The Importance of Independent Quality Control Materials

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Learning Objectives

- Define the purpose of Quality Control
- Recognize the difference between first, second and third-party QC
- Describe at least 3 risks when using manufacturer QC

Why are Quality Controls used?

Purpose of Quality Control Materials

- Intended to verify the **reliability** and **medical usefulness** of patient test results
- Generates QC data used for statistical process control (SPC)

Definitions

Reliability

Reliability is maintaining the level of quality over time

Medical Usefulness

Means that the test result(s) is appropriate for diagnosis, prognosis or treatment decisions

Repeatability

The extent to which an experiment, test, or measuring procedure yields the same results on repeated trials

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Use of Quality Control Materials

- Tested alongside patient samples
- Taken through all steps of the analysis

The Ideal Quality Control Material

- ✓ Closely mimics patient samples
- ✓ Has medically useful measure and concentrations
- ✓ Can undergo the complete analytical process

What are Instrument Manufacturer QC materials?

Instrument Manufacturer Quality Controls

- The instrument manufacturer produces the quality control material and provides it together with the instrument/test

- Instrument manufacturer controls are first party controls; they are provided as part of the reagent package and designed for the specific test/instrument

Definitions: Sources of Controls

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Third Party Control	• Manufactured independently of instrument manufacturer • Provides unbiased assessment because not optimized for a particular system • **Better estimation of how test system is performing**
Second Party Control	• Manufactured on behalf of the instrument manufacturer • Possibly optimized for specific system • May mimic the calibrator • **Risk of missing errors in the test system**
First Party Control	• Manufactured by the instrument manufacturer using same process and materials as device calibrators • Often supplied as part of a reagent package and optimized for a specific system • Often mimics the calibrator • **Higher risk of missing errors in the test system**

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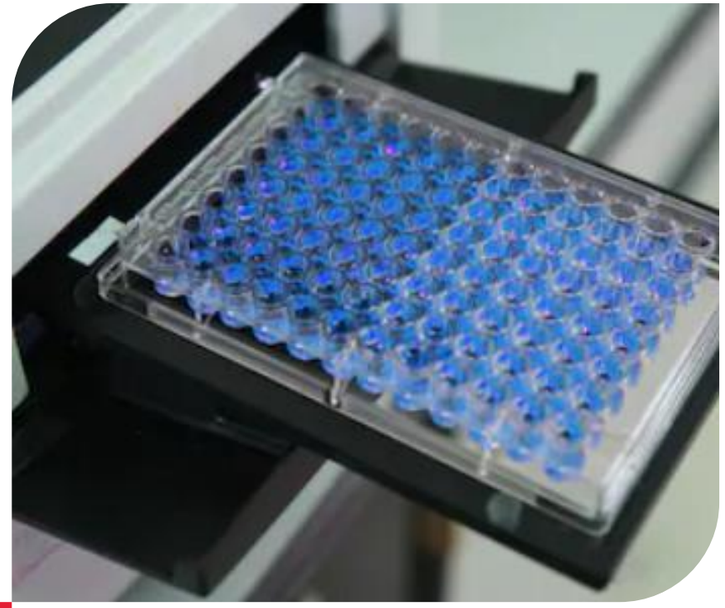
INCREASING RISK

Why use Instrument Manufacturer QC?

- Provided with the instrument or test kit, no need to obtain external materials
- Have values and limits assigned for the specific test method
- Manufacturer will provide full support for their QC products
- Seen as part of the kit (and included in price?)

Instrument Manufacturer Quality Controls

- Some in-kit quality control materials can be an important part of the test procedure
- These materials need to be run to ensure the correct performance of the test



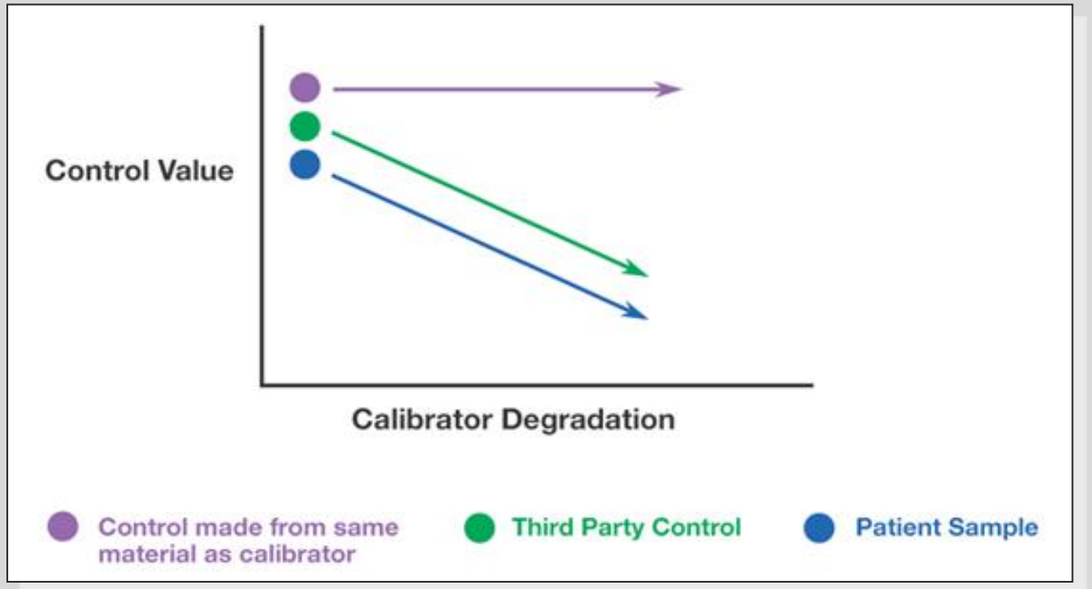
For example: some controls in kits are used to calculate the cut-off or validate the cut-off

But it's still advised to add an independent QC to test the complete analytical process and monitor across kit performance

Risks of Instrument Manufacturer QC

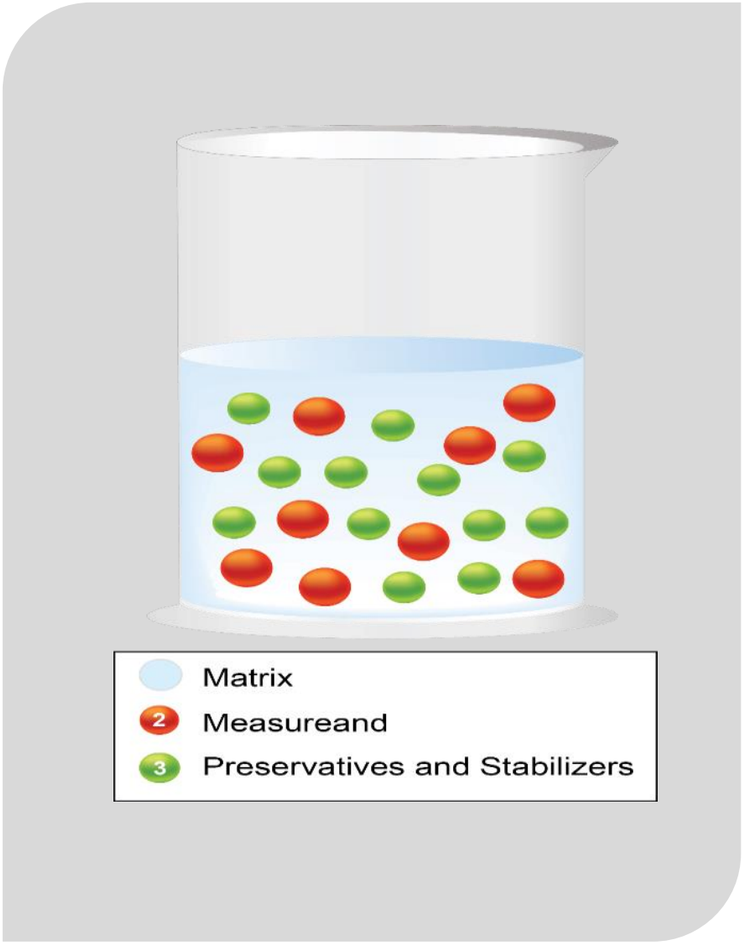
- Because the material is optimized for the instrument/test there is an increased risk of not detecting critical errors

- Are often made from the same material as the calibrator



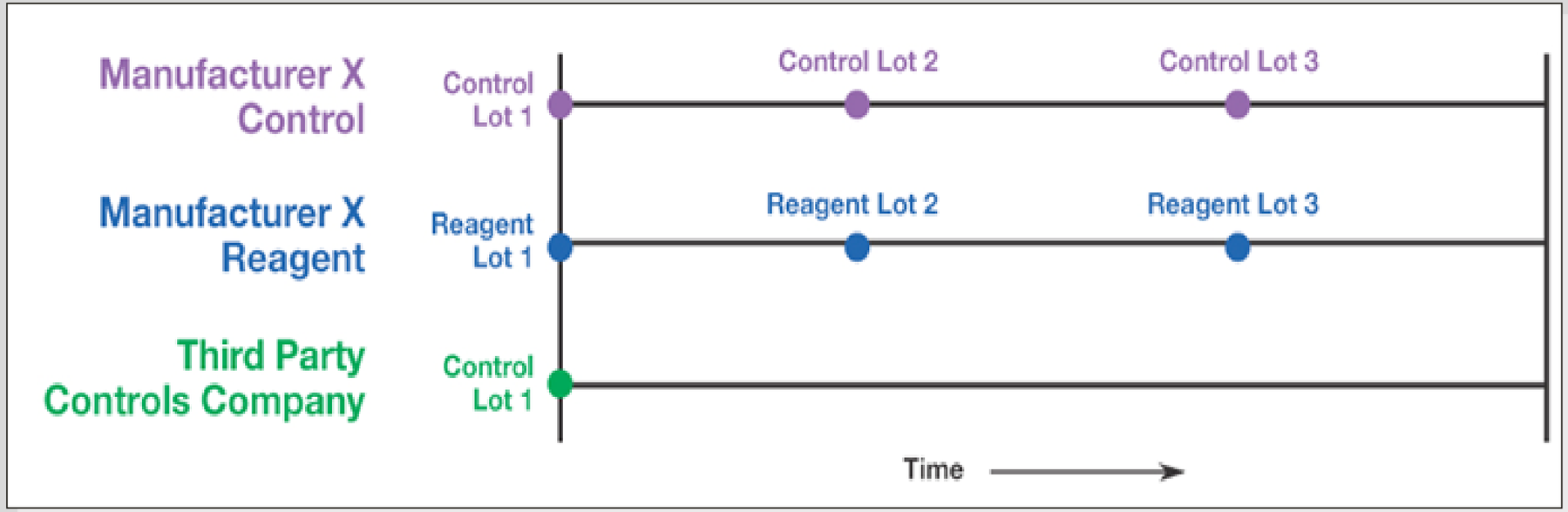
Risks of Instrument Manufacturer QC

- Matrix can be different than patient samples
- Ideal matrix material is human origin
- Other matrices often seen with manufacturer QC:
  - Chemically contrived (artificial)
  - Albumin based
  - Aqueous solutions
  - Bovine or equine serum



Risks of Instrument Manufacturer QC

- New lot of QC with each reagent kit; doesn't provide long term stability monitoring
- Can prevent detecting changes in reagent lot performance



New QC lots will also require expensive cross over studies to establish or verify the target and ranges

Example of calibrator standardization change

Manufacturer Report

Specialty Immunoassay • Lot 57460 •

25-Hydroxy Vitamin D (Total) Chemiluminescence ng/mL

Abbott AEROSET/ARCHITECT (c, i, ci models) • Abbott ARCHITECT 25-OH VIT D, REF 3L52

	Level 1 Mon	Level 1 Cum	Level 2 Mon	Level 2 Cum	Level 3 Mon	Level 3 Cum
Mean	12.06	11.05	22.39	20.76	56.24	53.78
SD	0.994	1.28	1.21	1.94	4.26	3.48
CV	8.2	11.6	5.4	9.3	7.6	6.5
# Points	60	332	64	626	93	857
# Labs	2	2	2	2	3	3

Abbott AEROSET/ARCHITECT (c, i, ci models) • Abbott ARCHITECT 25-OH VIT D, REF 5P02

	Level 1 Mon	Level 1 Cum	Level 2 Mon	Level 2 Cum	Level 3 Mon	Level 3 Cum
Mean	7.08	7.06	13.58	13.98	33.10	34.55
SD	0.548	0.506	0.903	0.821	1.54	1.84
CV	7.7	7.2	6.6	5.9	4.6	5.3
# Points	35	482	13	220	31	434
# Labs	3	5	2	3	2	4

The new ARCHITECT 25-OH Vitamin D assay LN5P02 provides the following changes from the LN3L52 assay for your laboratory:

Assay	3L52	5P02
Pretreatment Assay	Yes	No
Time to first result	36 min	29 min
Reagent Positions	2	1
Calibration Stability	7 days	30 days
LoQ	8.0 ng/mL (at 30 % total error)	2.4 ng/mL (at 20% CV)
Measuring Interval* [SI Unit]	8.0 – 160.0 ng/mL [20.0- 400.0 nmol/L]	3.4 – 155.9 ng/mL [8.5 - 389.8 nmol/L]
Standardization	Internal Standard	NIST SRM 2972 (National Institute of Standards & Technology Standard Reference material 2972)

*The measuring interval of the ARCHITECT 25-OH Vitamin D assay LN 5P02 has been defined based on the determined linearity range (3.4 to 155.9 ng/mL). Precision, bias and sensitivity (LoQ) performance support the range.

Example provided by Dr. S Ramanathan, MIOT Hospital Chennai India

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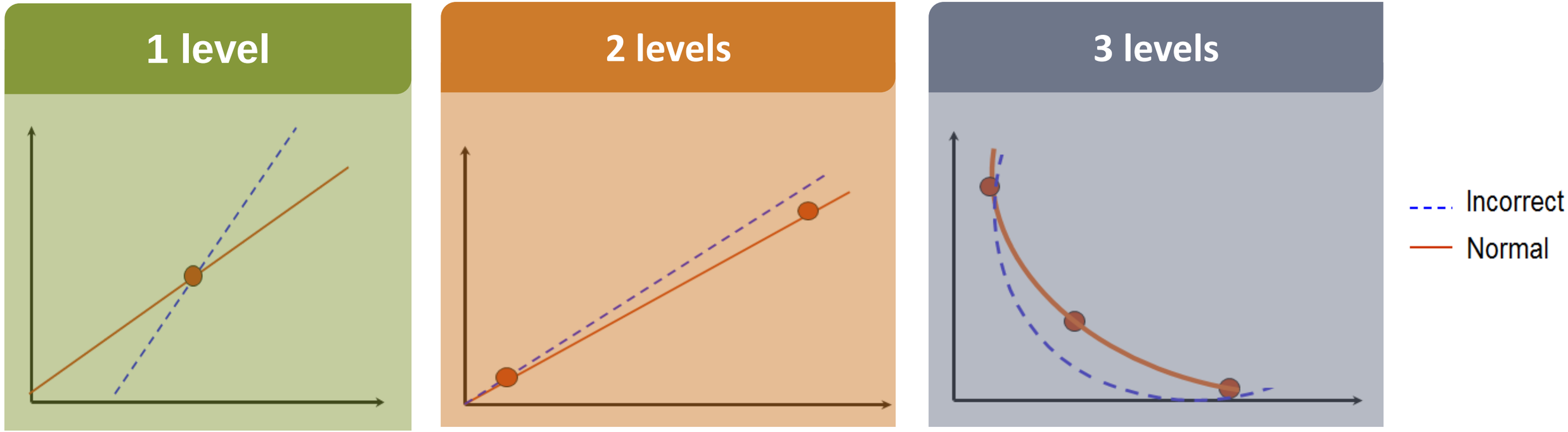
Risks of Instrument Manufacturer QC

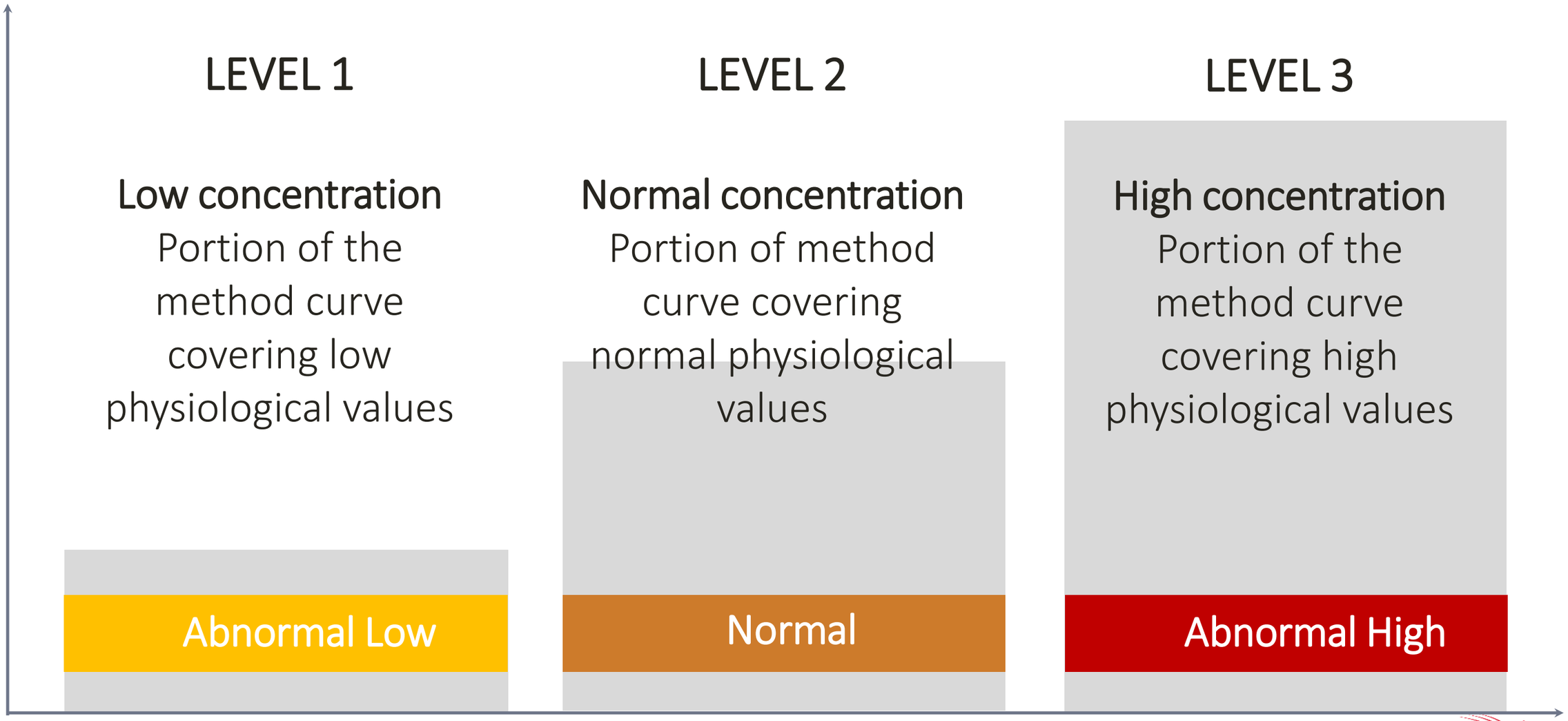
- How many quality control levels are provided and which concentrations are offered?
- Often 1 level only and not at important medical decision limits. No other options available.

How many QC levels should I use?

- 1 level can only check a very small part of the calibration curve (even if the QC looks fine there might be a problem with the method)
- 2 levels are good to check a linear calibration curve
- Multi-point calibrations often need 3 controls to cover the full measurement range



Concentrations near medical decision limits



Risks of Instrument Manufacturer QC

- A lot of manufacturer controls or in-kit controls are used for one or very few analytes
- The lab will have a lot of different control vials in use, creating a lot of manual work to set up a QC run

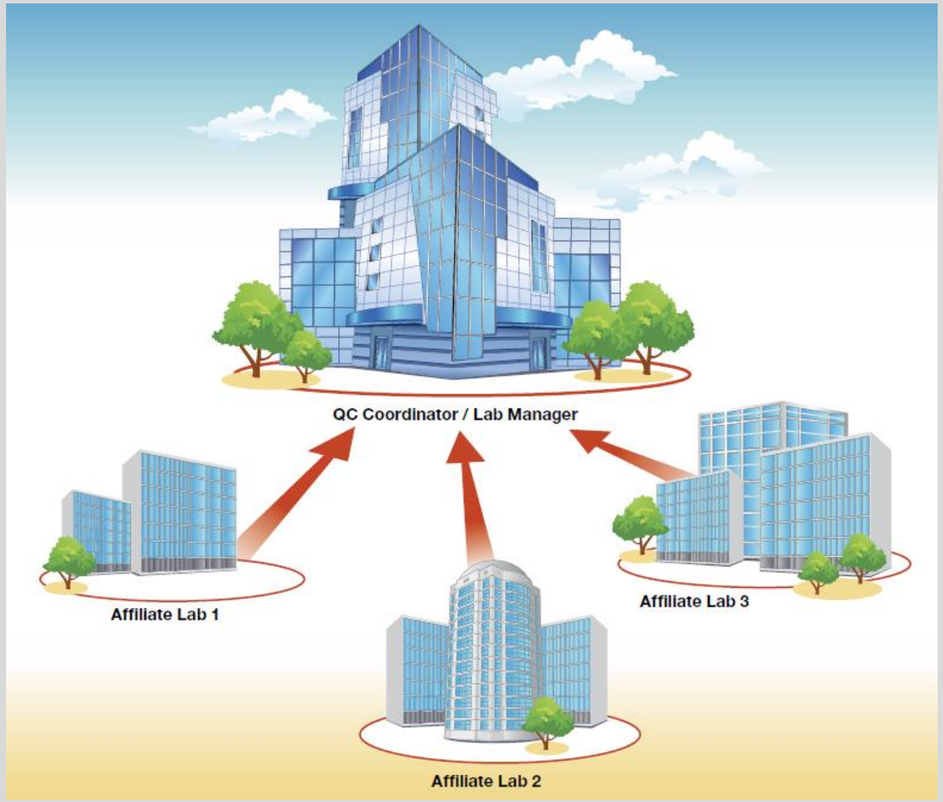
Consolidated QC with multiple analytes, which can be used across instruments, will reduce time and costs for the lab

Risks of Instrument Manufacturer QC

- When using multiple instruments from different manufacturers you can’t use one manufacturer or in-kit QC material
- Manufacturer controls are not validated for use on other platforms
- No possibility to really compare instrument performance due to these different materials

Risks of Instrument Manufacturer QC

- Labs within a group need a way to compare results across their sites
- Manufacturer's QC often can’t be used across different instruments and reagents



Comparison across laboratories

- Independent QC materials can be used across many instrument platforms

Glucose **Hexokinase** mg/dL

	Level	Mon	Cum	Level	Mon	Cum	Level	Mon	Cum
Mean	1	57.36	57.19	2	112.5	112.3	3	367.7	367.0
SD		1.10	1.27		1.64	1.65		5.74	6.52
CV		1.9	2.2		1.5	1.5		1.6	1.8
# Points		3164	13739		709	3173		3278	14334
# Labs		83	84		17	21		86	88
Mean	1	58.05	58.26	2	112.9	113.1	3	355.2	353.2
SD		1.39	1.45		1.52	2.13		8.32	28.03
CV		2.4	2.5		1.3	1.9		2.3	7.9
# Points		2089	10220		484	2656		2085	9874
# Labs		41	50		11	14		43	51
Mean	1	59.57	59.73	2	113.8	114.7	3	363.4	364.7
SD		1.43	1.34		3.95	2.58		7.79	7.89
CV		2.4	2.2		3.5	2.3		2.1	2.2
# Points		2888	14333		1188	6805		2885	14458
# Labs		75	79		20	25		75	79
Mean	1	59.20	59.41	2	116.0	116.1	3	358.7	359.9
SD		1.52	1.63		0.930	1.63		6.81	6.71
CV		2.6	2.7		0.8	1.4		1.9	1.9
# Points		2794	15089		21	169		2831	14933
# Labs		93	107		1	2		92	106
Mean	1	56.96	57.26	2	110.5	111.0	3	346.2	348.4
SD		1.53	1.54		2.60	2.66		7.43	7.77
CV		2.7	2.7		2.3	2.4		2.1	2.2
# Points		1880	8313		118	199		1806	8051
# Labs		53	55		2	2		52	55

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Other Features to Consider

- Interlaboratory comparison programs
  - Track performance and compare to peers

- QC management software
  - Access to specialized features and long-term storage

Independent QC providers expertise

- Manufacturer or in-kit QC is something which the manufacturer needs to provide to complement the kit
- Independent QC is made by quality control experts with many years of expertise

"For a truly independent assessment of the test system, it is very important to use controls that are not provided by the instrument manufacturer."

Carol Bartlett
QC Coordinator, USA

Case Study

Product Information on (September-10-2019)
→ New assay file, new reagent, new calibrator (6 point)

Immediately after starting the new calibrator:

- Third-Party QC results were low outside the lab range and peer group for two different lot numbers
  The two lots of independent control picked up the problem
- Manufacturer QC: all levels on a low side but within the range
  The manufacturer control did alert the lab of the problem
- Rerun Previous C.A.P survey (C-B 2019: 5 samples)
  One CAP sample was out and the other PT samples all had negative bias

Case Provided by A. Yagoot Supervisor Biochemistry Section M.N.G.H.A.
King Abdulaziz Medical City - Jeddah

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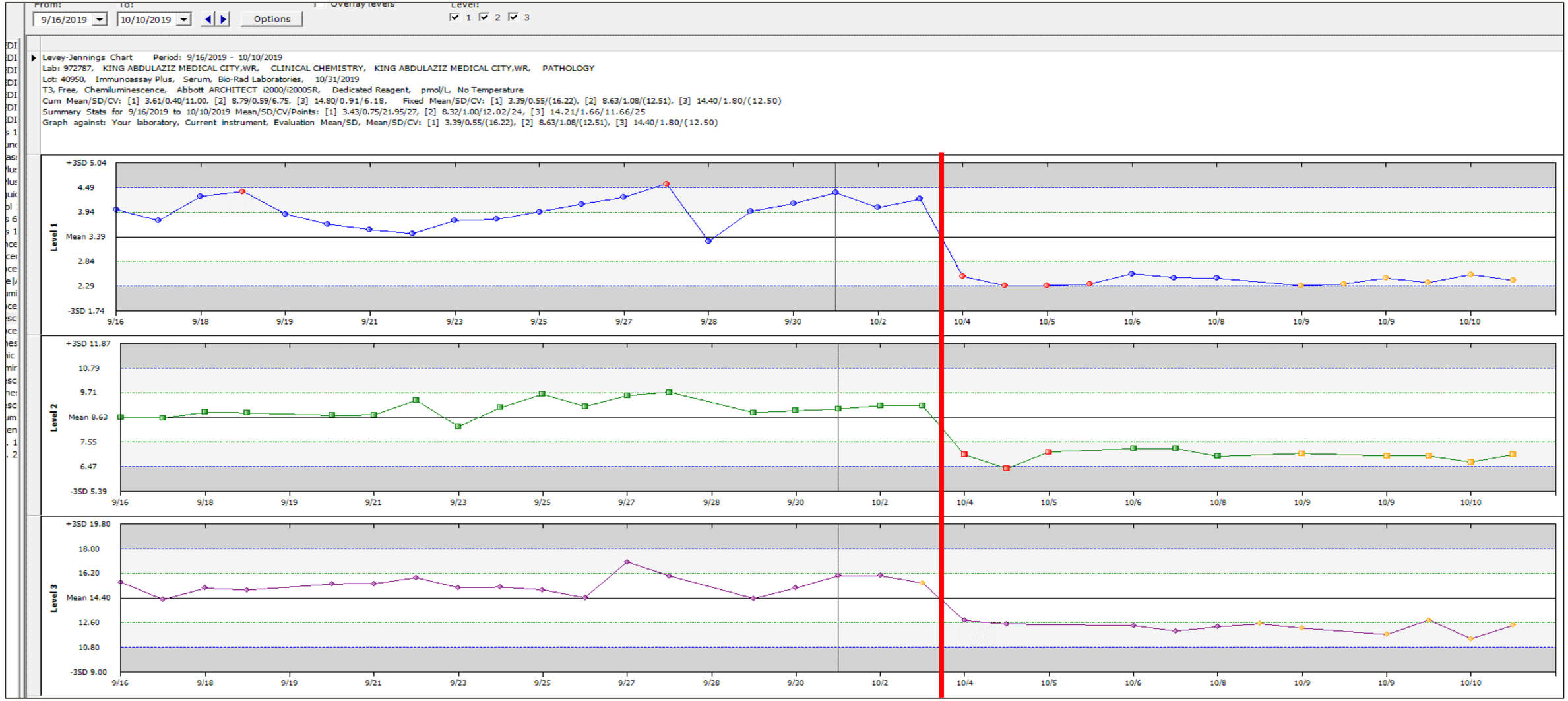
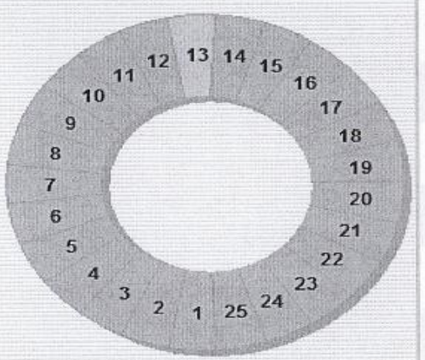
Case Study

QC detected the shift (red line) and rejected the incorrect QC results



Case Study

New calibrator material was received and after calibration the QC results returned to acceptable values



P	ASSAY	CAL STATUS	REMAINING TESTS	REAGENT STATUS
10	AFP_3	Active	81	OK
21	B-hCG STAT	Active	51	OK
9	CEA	Active	55	OK
6	CK-MB	Active	35	OK
16	Ferritin	Active	287	OK
7, 8	Folate II	Active	72	OK
18	Free PSA	Active	44	OK
5	FSH	Active	68	OK
13	FT3_6	Active	73	Disabled
22	FT4_6M	Active	478	OK

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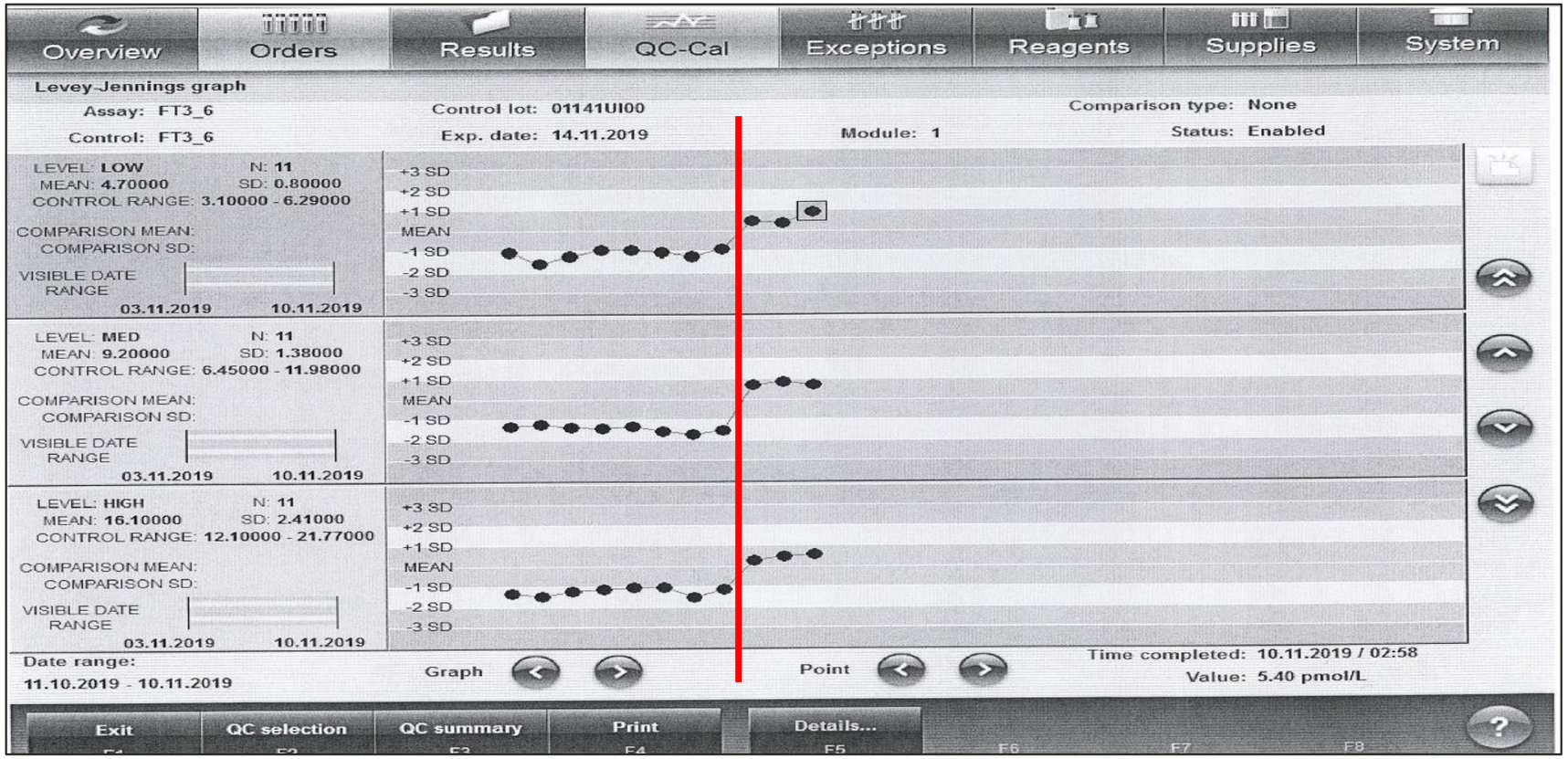

New calibration manufacturer QC was still within range before correction, but showed recovery

Case Provided by A. Yagoot Supervisor Biochemistry Section M.N.G.H.A. King Abdulaziz Medical City - Jeddah

What do the international regulations suggest?

Regulations

Regulatory requirements emphasize the need for using independent quality control materials

- While guidelines may vary, most regulatory organizations recognize that independent quality controls are an important part of an effective laboratory quality control system. There's a good reason these guidelines call for independent controls:
  - Instrument manufacturer controls are less sensitive to changes in device performance, and analytical errors could affect a patient sample which in turn may result in harm to the patient.

Regulations: ISO 15189

- **International Standard ISO 15189:2022** (Third Edition)
  Medical laboratories — Requirements for quality and competence

7.3.7.2 Internal quality control (IQC)

a3) The use **of third-party IQC material should be considered**, either as an alternative to, or in addition to, control material supplied by the reagent or instrument manufacturer

Guidelines: CLSI

- CLSI C24 (Fourth Edition) Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions

5.2.5 Relation to Calibrators

QC materials **should be different from the calibrator materials** to ensure that the QC results provide an **independent assessment** of the measurement procedure's performance in its entirety, including the procedure for calibration

Regulations: More local guidelines

NATA

"Controls independent of those produced by the manufacturer of the test or analyzer should be used. The laboratory must have a system of long-term monitoring of internal quality control results to assess method performance."

NATA (National Association of Testing Authorities) Australia, Interpretation of NPAAC Requirements and ISO 15189, Clause 5.6.2 Internal Quality Control, (ii) and (vi).

QCI

"Medical laboratories shall perform internal quality control. Use of third party human matrix quality control is recommended for all analytes."

Essential Standards for Registration of Medical Testing Laboratories in India, Quality Council of India 3.5.2 Quality Assurance.

Regulations: More local guidelines

Rilibak

"The control samples must be similar as possible to the patient samples being examined. Within the same measuring procedure the control and the calibration materials must not be identical.

Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations (Rili-BÄK). J Lab Med 2015; 31:26-69. Clause B1, 2.1.1 Procedure (5).

"If you work with manufacturer controls, you will miss a lot of analytical problems that may have an impact on patient results. Moreover, testing independent controls is a requirement of ISO 15189:2022."

J. M. Gras, MD | Clinique Saint-Luc | Bouge, Belgium

Summary

Manufacturer QC is often the first material received and used

Manufacturer QC has several risks identifying problems with test performance

Good laboratory practice and regulations suggest using independent QC as the preferred solution

Thank you