SANBTC 2017 Congress Monday 28th August

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Minimizing risk in the Blood bank following ISO 15189 recommendations for QC

BIO-RAD

Minimizing risk in the Blood bank following ISO 15189 recommendations for QC

Agenda :

- ❑ Introduction
- ❑ Recommendations of ISO 15189 for QC Data Management :

  Example of an HIV assay
  - Reagent Lot to lot variation
  - Monitoring of the results
  - Participation in an Interlaboratory Program
  - Interpretation of results
  - Measurement uncertainty
- ❑ Recommendations of ISO 15189 for QC material

Introduction : Why are we running QC ?

“The laboratory shall design internal quality control procedures that verify the attainment of the intended quality of results.”
– ISO 15189:2012(E), Subclause 5.6.2.1

The laboratory use QC to validate **the reliability of results**
the 2 conditions for my QC to validate this reliability are :

Having the good QC Material

Using it and Managing the data in the correct way

Introduction

We will follow during this presentation the QC results for HIV1 on a random access instrument with Independent QC across the year

Data was provided by a dedicated Virology lab in a French Hospital (providing anonymous HIV testing).

HIV activity in this lab :

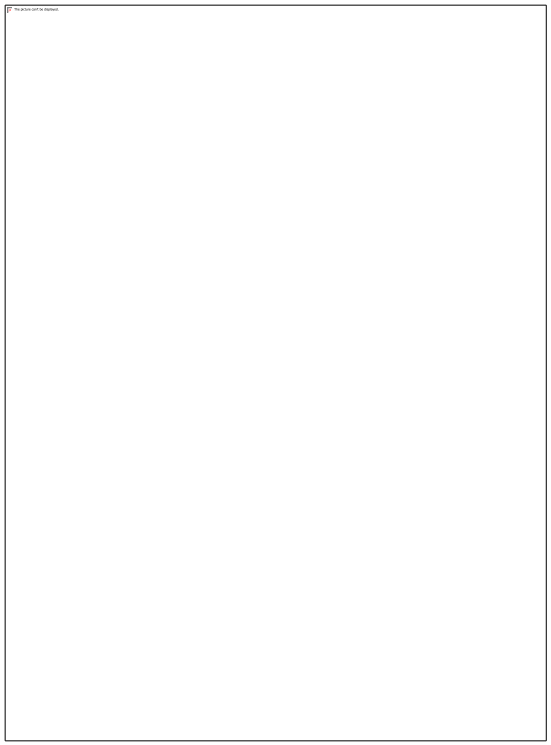
- around **22000 HIV per Year**
- around **5 to 10 positive results per week**

Lot to lot variation

One important use of QC results is to monitor lot-to-lot variation **of reagents**.

Each new QC lot may have **slightly different reactivity** compared with the previous lot.

It is optimal to use a single lot of QC material for the **longest period as possible**.



Let see what happened in a Virology lab and how to manage and follow variations between reagent lots…

Lot to lot variation : Levey-Jenning

Lab began with this lot of Virotrol on March 28

Until June 6 , mean : 6,47S/CO CV : 5,68%

On June 6 : New reagent lot => results fall **outside** 3 SD

Cross over study

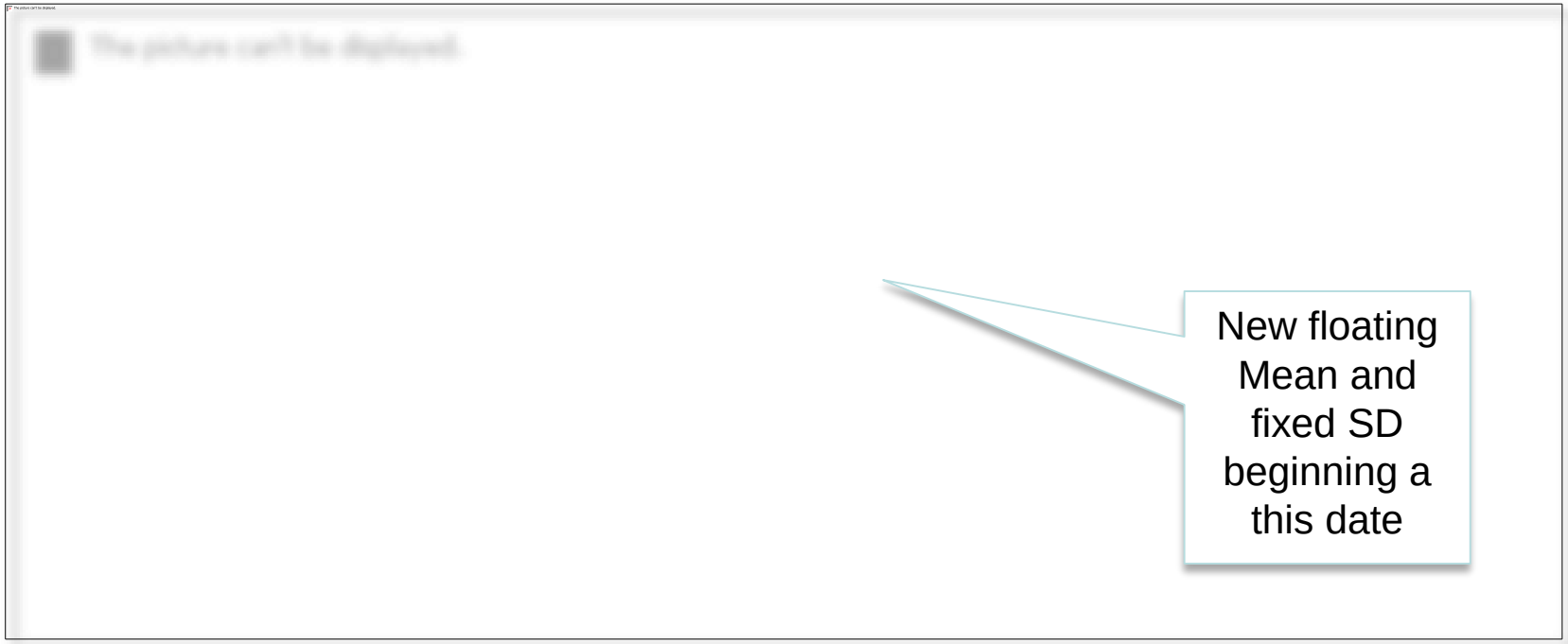
at least N=20 data points is suggested.(20days)

Previous QC lot in charge to monitor the assay during this time

Lot to lot variation : Evaluation Mean/SD

What did the lab manager do ?

He recalculated a new Mean using the *« Evaluation Mean/SD »* functionality of the QC Data management software.



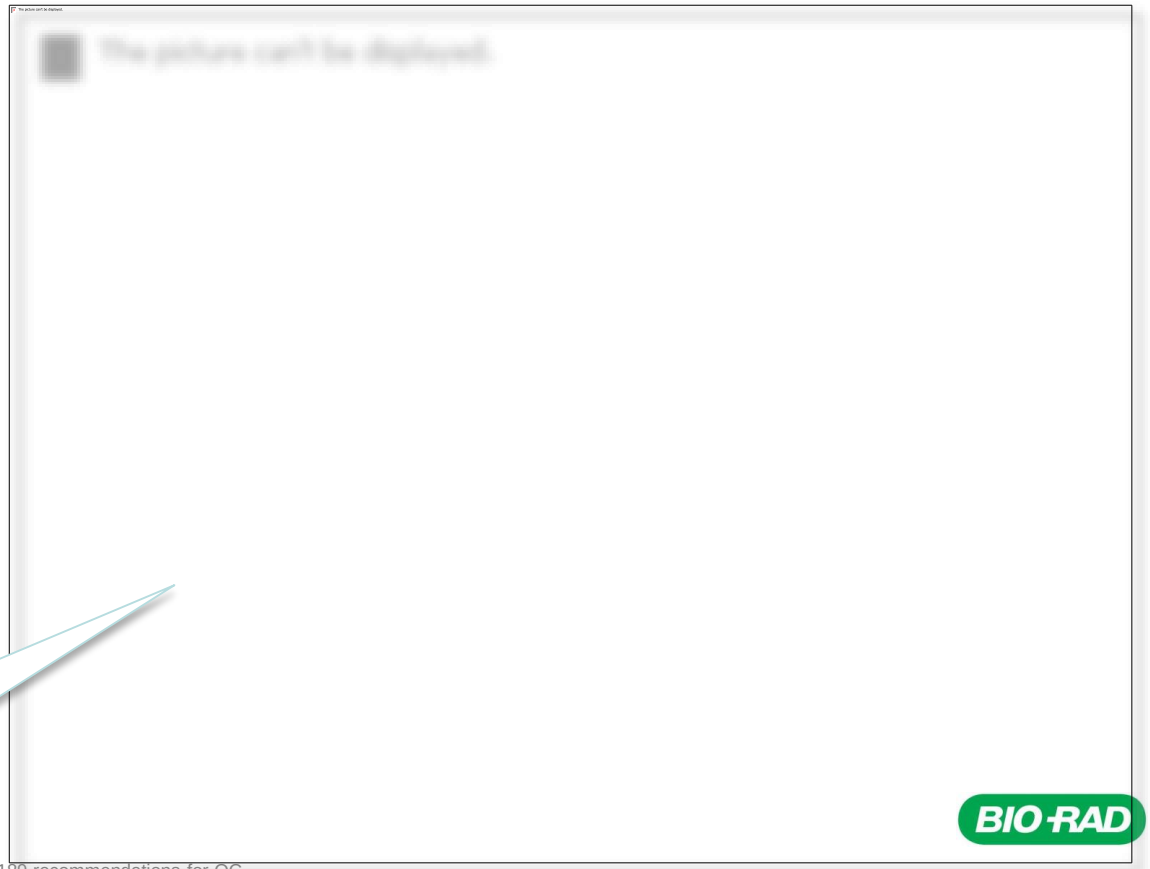
The laboratory must keep track of this lot reagent change

Lot to lot variation : Traceability

*“**Records shall be maintained** for each reagent and consumable that contributes to the performance of examinations.”*
– ISO 15189:2012(E), Subclause 5.3.2.7

“Action messages” should be available or created by the user to be added to QC results to explain shift, trend, and appropriate corrective actions

With traceability of the user

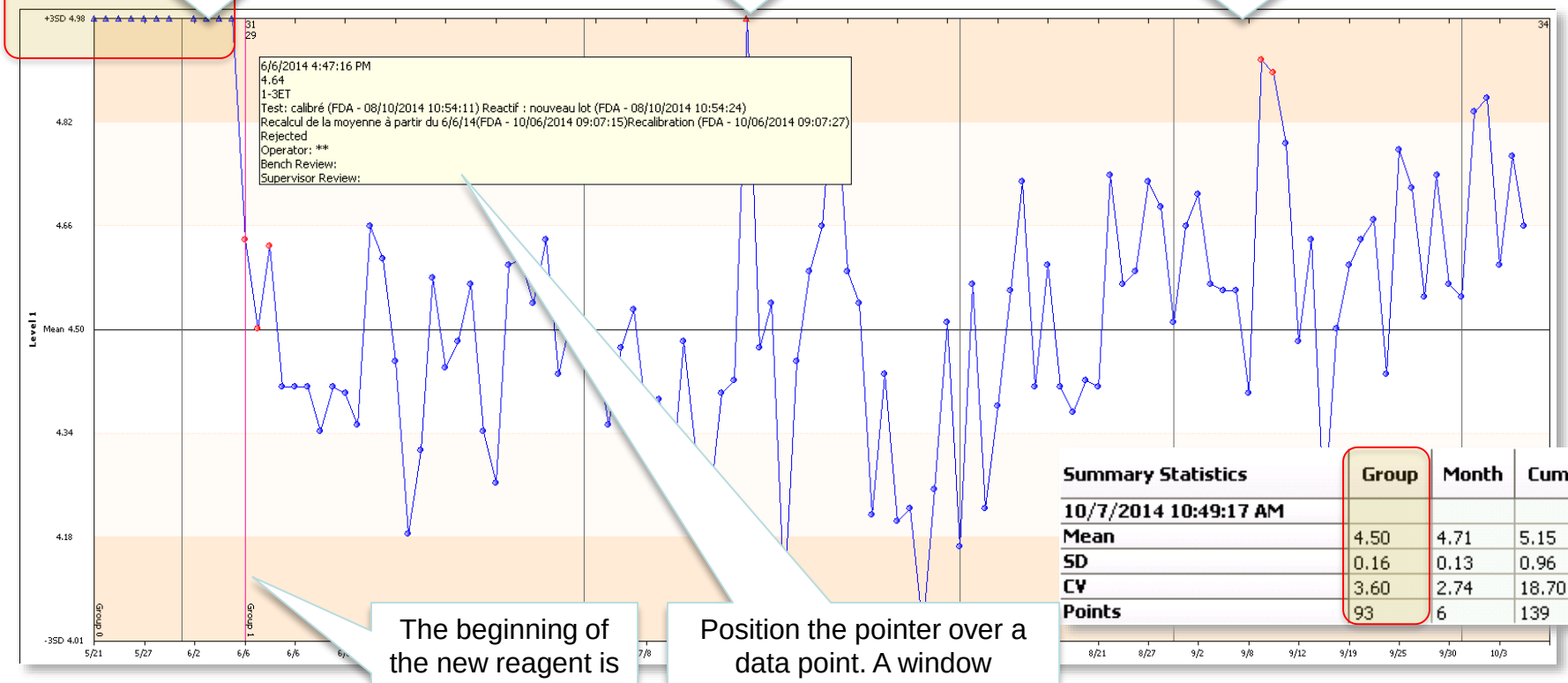


Lot to lot variation : Levey-Jennings

But should we forget the previous values ??

With this new recalculated mean , the data points look fine

New reagent : from June 6 to October 7
mean = 4,50 s/co
CV = 3,6%



Summary Statistics	Group	Month	Cumulative
10/7/2014 10:49:17 AM			
Mean	4.50	4.71	5.15
SD	0.16	0.13	0.96
CV	3.60	2.74	18.70
Points	93	6	139

The beginning of the new reagent is displayed in the LJ

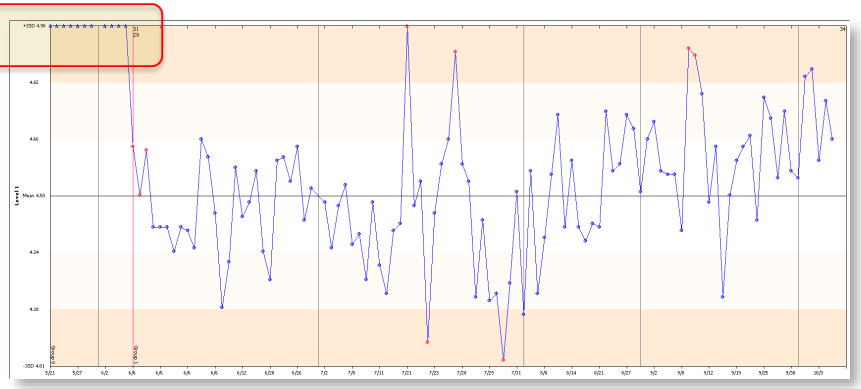
Position the pointer over a data point. A window appears with comments about change of mean / SD

Lot to lot variation : Levey-Jennings

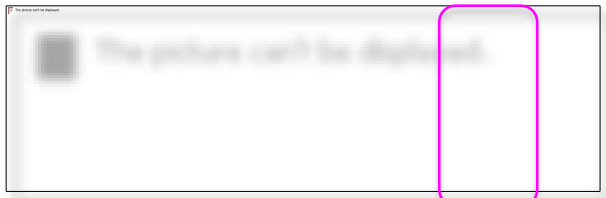
Performance with **previous** reagent lot mean =6,47S/CO
CV : 5,68%

But how to evaluate the **impact** of the shift ?

Performance with **new** reagent lot mean = 4,50 S/CO
CV = 3,6%



individually, the performances of the 2 reagents lots look fine



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Points	93	6	139

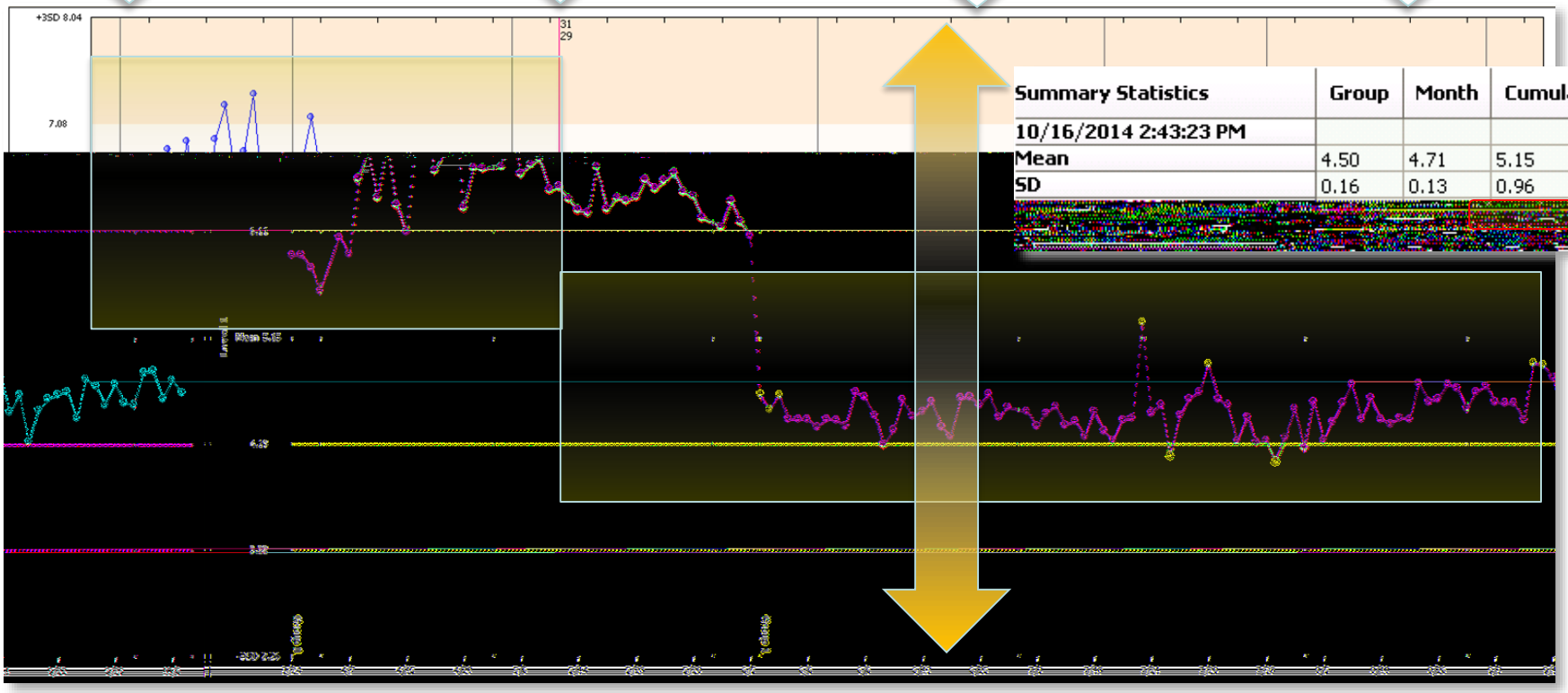
Lot to lot variation : Levey-Jennings

We can see now the life of the test during 6 months

With all traceability regarding the new reagent lot

The **global** performance of the test is different than those of each reagent lot separately

The real CV of the test is 18,7%



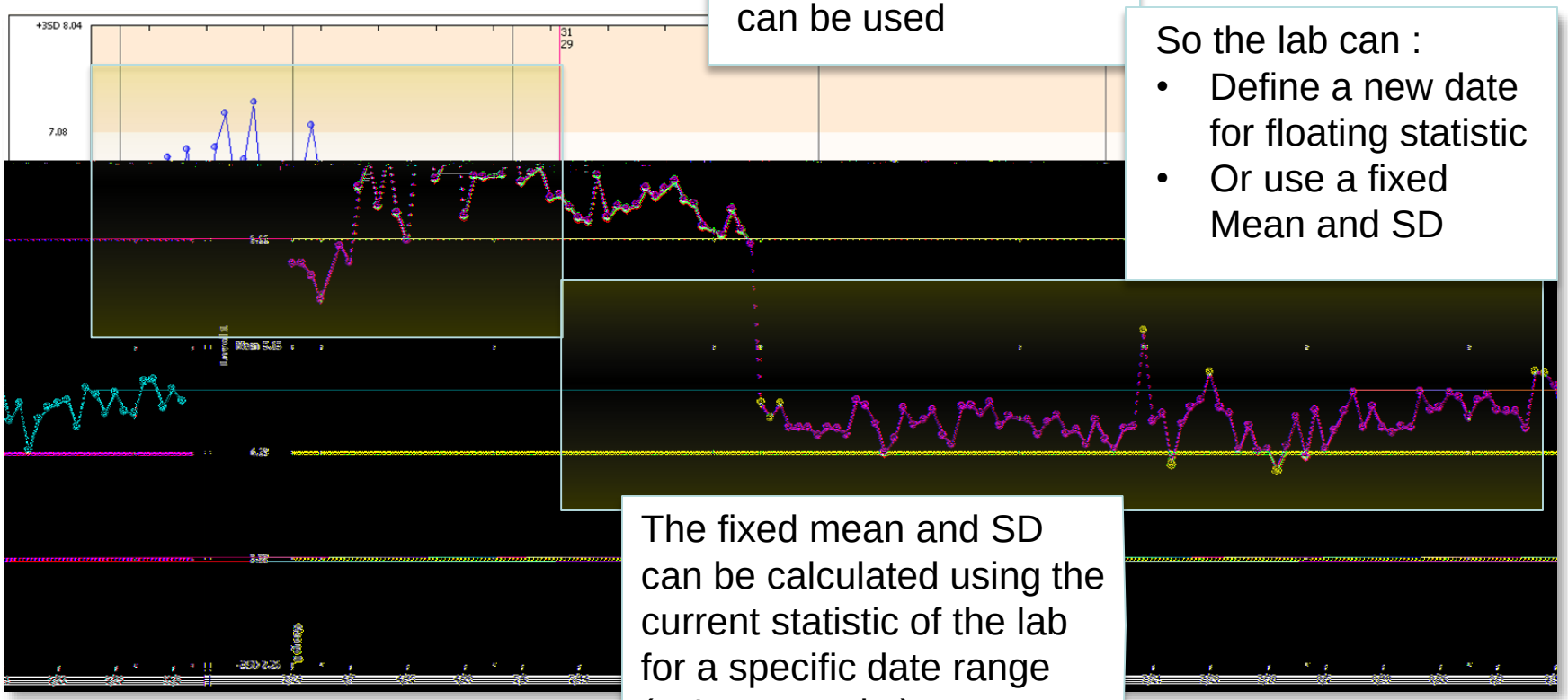
Lot to lot variation : Levey-Jennings

Due to the reagent lot to lot variation, the long term CV can be too high to be used in association with the Westgard Rules.

Only the CV observed for each reagent lot can be used

So the lab can :

- Define a new date for floating statistic
- Or use a fixed Mean and SD



The fixed mean and SD can be calculated using the current statistic of the lab for a specific date range (= 1 reagent lot)

Lot to lot variation : Multi Levey-Jennings

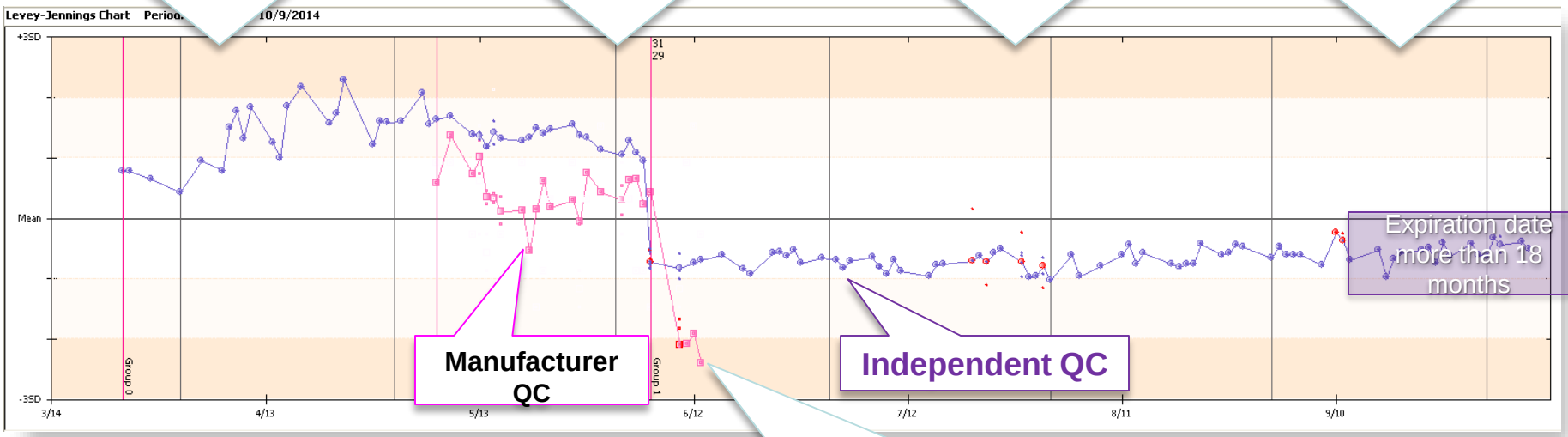
It should be interesting at this point , to compare the results of HIV1 in Independent QC with the results of HIV1 in manufacturer QC during the **same period**

The Independent and the Manufacturer QC are displayed in the same graph

The Shift is equivalent in both QC

We can see how different are the lifespans of the 2 QC

Independent QC will follow the test for further 15 months



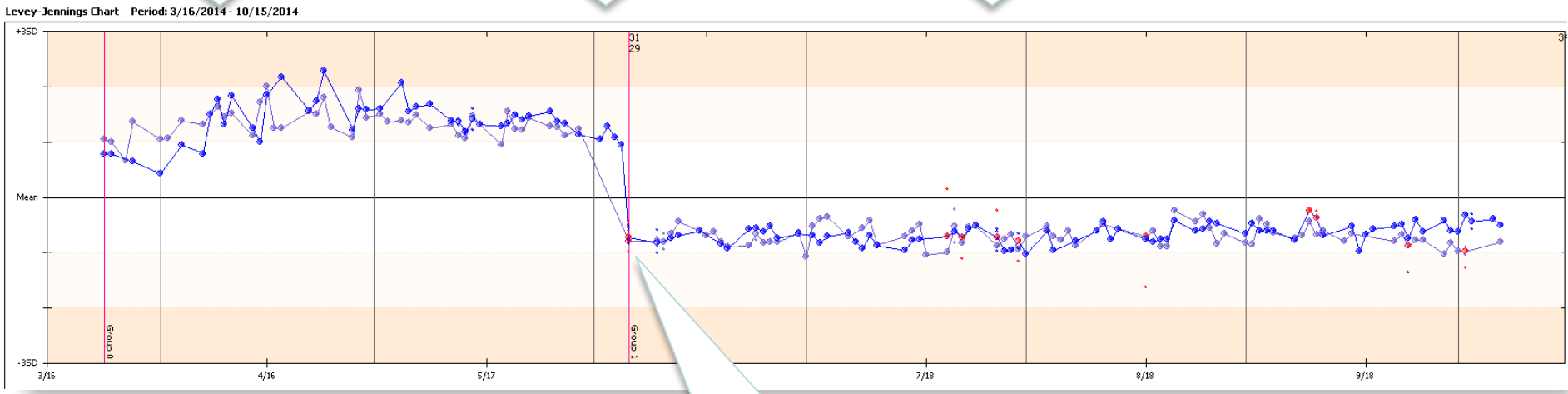
End of the story for Manufacturer QC , how to find a conclusion in this case ?

Lot to lot variation : Multi Levey-Jennings

The LJ can also display the result of the second instrument

The new reagent lot was installed and calibrated the same day

Displayed against the same means , the data show a perfect correlation



The shift occurs in the same manner on both instruments

Monitoring the results in an efficient QC Data management SW

QC data management software should allow to compare the performances of 2 different instruments

Example :
Set B1 = Instrument 1
Set B2 = Instrument 2
Set B3 = Instrument 1 + 2

Set A = Peer group, if lab participates in an interlaboratory program,

demo 2 | Data Set Configuration | Configure TEa | Configure Alert | Export | Print | Close

Level 1 | All Levels

Data Set	Analyte	Unit	Level	Mean	SD	CV	Pts	Labs	SDI	CVR	Bias%	TE p<0.05	Sigma	TEa	TEa Selection
A	HIV-1 Ab	Sample/C...	1	4.80	0.82	17.00	1221	8						20.00	User Defined
B1		Sample/C...	1	5.15	0.96	18.70	139	1	0.42	1.10	7.21	38.06	0.68		
B2		Sample/C...	1	5.06	0.78	15.36	127	1	0.31	0.90	5.30	30.65	0.96		
B3		Sample/C...	1	5.11	0.88	17.21	266	2	0.37	1.01	6.29	34.69	0.80		
A	HCV Ab, Total	Sample/C...	1	3.74	0.27	7.15	942	9						20.00	User Defined
B1		Sample/C...	1	3.79	0.42	10.95	112	1	0.20	1.53	1.42	19.49	1.70		
B2		Sample/C...	1	3.72	0.24	6.51	132	1	-0.06	0.91	-0.45	11.20	3.00		
B3		Sample/C...	1	3.75	0.33	8.90	244	2	0.06	1.25	0.40	15.09	2.20		
A	HBsAg	Sample/C...	1	4.53	0.22	4.95	1051	10						20.00	User Defined
B1		Sample/C...	1	4.53	0.27	5.98	136	1	0.01	1.21	0.03	9.89	3.34		
B2		Sample/C...	1	4.49	0.15	3.24	128	1	-0.17	0.65	-0.85	6.19	5.91		
B3		Sample/C...	1	4.51	0.22	4.87	264	2	-0.08	0.98	-0.39	8.43	4.03		

Participate in an Interlaboratory Program

*"The laboratory **shall participate in an interlaboratory comparison** programme(s) (such as an external quality assessment programme or proficiency testing programme) appropriate to the examination and interpretations of examination results.*
– ISO 15189:2012(E), 5.6.3.1 Interlaboratory comparisons

Note :
*"The laboratory should participate in interlaboratory comparison programmes that **substantially fulfil the relevant requirements of ISO/IEC 17043.***

– ISO 15189:2012(E), Subclause 5.6.3 Interlaboratory comparisons

Participate in an Interlaboratory Program

Two kinds of interlaboratory programs :

- EQA
- Externalization of IQC

EQA Program

1 QC per month:

→ Snapshot of performance at a **specific time T.**

- Evaluation of **accuracy**, monthly.

Corrective actions are taken upon publication of the monthly report.

Externalization of IQC Program

All daily QC:

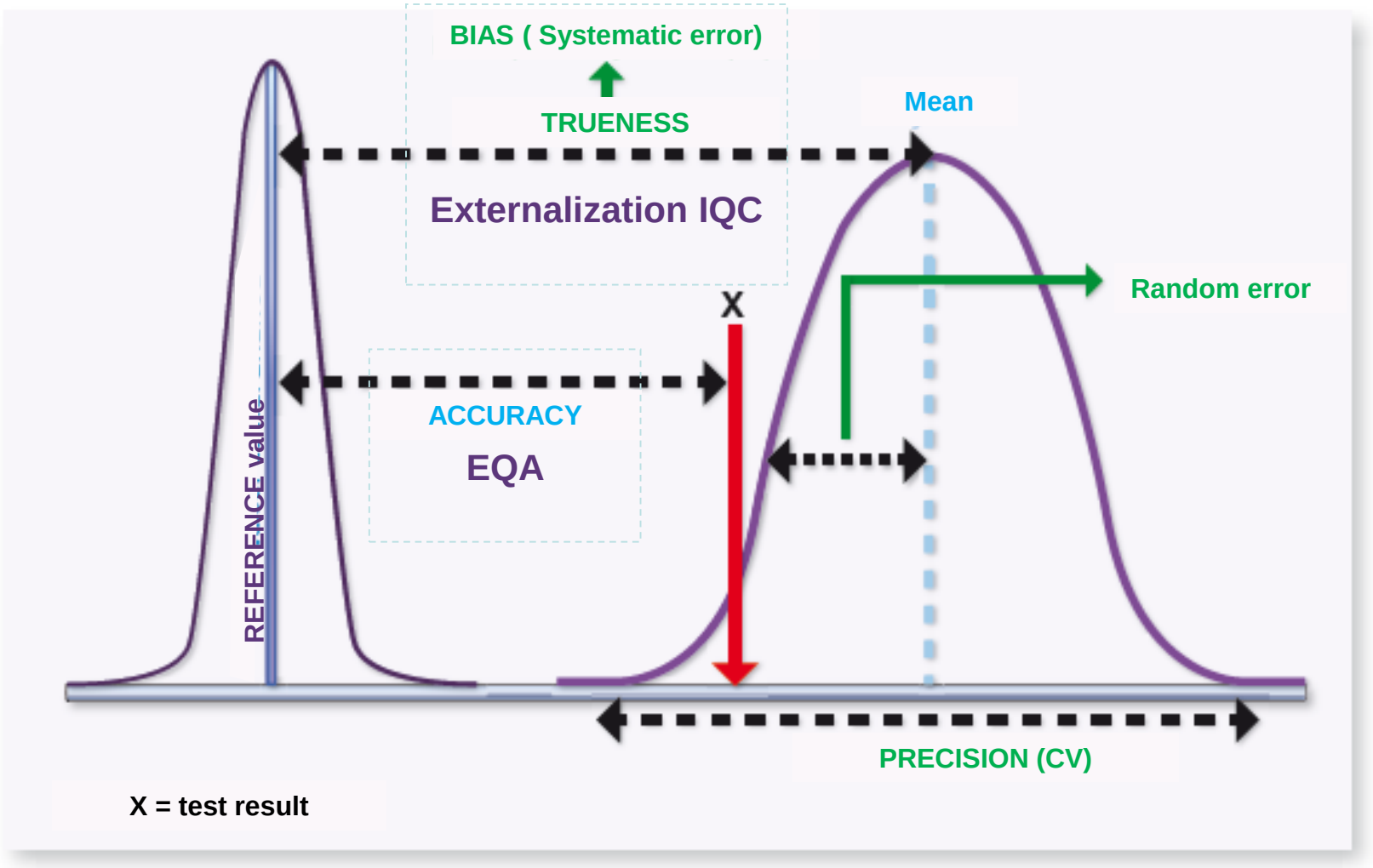
→ **Ongoing** performance monitoring.

- Evaluation of **trueness** **(**Bias) daily

Corrective actions are taken immediately.

These 2 kind of programs are fully complementary, ensuring the satisfaction of ALL standard requirements for achieving accreditation.

Participate in an Interlaboratory Program



Participate in an Interlaboratory Program

EQA → performance T

Extern° IQC ongoing performance

S = Submission
R = Report

Participate in an Interlaboratory Program

- Evaluation mean/SD
- Cumulative
- Date range:

From: 3/ 1/2014 To: 6/ 5/2014

Data Set Configuration | Configure TEa | Configure Alert | Export | Print | Close

Data Set	Analyte	Unit	Mean	SD	CV	Pts	Labs	SDI	CVR	Bias%	TE p<0.05	Sigma	TEa	TEa Selection
A	HIV-1 Ab	Sample/Cutoff..	6.47	0.37	5.68	46	1						20.00	User Defined
B1			4.80	0.82	17.00	1221	8	2.04	0.33	34.65	44.03	-2.58		
A	HCV Ab, Total	Sample/Cutoff..	3.82	0.31	8.08	41	1						20.00	User Defined
B1			3.74	0.27	7.15	942	9	0.31	1.13	2.24	15.57	2.20		
A	HBsAg	Sample/Cutoff..	4.70	0.24	5.17	46	1						20.00	User Defined
B1			4.53	0.22	4.95	1051	10	0.76	1.05	3.76	12.30	3.14		

- Evaluation mean/SD
- Cumulative
- Date range:

From: 3/ 1/2014 To: 6/ 5/2014

Data Set Configuration | Configure TEa | Configure Alert | Export | Print | Close

Data Set	Analyte	Unit	Mean	SD	CV	Pts	Labs	SDI	CVR	Bias%	TE p<0.05	Sigma	TEa	TEa Selection
A	HIV-1 Ab	Sample/C...	5.15	0.96	18.70	139	1						20.00	User Defined
B1			4.80	0.82	17.00	1221	8	0.42	1.10	7.21	38.06	0.68		
A	HCV Ab, Total	Sample/C...	3.79	0.42	10.95	112	1						20.00	User Defined
B1			3.74	0.27	7.15	942	9	0.20	1.53	1.42	19.49	1.70		
A	HBsAg	Sample/C...	4.53	0.27	5.98	136	1						20.00	User Defined
B1			4.53	0.22	4.95	1051	10	0.01	1.21	0.03	9.89	3.34		

$$SDI = \frac{\bar{x}_{Lab} - \bar{x}_{Group}}{s_{Group}}$$

$$CVR = \frac{\text{Within Laboratory CV}}{\text{Consensus Group CV}}$$

A= lab during different periods of time
B1 = Peer group cumulative data

Interpretation : conclusion

If control ranges have been significantly impacted by the new reagent lot, the laboratory may wish to determine if **patient results** have been similarly affected.

A significant change would include a change in result **interpretation** (i.e., a positive result becoming negative)?

Interpretation

The cut off is established to ensure the best performance of a HIV test: ,

100% sensitivity, specificity 99.5%

to minimize the number of false positive, and to detect the seroconversion as early as possible after infection

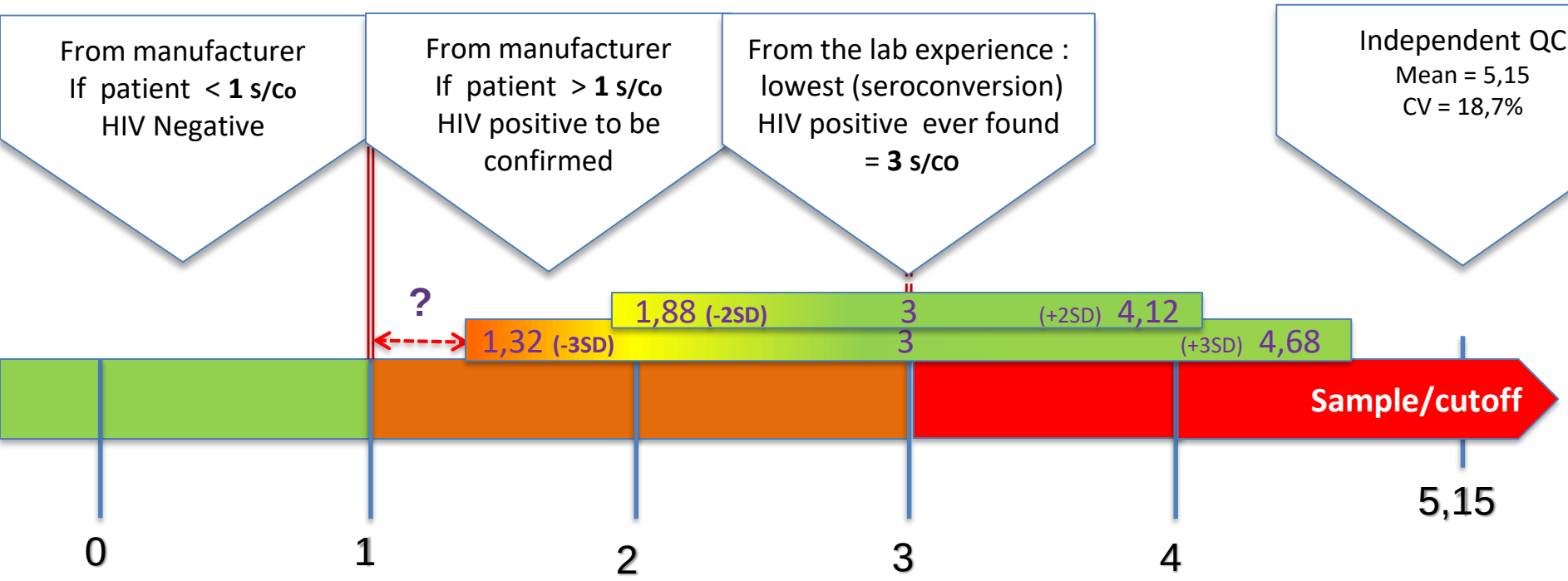
With a CV of the method = 18,7%, the result of a patient = 3 s/co could be found between 1,88 and 4,12 (2SD : 95,5% of confidence)

From manufacturer
If patient < **1 s/co**
HIV Negative

From manufacturer
If patient > **1 s/co**
HIV positive to be confirmed

From the lab experience :
lowest (seroconversion)
HIV positive ever found
= **3 s/co**

Independent QC
Mean = 5,15
CV = 18,7%



Measurement uncertainty

*"The laboratory shall determine measurement **uncertainty for each measurement** procedure in the examination phase used to report quantity values on patients' samples."*
– ISO 15189:2012(E), Subclause 5.5.1.4

NOTE 2
*" Measurement uncertainties may be calculated using quantity values obtained by the measurement of **quality control materials** under intermediate precision conditions that include as many routine changes as reasonably possible in the standard operation of a measurement procedure…"*
– ISO 15189:2012(E), Subclause 5.5.1.4

Measurement uncertainty

NOTE 3

*"Examples of the practical utility of measurement uncertainty estimates might include confirmation that patients 'values meet quality goals set by the laboratory and meaningful comparison of a patient value with a previous value of the same type or **with a clinical decision value.**"*

– ISO 15189:2012(E), Subclause 5.5.1.4

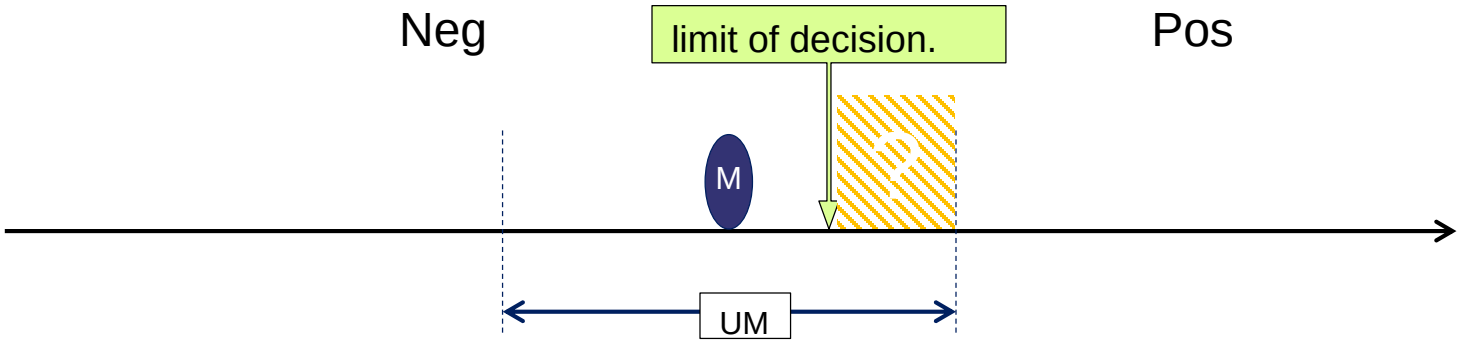
Comparison with a clinical decision value

- If the limit of decision is **inside** the interval = result +/- UM

=> We are not able to provide a conclusion on this result compared to limit of decision.

- If the limit of decision is outside the interval = result +/- UM

=> We can provide a conclusion on this result compared to decision value



A true story

In a Transfusion Centre in General hospital in Slovenija, using the same instrument as described in this example…

"we were running samples having not detected an error...

A sales rep helped us identify an error with the use of interlaboratory reports with Independent QC ...

we identified that we had put at risk 4000 patient results"..

Provide Staff Training and Education

*"The laboratory shall provide training for all personnel which includes the following areas: the **quality management system**."*
– ISO 15189:2012(E), Subclause 5.1.5

*Personnel shall take part in **continuing education.** The effectiveness of the continuing education program shall be **periodically reviewed.***
– ISO 15189:2012(E), Subclause 5.1.8

“The laboratory shall design internal quality control procedures that verify the attainment of the intended quality of results.”
– ISO 15189:2012(E), Subclause 5.6.2.1

The laboratory use QC to validate **the reliability of patient results**
the 2 conditions for my QC to validate this reliability are :

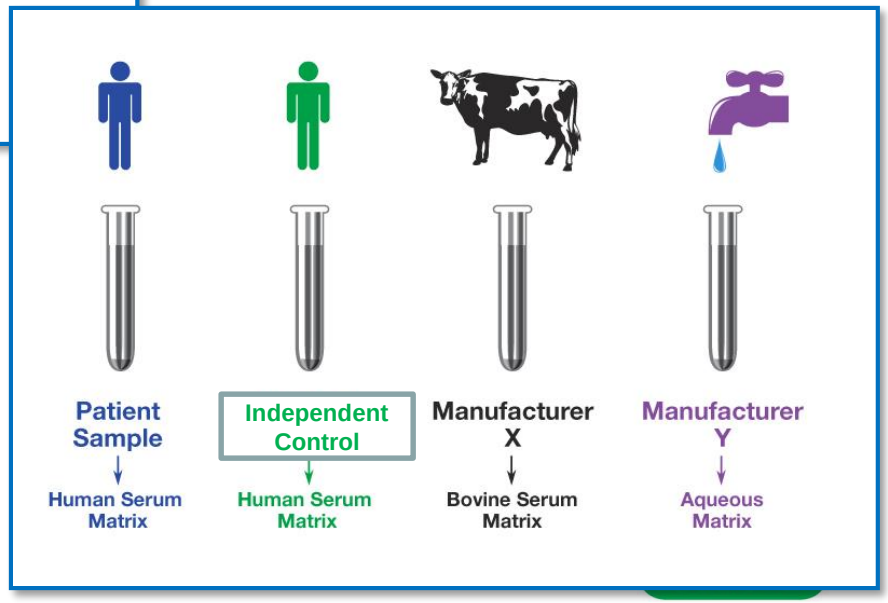
Having the good QC Material

Using it and Managing the data in the correct way

QC as close as possible to patient samples

*"The laboratory shall use quality control materials that react to the examining system in a manner as close **as possible to patient samples.**"*
– ISO 15189:2012(E), Subclause 5.6.2.2

QC materials should be manufactured starting from human biological matrix



QC as close as possible to patient samples

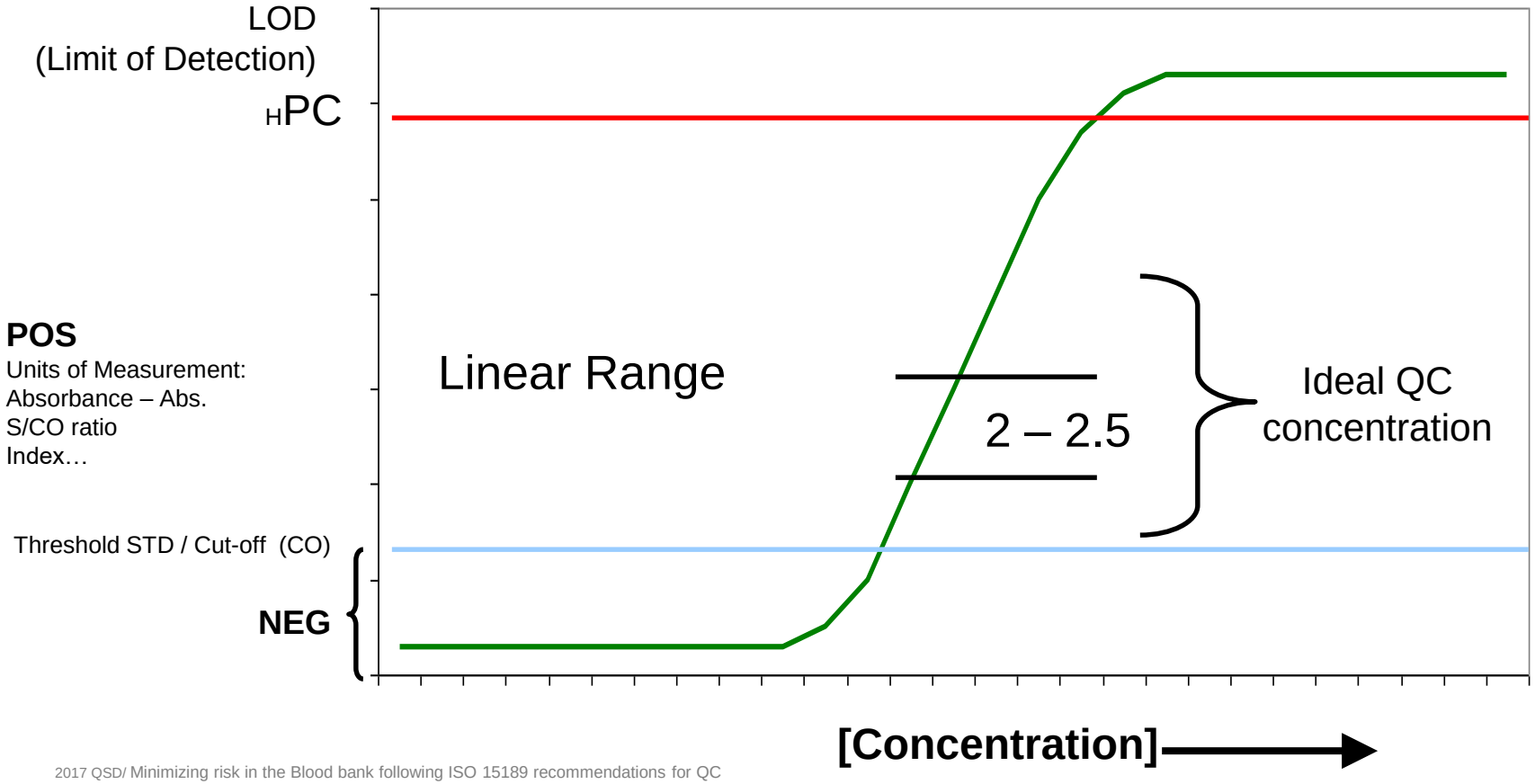
Note 2 :
*Use of **independent** third party control materials should be considered, either instead of, or in addition to, any control materials supplied by the reagent or instrument manufacturer.*
– ISO 15189:2012(E), Subclause 5.6.2.2

Third party controls are manufactured independently of the test system calibrators and reagents.
Third party controls offer a longer shelf life. This allows use of the same control lot over multiple changes in reagents and calibrators.

	Year 1	Year 2	Year 3
Instrument Manufacturer Reagent	Lot 1	Lot 2	Lot 3
Instrument Manufacturer Control	Lot 1	Lot 2	Lot 3
Third Party Control	Lot 1		

QC Targeting

Note 1 :
The laboratory should choose concentrations of control materials, whenever possible, especially at or ***near clinical decision values****, which ensures the validity of decisions made.*
– ISO 15189:2012(E), Subclause 5.6.2.2



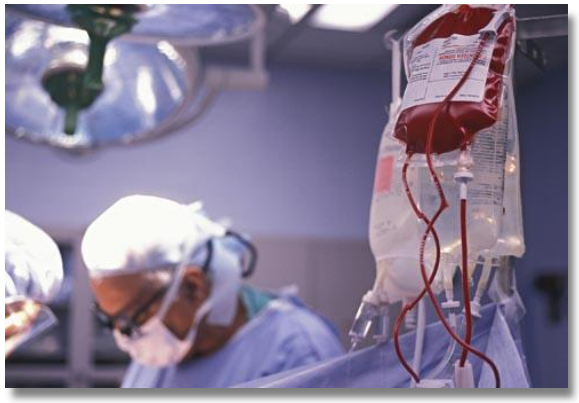
Conclusion

Blood Banks Labs have to Design a good QC Strategy :

- Define **QC material**
- Choose **number of QCs** tested, **QC rules,** and **Limits of acceptability**
- Choose **frequency** of QC
  - require serious mathematical computations that can **only be done with computer software**

Message to bring home :
Why are quality controls used ?

⇒ to help to guarantee the safety of blood donations



Thanks a lot