



# Inter-Laboratory Harmonization

Theory & Practice

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# DEFINITIONS USED

- **STANDARDIZATION** among laboratories includes the use of same platforms, methodologies, reagents and procedures.
- **HARMONIZATION** among laboratories is the ability to generate results that are statistically combinable without additional manipulation.
- **HARMONIZATION PROCESS (per CLSI)**: is a process of recognizing, understanding, and explaining differences while taking steps to achieve ... uniformity.



# BACKGROUND

## MY PAST EXPERIENCE

- Pharmaceutical research now outsources all clinical testing during studies.
- Lab data needs to be statistically combinable for clinical research purposes
- One single laboratory is ideal where sample shipment constraints will allow.
- However multiple laboratories are needed in practice.
- This makes inter-lab harmonization necessary

# GLOBAL LOCATIONS





# RELEVANCE TO HOSPITAL LABORATORY NETWORKS

- A parallel situation exists in hospital lab networks such as VIHA.
- Use of a single LIMS makes it impractical to support multiple reference intervals.
- Health Authorities in BC mandated to standardize their laboratory practices.
- There are many advantages.



# HOW TO GET THERE

- **STANDARDIZATION** is the first step to ensuring harmonization that can be progressively tightened.
  - Same platforms/analyzers
  - Same reagents - esp calibrators, QC material & EQA programs
  - Same lot # of reagents if possible
  - Same test protocols
- **HARMONIZATION** is introduced by ongoing monitoring of the EQA & QC data of the network & trouble-shooting out-of-specification instances.
- Acceptable harmonization can sometimes be achieved without standardization – more difficult – less benefit



# ADVANTAGES

## ■ Advantages of Standardization:

- Same SOPs & manuals at every lab site – one write
- Better reagent utilization (sharing, less expiry issues)
- Better pricing on analyzers and reagents
- Faster detection, diagnosis & resolution of problems



# ADVANTAGES

## ■ Advantages of Harmonization:

- Improved quality and patient care
- Follow individual patients across the network
- Measure outcomes across the network
- Clinical research within network, Int. & Ext.
- Statistical mining of data retrospectively
- Use of a central LIMS for all the laboratories



# STEPS OF THE PROCESS

- Comparative listing of analyzers (template).
- Replacement / new analyzers should be from same manufacturer & same model if possible.
- Use the same SOP for the same assay method at every laboratory site performing the assay.
- Move to standardization of future reagent procurement including same lot #s
- Move to using the same EQA & QC programs
- Monitor harmonization with EQA & QC data



# IMPORTANT MILESTONES

- **Form a Harmonization Group – all labs represented**
  - Include QC Techs, Lab Mgrs and Lab Physicians - critical
- **Develop consensus on platforms & methods**
- **Develop common SOPs**
  - For assay methods
  - For introduction of new QC lots (Calibrators as well if poss)
  - For maintenance, calibration & QC actions
  - For Trouble-shooting
- **Develop consensus on quality monitoring activities**
  - Common QC & EQA programs
  - Certification by centers of excellence
  - Sample exchange if necessary
- **Regularly meetings (TCs) to review monitoring results.**





# QC STANDARDIZATION

## E.g for Clinical Chemistry

- ❑ Agree on future QC material vendor & program
- ❑ Determine current lab practices & expiry dates
- ❑ Involve as many labs as possible initially
- ❑ All start workup at same time per same SOP after recalibration & maintenance up to date
- ❑ Collect & record all workup data: set points & SDs
- ❑ Establish a single network SD for each analyte
- ❑ All start using QC material on same date
- ❑ Collect & record QC means & SDs / analyte / month

# SODIUM QC DATA

	Setpoint
LAB 1	150.3
LAB 2	1.2
LAB 3	150.3
LAB 4	1.2
LAB 5	151.8
LAB 6	1.1
LAB 7	151.7
LAB 8	1.1
LAB 9	151.8
LAB 10	1.0
LAB 11	153.3
LAB 12	0.7
LAB 13	152.0
LAB 14	1.5
LAB 15	155.0
LAB 16	1.9
LAB 17	155.0
LAB 18	1.1
LAB 19	153.0
LAB 20	2.8
LAB 21	155.5
LAB 22	1.6
LAB 23	155.5
LAB 24	0.7
LAB 25	152.4
LAB 26	1.1
LAB 27	151.6
LAB 28	0.8
LAB 29	152.0
LAB 30	2.5
LAB 31	152.4
LAB 32	0.7
LAB 33	150.0
LAB 34	1.4
Total mean	152.6

# SODIUM QC DATA

	Setpoint	Sep-07	Oct-07	Nov-07	Dec-07	Jan-08	Feb-08	Mar-08	Apr-08	May-08
LAB 1	150.3	149.9	149.8	150.3	150.2	150.8	150.7	150.8	151.0	150.5
LAB 2	1.2	0.7	0.8	0.6	0.7	0.6	1.2	1.1	1.3	1.4
LAB 3	150.3	150.0	150.0	152.0	149.5	148.7	149.0	147.8	146.3	149.0
LAB 4	1.2	0.8	0.0	0.7	0.8	2.9	0.9	1.5	0.0	0.0
LAB 5	151.8			151.7	151.7	151.6	151.6	151.5	151.4	151.4
LAB 6	1.1			0.9	0.9	0.9	0.9	0.7	0.7	0.7
LAB 7	151.7			151.7	151.6	151.5	151.4	151.1	151.2	151.2
LAB 8	1.1			1.0	0.9	0.9	0.9	1.4	1.4	1.4
LAB 9	151.8	151.8	151.7	152.4	152.5	150.9	152.6	153.8	153.6	153.8
LAB 10	1.0	1.0	0.9	0.9	0.9	2.4	1.1	1.2	0.8	0.8
LAB 11	153.3			153.3	152.8	152.3	152.2	152.2	152.4	152.6
LAB 12	0.7			0.7	0.9	1.0	1.0	0.9	1.0	0.8
LAB 13	152.0			153.0	153.0	153.0	152.0	151.5	153.0	153.0
LAB 14	1.5			1.0	1.0	1.5	1.7	1.5	1.5	1.2
LAB 15	155.0			152.1	151.5	151.6	151.9	151.7	152.1	152.1
LAB 16	1.9			0.9	1.3	1.2	0.9	1.3	1.3	0.8
LAB 17	155.0			155.0	153.5	153.0	153.1	152.6	153.2	153.0
LAB 18	1.1			1.1	0.8	0.7	0.7	0.8	0.8	0.9
LAB 19	153.0			154.0	152.0	150.0	152.0	152.0	153.0	152.0
LAB 20	2.8			3.2	1.8	3.1	3.0	5.6	6.2	1.3
LAB 21	155.5					154.6	154.8	154.7	154.7	155.1
LAB 22	1.6					1.1	1.6	1.1	1.6	1.0
LAB 23	155.5								155.5	153.1
LAB 24	0.7								2.8	1.4
LAB 25	152.4	152.0	152.0	154.0	154.0	152.0	152.2	152.7	155.2	152.0
LAB 26	1.1	2.6	1.1	6.3	1.1	2.9	3.3	1.8	11.8	1.5
LAB 27	151.6	152.6	151.9	152.0	152.1	152.2	152.2	152.1	153.0	153.0
LAB 28	0.8	0.6	0.6	0.7	0.7	0.7	0.5	0.6	0.6	0.6
LAB 29	152.0				152.5		152.7	152.4	152.4	151.4
LAB 30	2.5				3.0		1.7	2.0	1.9	2.5
LAB 31	152.4			153.2	153.8	153.1	152.4	152.6	153.0	
LAB 32	0.7			1.1	1.5	0.8	0.8	0.8	0.7	
LAB 33	150.0								152.4	152.2
LAB 34	1.4								0.8	0.7
Total mean	152.6	151.3	151.1	152.7	152.2	151.8	152.1	152.0	152.6	152.2







# EQA STANDARDIZATION

## E.g. Clinical Chemistry

- Agree on future EQA material vendor/program
- Determine current lab practices & end of cycle dates
- Involve as many labs as possible initially
- Start submitting EQA data as soon as possible
- Collect all EQA reports centrally & summarize
- Establish network 'method group' for each analyte
- Monitor EQA results & SDIs or ALPs for each analyte per lab. (Allowable Limits of Performance)



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# SODIUM EQA DATA

SODIUM	mmol/L												
Sample	1	2	3	4	5	6	7	8	9	10	11	12	Mean
Lab 1	162.0	133.0	120.0	151.0	132.0	123.0	150.0	164.0	122.0				139.7
Lab 2	167.0	134.0	128.0	156.0	136.0	126.0	155.0	168.0	126.0				144.0
Lab 3	166.0	136.0	125.0	149.0	134.0	124.0	153.0	163.0	124.0				141.6
Lab 4	165.0	136.0	118.0	156.0	135.0	126.0	151.0	165.0	125.0				141.9
Lab 5	164.0	139.0	127.0	152.0	136.0	125.0	152.0	163.0	127.0				142.8
Lab 6	162.0	136.0	123.0	150.0	135.0	125.0	150.0	164.0	124.0				141.0
Lab 7	160.0	134.0	125.0	150.0	135.0	123.0	153.0	164.0	124.0				140.9
Lab 8	164.0	136.0	125.0	152.0	136.0	124.0	151.0	163.0	125.0				141.8
Lab 9	165.0	134.0	125.0	149.0	133.0	126.0	149.0	162.0	124.0				140.8
Lab 10	162.0	137.0	121.0	153.0	137.0	126.0	151.0	162.0	125.0				141.6
Lab 11	164.0	136.0	125.0	153.0	136.0	125.0	152.0	165.0	129.0				142.8
Lab 12	163.0	135.0	123.0	151.0	134.0	124.0	149.0	165.0	126.0				141.1
Lab 13	163.0	135.0	127.0	153.0	137.0	127.0	152.0	162.0	127.0				142.6
Lab 14	163.0	134.0	124.0	150.0	131.0	123.0	151.0	164.0	128.0				140.9
VIHA mean	163.6	135.4	124.0	151.8	134.8	124.8	151.4	163.9	125.4				141.7
Method Mean	163.6	135.0	124.4	151.9	135.2	124.6	151.2	163.0	124.7	152.0	135.6	163.3	143.7
Method SD	2.5	1.8	2.3	2.5	1.9	1.5	2.0	2.1	1.6	1.8	2.3	1.9	2.0
ALP/2	2.5	1.8	2.3	2.5	1.9	1.5	2.0	2.1	1.6	1.8	2.3	1.9	
Bias	+2SD					VIHA	+3.0 mmol/L (RCPA)						
Lab 1	-0.6	-1.1	-1.9	-0.4	-1.7	-1.1	-0.6	0.5	-1.7				-1.0
Lab 2	1.3	-0.6	1.6	1.7	0.4	0.9	1.9	2.4	0.8				1.2
Lab 3	0.9	0.6	0.3	-1.2	-0.6	-0.4	0.9	0.0	-0.4				0.0
Lab 4	0.6	0.6	-2.8	1.7	-0.1	0.9	-0.1	1.0	0.2				0.2
Lab 5	0.2	2.2	1.1	0.0	0.4	0.3	0.4	0.0	1.4				0.7
Lab 6	-0.6	0.6	-0.6	-0.8	-0.1	0.3	-0.6	0.5	-0.4				-0.2
Lab 7	-1.4	-0.6	0.3	-0.8	-0.1	-1.1	0.9	0.5	-0.4				-0.3
Lab 8	0.2	0.6	0.3	0.0	0.4	-0.4	-0.1	0.0	0.2				0.1
Lab 9	0.6	-0.6	0.3	-1.2	-1.1	0.9	-1.1	-0.5	-0.4				-0.3
Lab 10	-0.6	1.1	-1.5	0.4	0.9	0.9	-0.1	-0.5	0.2				0.1
Lab 11	0.2	0.6	0.3	0.4	0.4	0.3	0.4	1.0	2.7				0.7
Lab 12	-0.2	0.0	-0.6	-0.4	-0.6	-0.4	-1.1	1.0	0.8				-0.2
Lab 13	-0.2	0.0	1.1	0.4	0.9	1.6	0.4	-0.5	1.4				0.6
Lab 14	-0.2	-0.6	-0.2	-0.8	-2.2	-1.6	-0.2	1.0	2.1				-0.3
Network	0.0	0.4	-0.4	-0.1	-0.4	0.2	0.2	0.9	0.7	#VALUE!	#VALUE!	#VALUE!	

# EQA SDI SUMMARY

	CALCIUM TOT										
Lab 1											
Lab 2											
Lab 3											
Lab 4											
Lab 5											
Lab 6			-3.3		-2.1						
Lab 7											
Lab 8											
Lab 9		-2.5			-2.4						
Lab 10											
Lab 11											
Lab 12											
Lab 13											
Lab 14											

	MAGNESIUM										
Lab 1											
Lab 2											
Lab 3											
Lab 4											
Lab 5											
Lab 6											
Lab 7											
Lab 8							2.1				
Lab 9											
Lab 10											
Lab 11											
Lab 12											
Lab 13											
Lab 14											

	POTASSIUM										
Lab 1											
Lab 2											
Lab 3											
Lab 4											
Lab 5											
Lab 6											
Lab 7											
Lab 8											
Lab 9											
Lab 10											
Lab 11											
Lab 12											
Lab 13											
Lab 14											

	SODIUM										
Lab 1											
Lab 2								2.4			
Lab 3											
Lab 4											
Lab 5											
Lab 6											
Lab 7											
Lab 8											
Lab 9											
Lab 10											
Lab 11										2.7	
Lab 12											
Lab 13											
Lab 14						2.2				2.1	



# SPECIAL ASSAYS

- Certification with international / recognized bodies:
  - HbA1c certification – NGSP
  - Lipid certification – CDC, DigitalPT etc
  - Creatinine and eGFR certification – DigitalPT
- Laboratories with such a certification are harmonized with each other for the assay



# HARMONIZATION SOPS

## SOPs, e.g.:

- Introduction of new reagent, calibrator or QC lots
- Generation and submission of QC & EQA data
- Collection, display and circulation of QC & EQA data
- Regular joint review process for all laboratories
- Steps for trouble-shooting out-of-spec results
- End of Cycle reporting format & actions



# CAVEATS & OBSTACLES

- Same vendor can employ differing methods across their analyzer range
- Same method reagents can vary lot-to-lot
- DAP reporting rules and use of modified acceptability criteria or different method means may be an issue



# TAKE HOME MESSAGES

- Standardization can cut costs and is usually the first step to Harmonization
- Harmonization results in better patient care, quality and usefulness of data
- Needed:
  - A group with representation from every lab
  - Involvement of management & decision makers
  - Group consensus
  - Same SOPs
  - Regular joint-review of EQA & QC data



THANK YOU