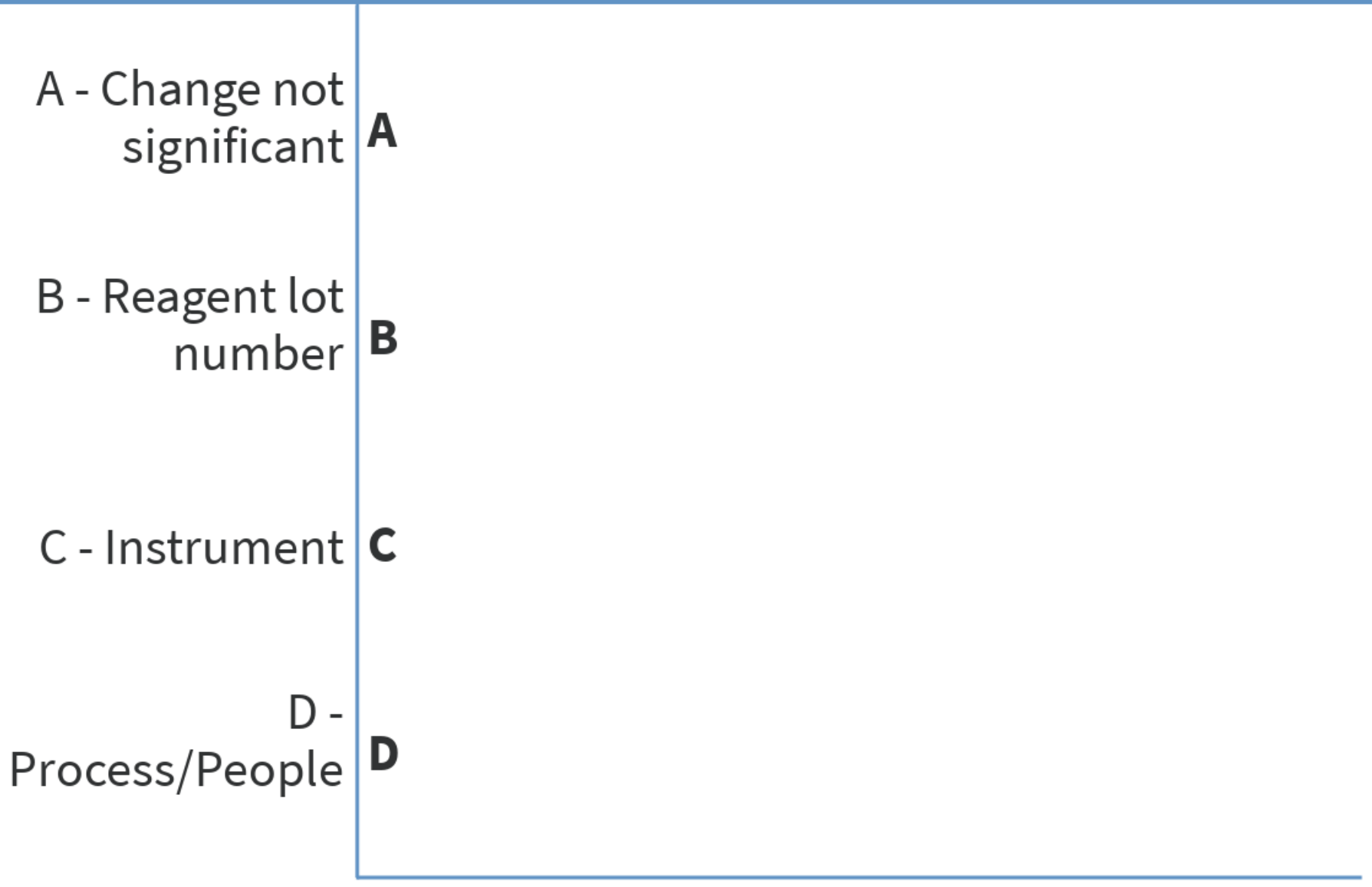
Scenario 3

Scenario 3

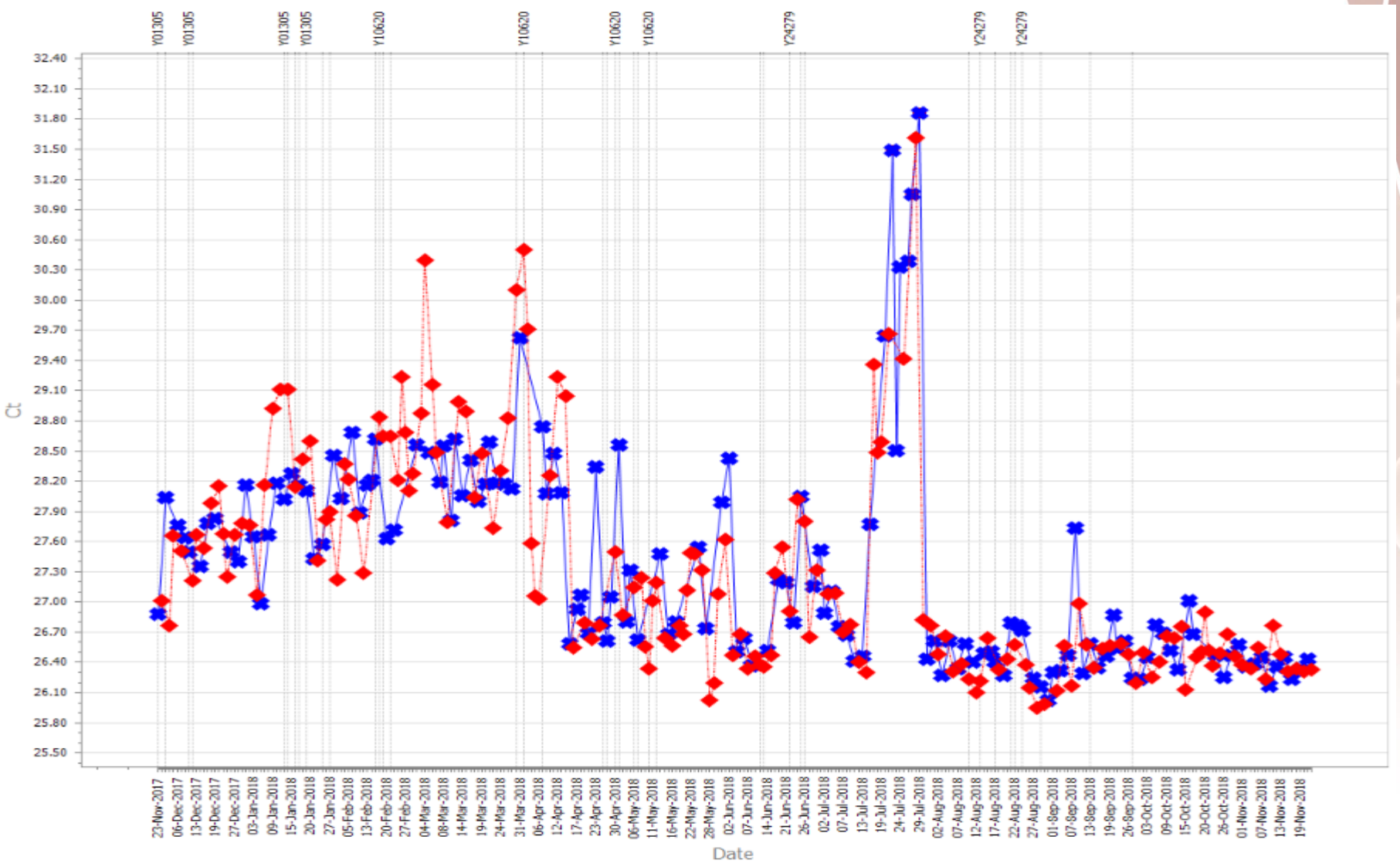


HPV NAT on Roche COBAS HPV Assay

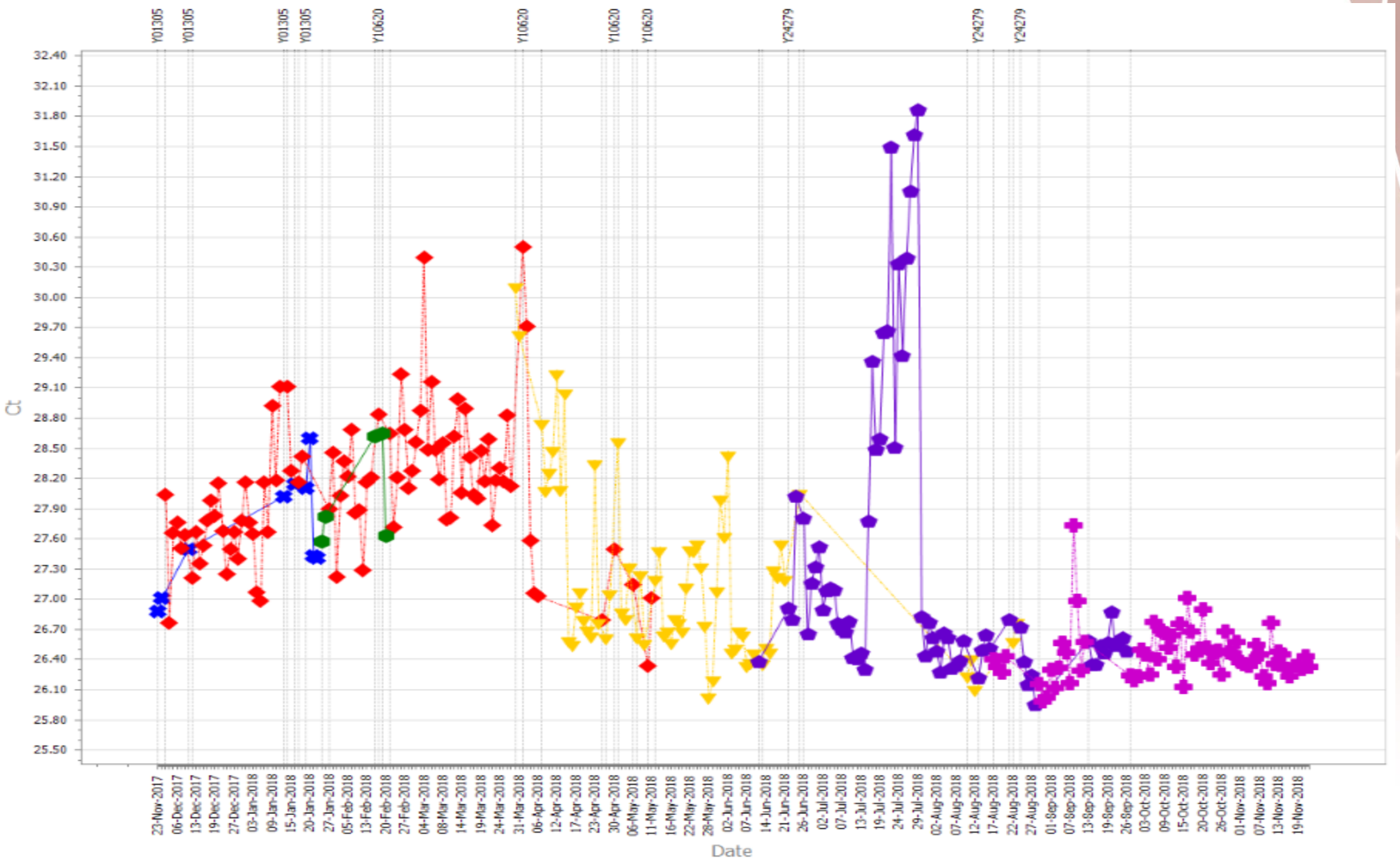
What is the cause of the change



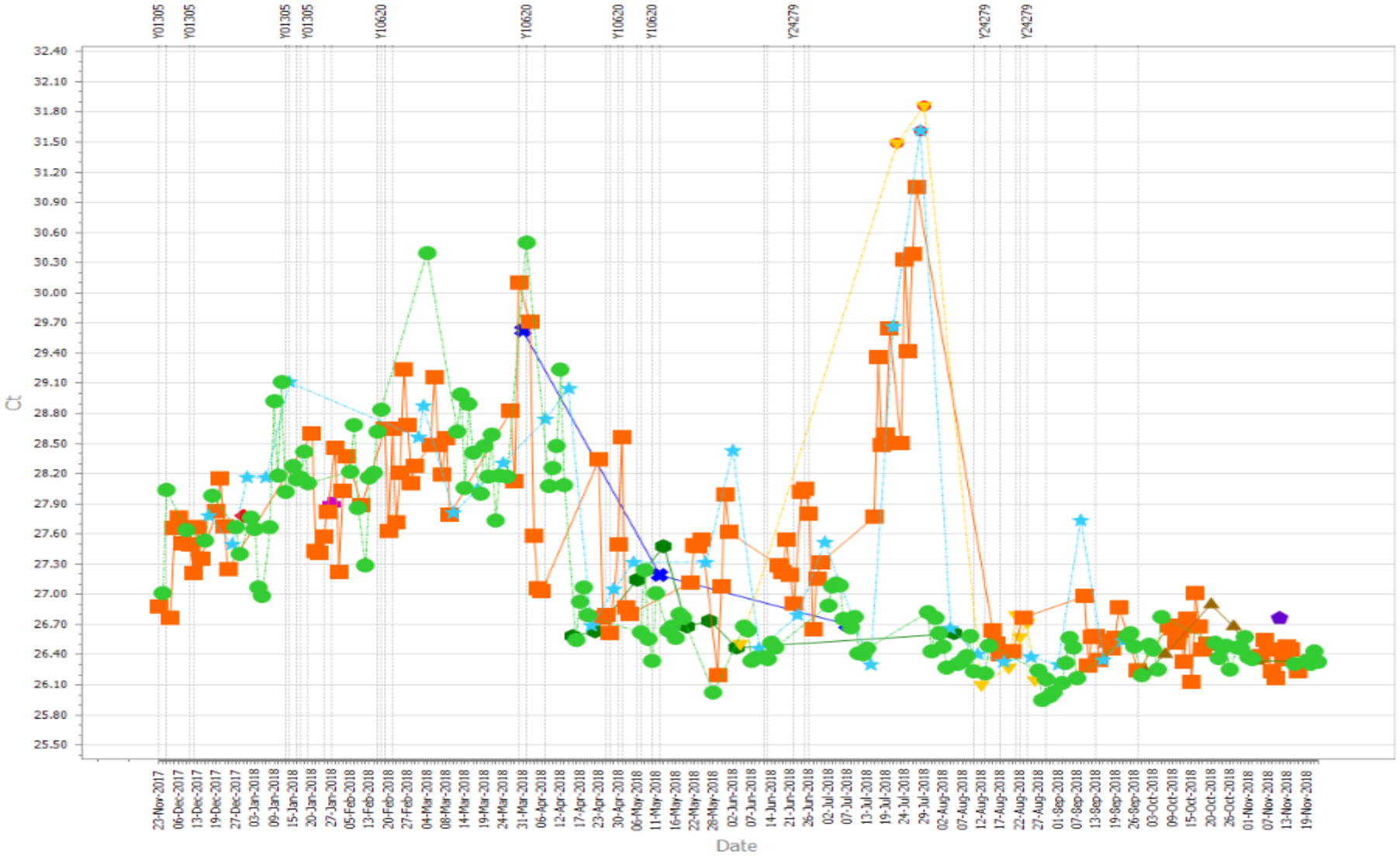
Trending by Instrument



Trending by Reagent Lot



Trending by Operator



Scenario 3

- Investigation initiated
- Observed processing of samples by each operator
- Discrepancies in processes detected
- Re-trained all operators
- Results returned to expected level

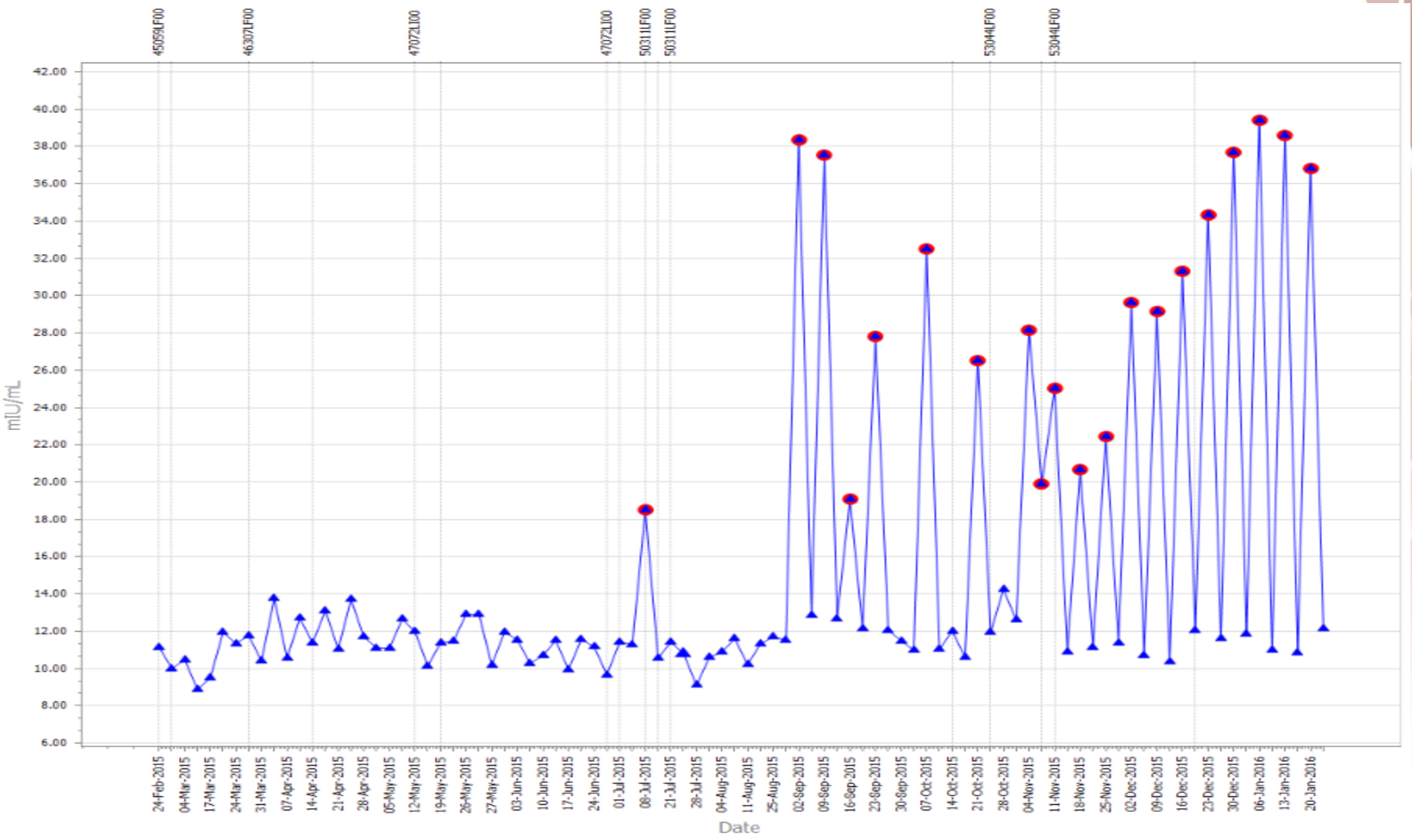
Scenario 3

Answer:

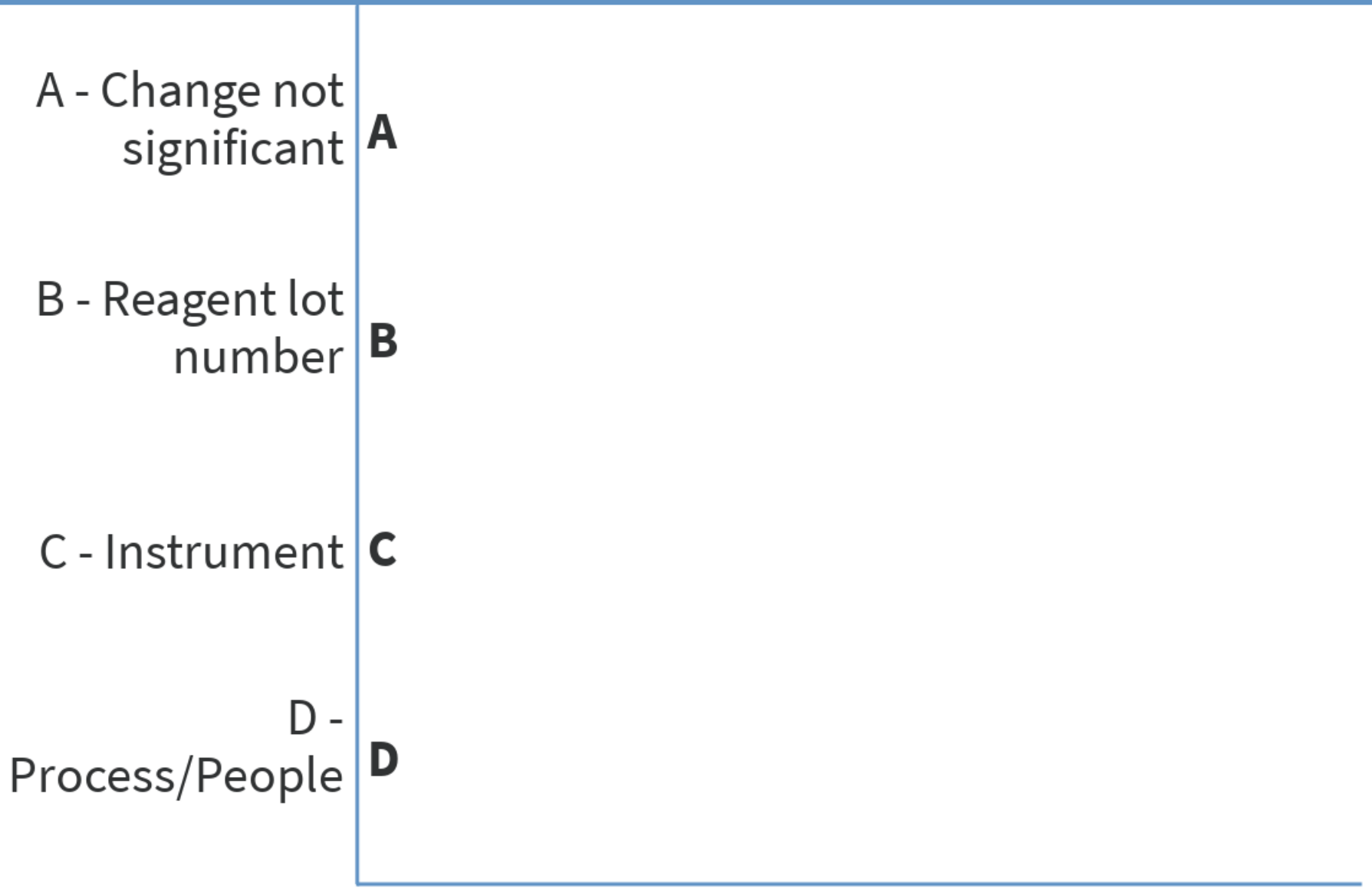
Process issue

Scenario 4

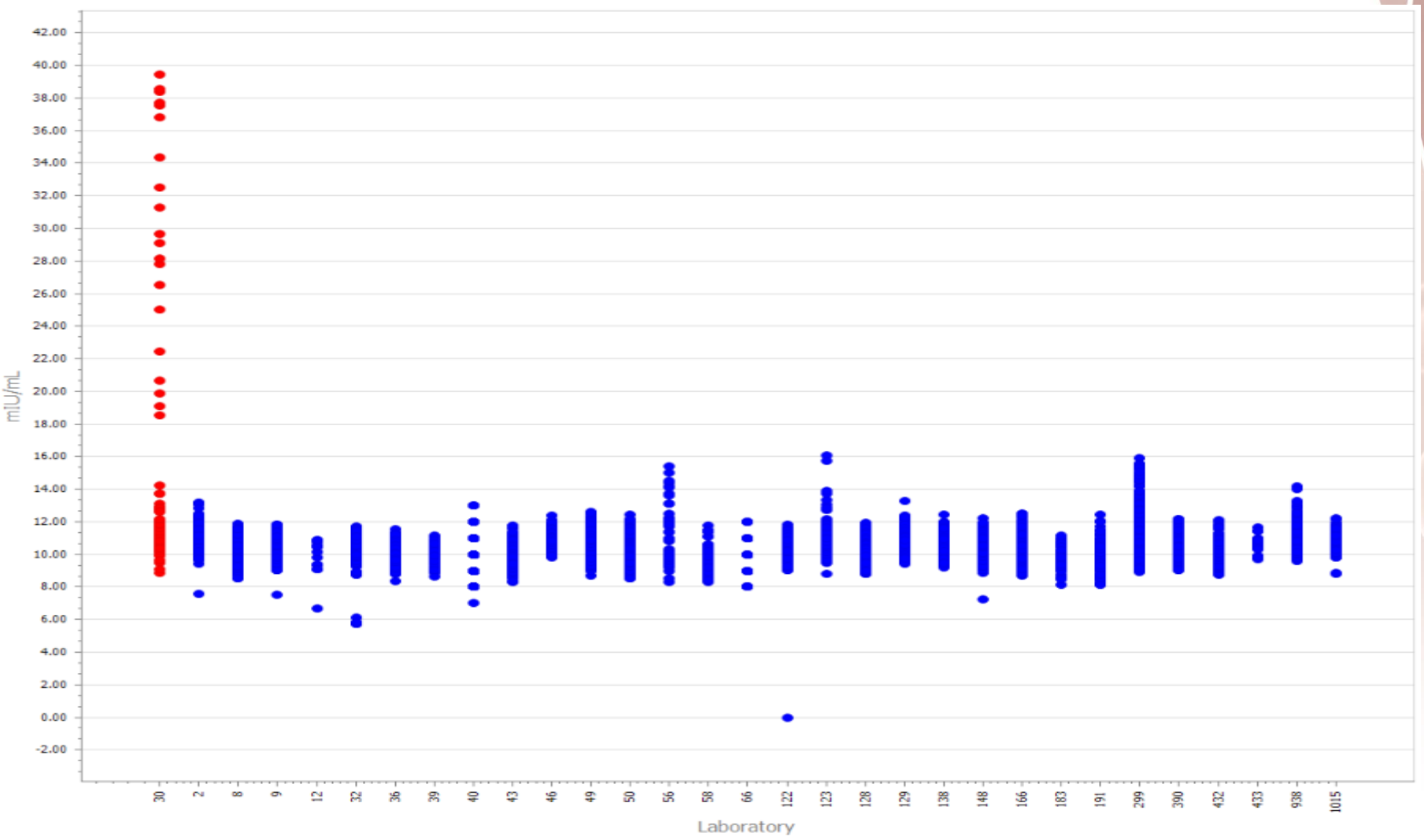
Anti-HBs testing on Abbott Architect



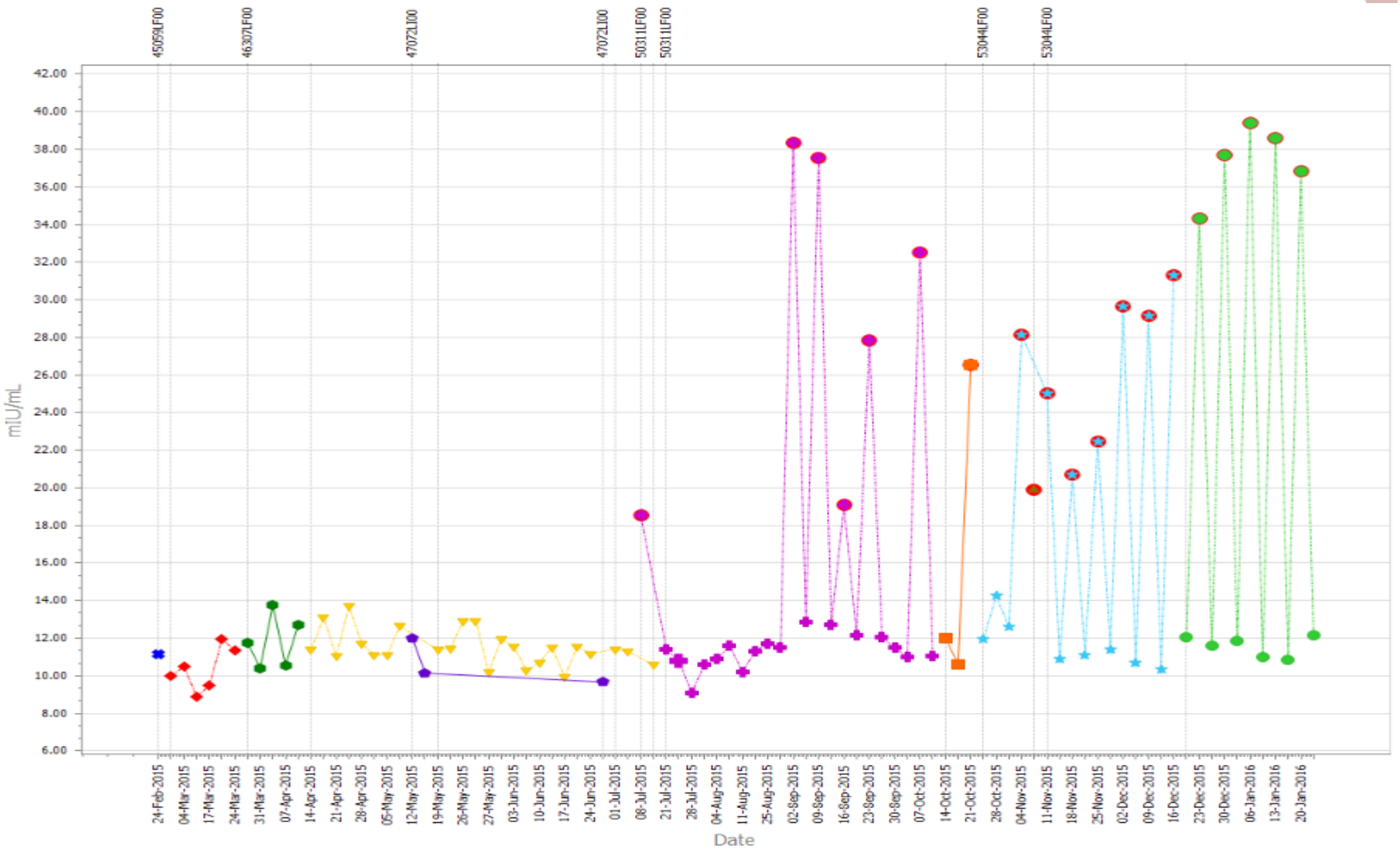
What is the cause of the change



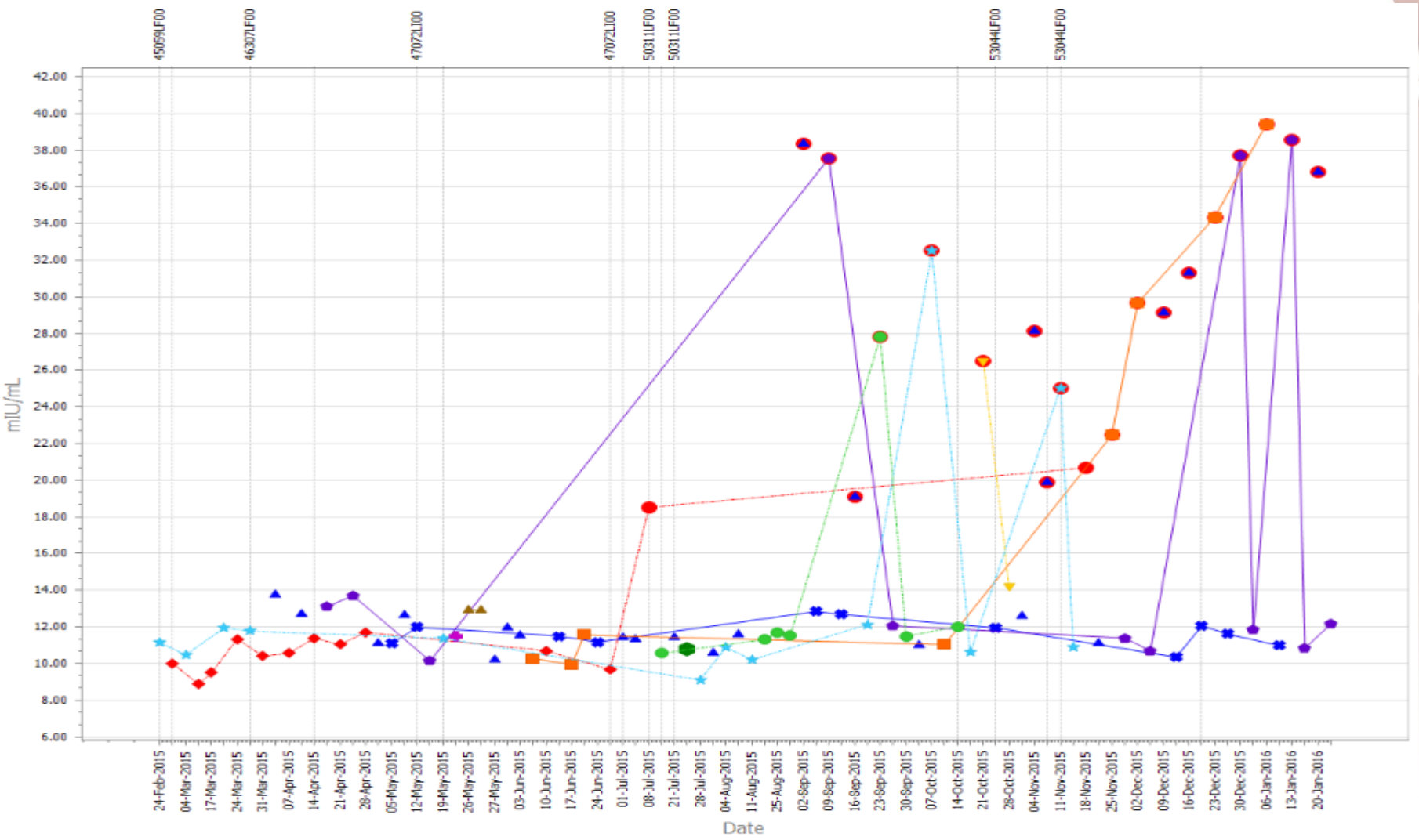
Comparison with Peers



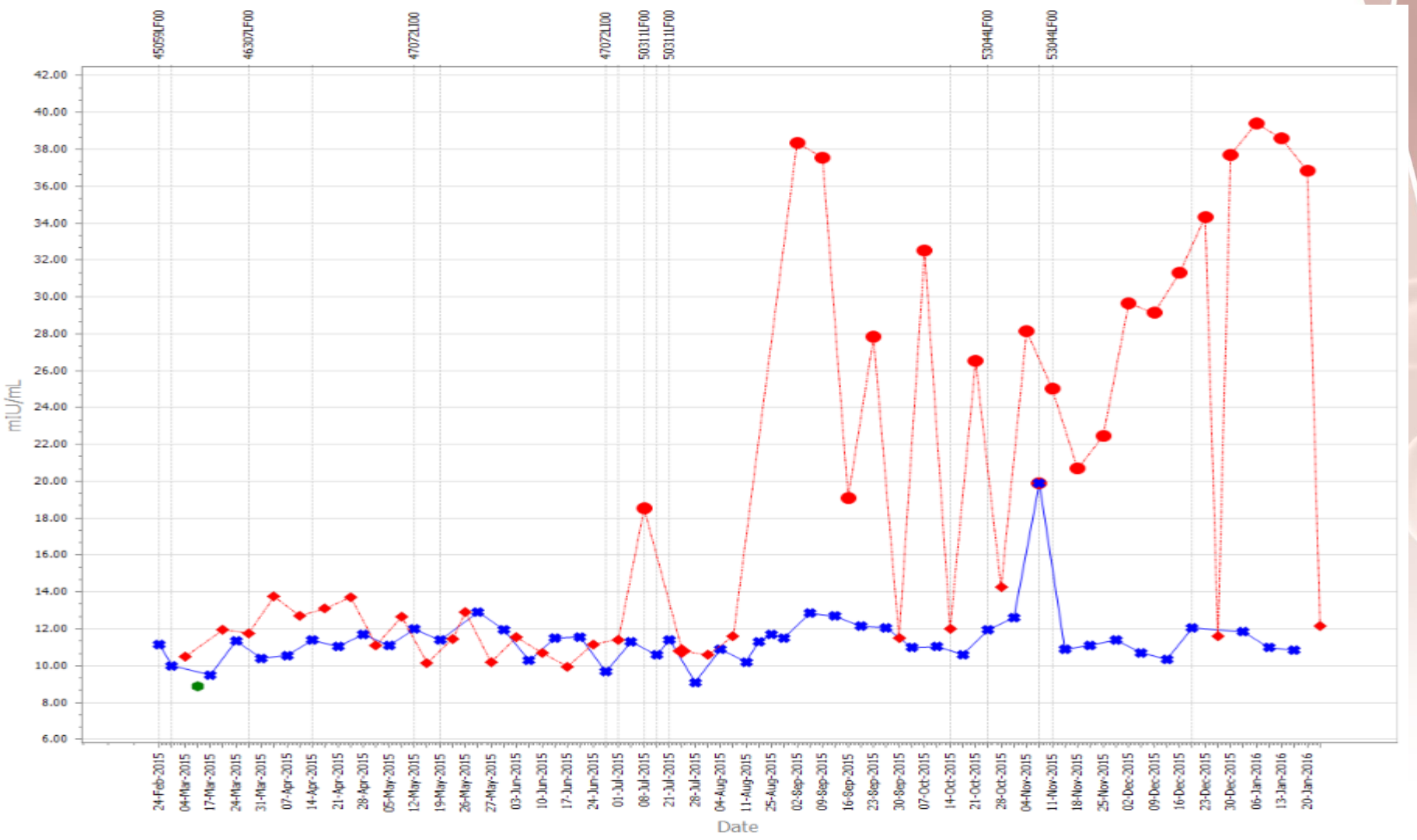
Trending by Reagent Lot



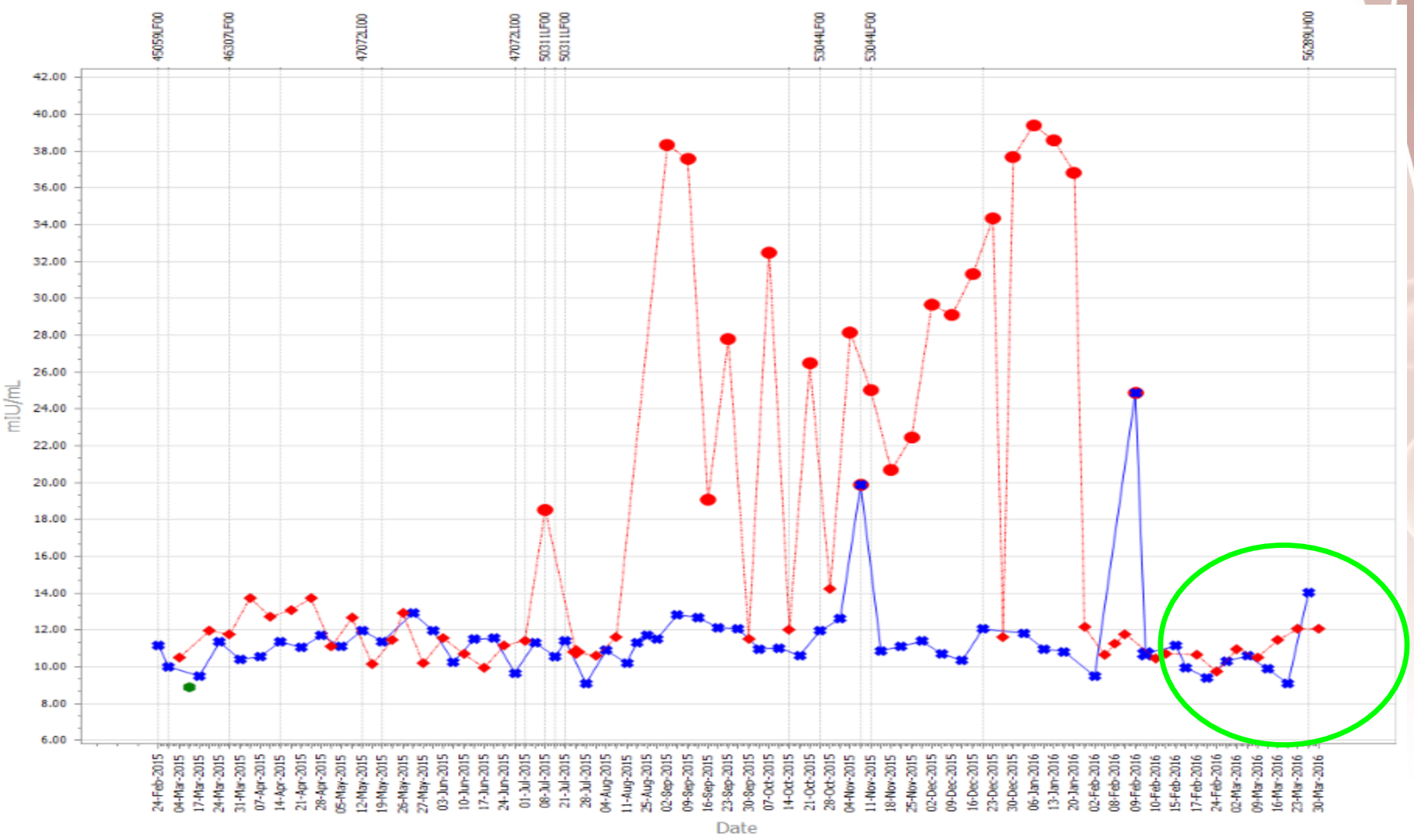
Trending by Operator



Trending by Instrument



Resolution of Issue



Scenario 4

Answer:

Instrument Issue

Conclusions

Conclusions

- Measuring systems must be fit for purpose
- Measurement systems have normal variation
- Variation is derived from people, process, components and equipment
- Dynamic range of serology assays is not always linear
- Choose QC sample that reacts at the linear portion of the dilution curve

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Conclusions

- Fundamental differences between testing for an inert chemical and a functional, biological analyte
- Recommend QC at start of day for automated platforms or every microtiter plate
- Monitoring QC results without reference to a peer-group only monitors precision
- Traditional QC approach assumptions are not true for infectious disease serology

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Conclusions

- Commutability of serology QC samples and patient samples should not be assumed
- Using a diluted sample to mimic early infection is a flawed concept
- Reagent lot variation is the major contributor to normal variation of serology assays

Conclusions

- There are usually insufficient runs to re-set limits before reagent lot is exhausted
- By re-setting limits, you are accepting that the variation is normal
- Viral Load Testing has similarities with clinical chemistry and serology
- Promotion of methods for establishing acceptance criteria for viral load QC needs to be based on real data

Conclusions

- Collect metadata with QC results
  - Date
  - Instrument(s) identification
  - Reagent lot number(s)
  - Operators
  - QC lot number
  - Calibration and maintenance data

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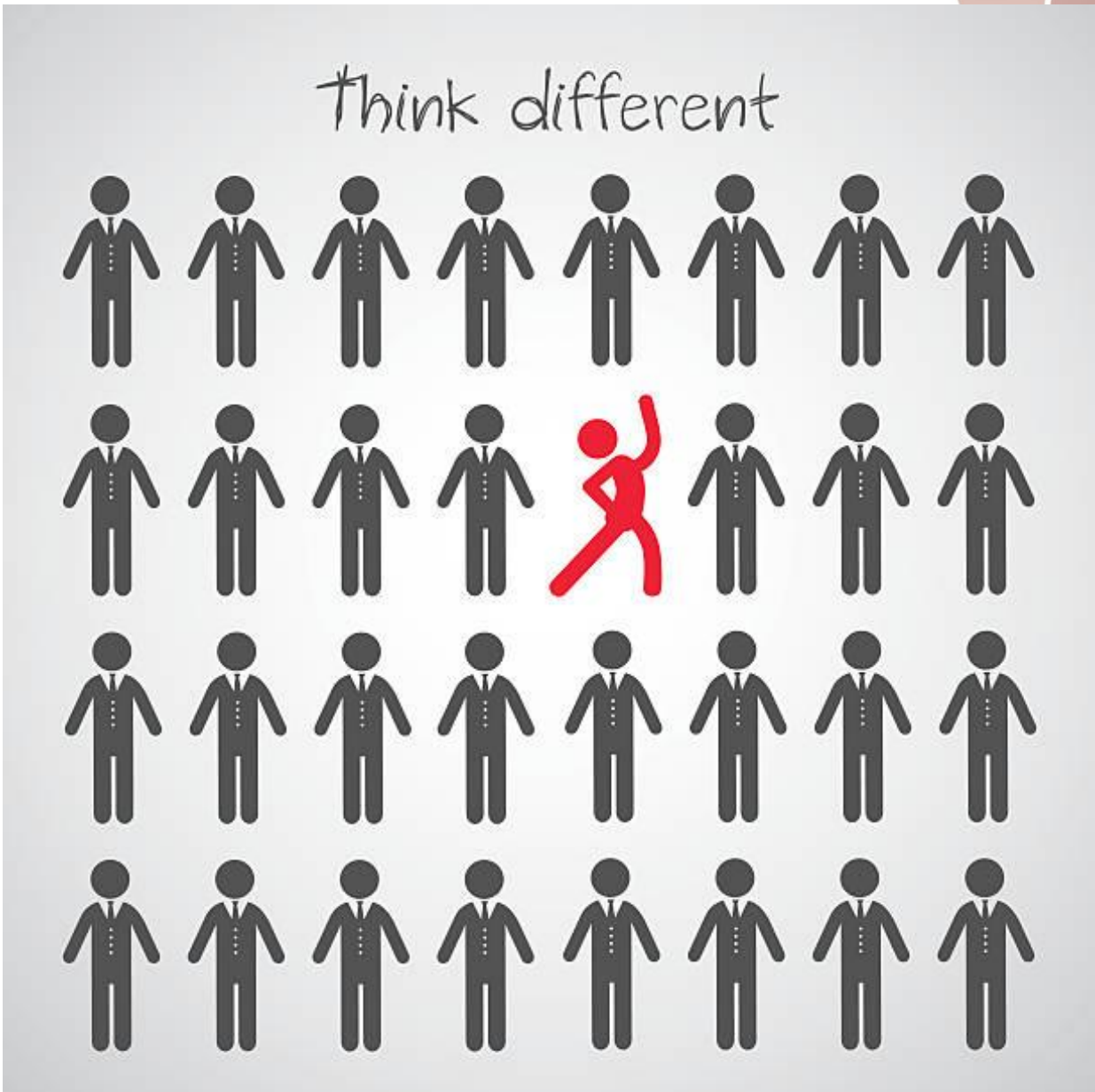
Conclusions

- Monitoring Quality Control in a systematic manner can identify unexpected variation that may, in time, contribute to incorrect patient results
- QC is done in addition to kit controls and EQA and QMS
- Do not blindly follow without evidence – you are scientist

Thank-you!



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