ISPE

QUESTIONS FOR YOUR SOFTWARE VENDOR:

TO ASK BEFORE YOUR AUDIT

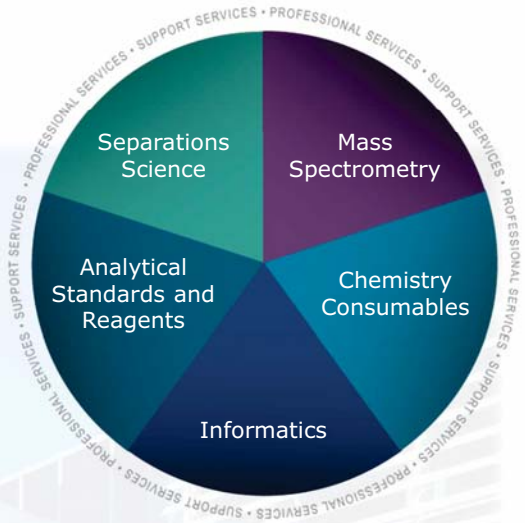
Heather Longden
Senior Marketing Manager
Waters Corporation

Boston Chapter Educational Meeting
June 2016

About Waters Lab Informatics

Empower™ 3

NuGenesis® LAB MANAGEMENT SYSTEM



Informatics development and service centers

Milford, MA, USA
Manchester, UK
Frechen, Germany
Brasov, Romania

>550 employees focused on Informatics

Installed Base

> 4,000 Empower networks installed worldwide

> 400,000 Empower licenses

- > 10 languages
- > All Top Pharma uses Empower
- > Wide global skill base

> 50,000 NuGenesis licenses

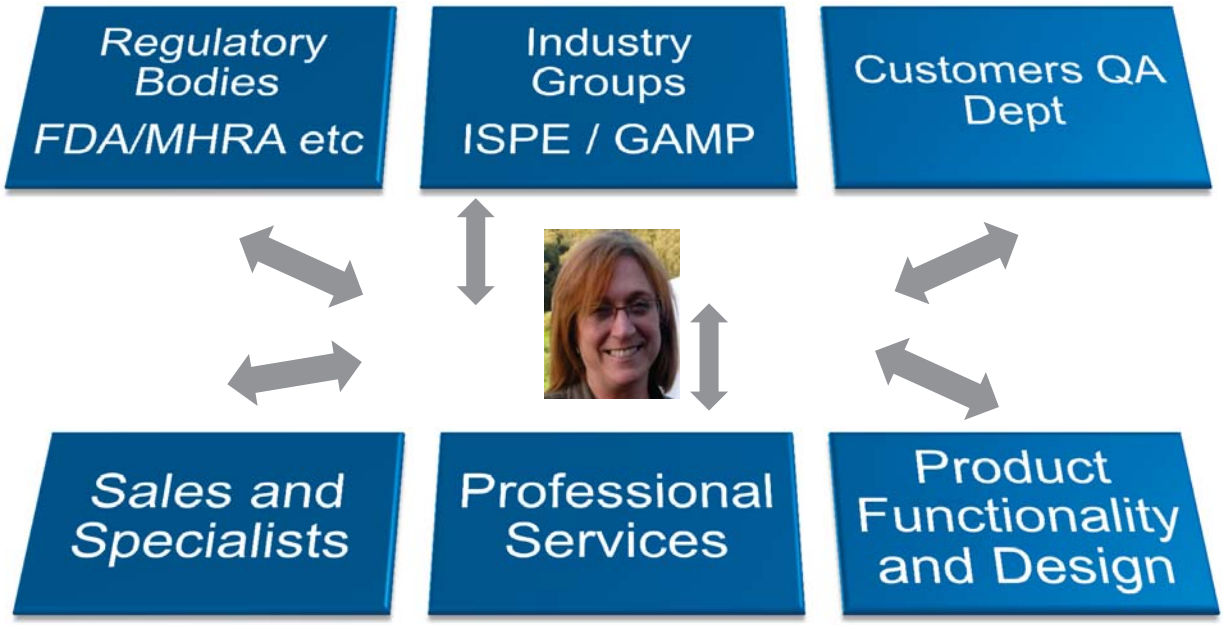
MassLynx™

Paradigm™ SCIENTIFIC SEARCH

Progenesis® QI

UNIFI™ SCIENTIFIC INFORMATION SYSTEM

Gathering & Sharing Regulatory Information



What do I have to do? and Training

"I need you to tell me what is the minimum I have to do to meet my regulatory requirements"

"Can you send SOPs on how to use this equipment?"

"Can you train users on how to use those SOPs?"

"Can you train QA on how they should review my data?"

Computerized System Validation

"Please send me a user requirement specification for this computerized system?"

"Where is my validation certificate?"

"If you've tested the software, why do I have to do it?"

"You qualified the equipment, isn't that enough?"

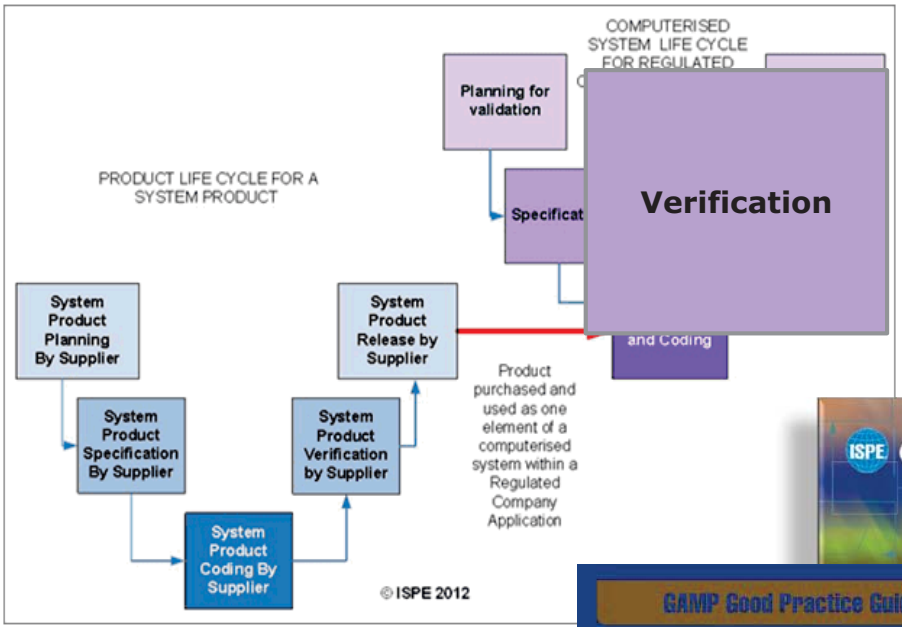
"How can I prove the numbers/ calculations are right?"

"I need copies of all your test cases..."

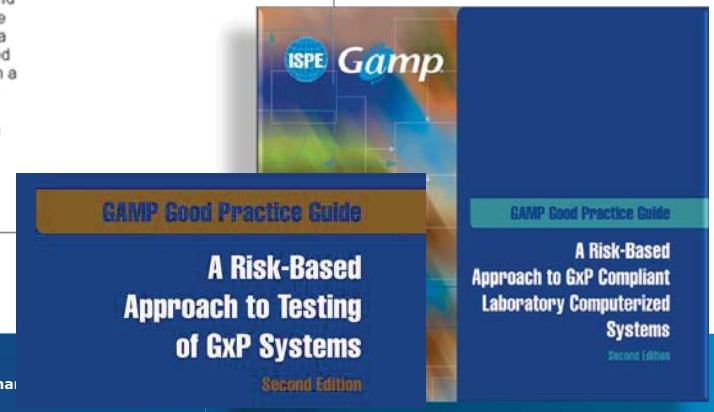
"I'm not sure I if I should trust the vendor testing, so I'm going to test every function and button just in case…"

GAMP Good Practice Guides

Leveraging work already done in the suppliers product lifecycle



- **Vendor Instrument and Software Qualification**
- **Vendor Verification Testing**
- **3rd Party Testing**
- **User Acceptance Testing**



Technical Controls

"Is your software compliant?"

> Does your software have all the technical controls to meet part 11?

> Why wasn't it configured to work correctly in my regulated environment?

"Is it OK if we share one user account so I don't have to buy more licences?"

"Do you have an audit trail in your software?"

> If there is one... why should look at it all the time?

"Why do I have to enter a reason/comment every time?"

Leveraging Vendor Testing

- **Supplier Assessment**
- **Regulatory FAQs**
- **Release Acceptance Tests: Test Summaries**

> Unlikely to have access to actual Test Documents, except in a live audit under NDA

> Compare to EU Annex 11 requirement to share 3rd party supplier assessment documentation

> Consider sharing the overall assessment report

- **ISO /Lloyds certificates**
- **Examples of your own escalation and resolution through your vendor**

Technical Controls

Does your software have…

- **Part 11 compliance?**
- **Audit trail?**
- **Backup and restore?**

"Yes …but…"

> Can you explain and show that you understand and have "challenged" these technical controls?

> Have you configured, tested and locked configurations to match your SOPs?

– (passwords on a sticky note… backup that happen sporadically or were not tested)

Data Review

How should I review my data: the good the bad and the audit trail?

- **Audit trails are MORE than simply the tables of changes**
- **Includes records and artifacts created along the way**
- **See guidance definitions**

eg *audit trails may include discrete event logs, history files, database queries or reports*

How does the software record that I reviewed all the data I should?

- **Unlikely to track /audit trail "opening and looking at screens"**
- **From WHO:**
  data review should be documented.
  For electronic records, this is typically signified by electronically signing the electronic data set that has been reviewed and approved.

Data Integrity Guidances

United States Food & Drug Administration

Medicines & Healthcare Products Regulatory Agency (UK)

Level 2 Guidance
on www.fda.gov, 2012
Updated in 2015

Data Integrity and Compliance with CGMP Guidance for Industry
DRAFT April 2016

GMP Data Integrity Definitions and Guidance for Industry
March 2015

Guidance on Good Data and Record Management Practices
DRAFT September 2015

Guidance on Good Data and Record Management Practices
Released JUNE 2015
As WHO_TRS_996
Annex 5

MHRA updated guidance on Data Integrity: Primary Records

The effort and resource assigned to data governance should be commensurate with the risk to product quality, and should also be balanced with other quality assurance resource demands.

As such, manufacturers and analytical laboratories are not expected to implement a forensic approach to data checking on a routine basis, but instead design and operate a system which provides an acceptable state of control based on the data integrity risk, and which is fully documented with supporting rationale.

WHO TRS_996_Annex 5

A risk-based approach to reviewing data requires process understanding and knowledge of the key quality risks in the given process that may impact patient, product, compliance and the overall accuracy, consistency and reliability of GxP decision-making

When original records are electronic, a risk-based approach to reviewing original electronic data also requires understanding of the computerized system, the data and metadata and data flows.

WHO TRS_996_Annex 5

Quality assurance should also review a sample of relevant audit trails, raw data and metadata as part of self-inspection to ensure ongoing compliance with the data governance policy/procedures.

In the hybrid approach, which is not the preferred approach, paper printouts (or PDFs) of original electronic records from computerized systems may be useful as summary reports if the requirements for original electronic records are also met.

To rely upon these printed summaries of results for future decision-making, ***a second person would review the original electronic data and any relevant metadata such as audit trails, to verify that the printed summary is representative of all results.***

This verification would then be documented and the printout could be used for subsequent decision-making.

FDA Question 7: How often should audit trails be reviewed?

..reviewed with each record and before final approval of the record.

BUT: does not apply to all audit trails??

include, but are not limited to, the following:

- *the change history of finished product test results,*
- *changes to sample run sequences,*
- *changes to sample identification,*
- *changes to critical process parameters. (not "processing" parameters)*

routine scheduled audit trail review based on the complexity of the system and its intended use.

Question 8: By WHOM?

Personnel responsible for Record Review

Data Review

How should I review my data: the good the bad and the audit trail?

How does the software record that I reviewed all the data I should?

Print Audit Trails	Review Audit Trails Electronically
Include data relevant audit trails in regular reports	Use the tools (if any) built into the software
Periodically print out System wide audit trail reports to "review"	Review as PART of the data/integration /method review
Sign reports as "evidence" of review	Write a clear SOP defining which audit trails to review and when
	Only flagged or suspicious results?
	Signing results includes declaration of electronic review

Monitoring User Behaviour

Does the audit trail capture..

- How you made up the reagents?
- How you set up the instrument?
- How the system equilibrated?
- Other things that analysts do?

How can I stop users running practice analyses?

Can't your software stop a user

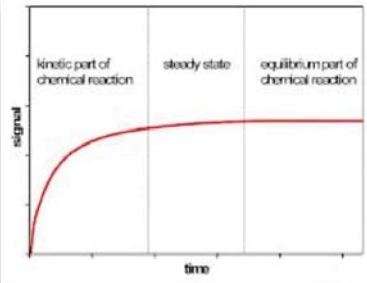
a) using single injections?

b) repeating same sample again under a different name?

How can I change the analytical method so that the samples pass?

Acquiring Chromatography Samples: SOP

Test Injections: System Readiness checks



- Never Samples, Possibly Stds
- Preferably an independent solution which mimics real samples
  - Pooled samples?
- Never delete them but not normal to include in reports
- Individual Injections or Sample Sets?

System Suitability: As part of the Sample Set/Result Set

- Built in validated Equilibrate step
- If System Suitability fails… or “just” passes
  - should you continue the run?
  - Or repeat from the beginning with justification

Monitoring User Behaviour: Chromatographic Integration

How do I integrate chromatograms so the samples pass?

Can't your software stop a user

a) changing the processing parameters?

b) integrating chromatograms more than once?

c) doing manual integration because that is a crime?

Is it realistic to expect perfect integration of peaks first time every time?

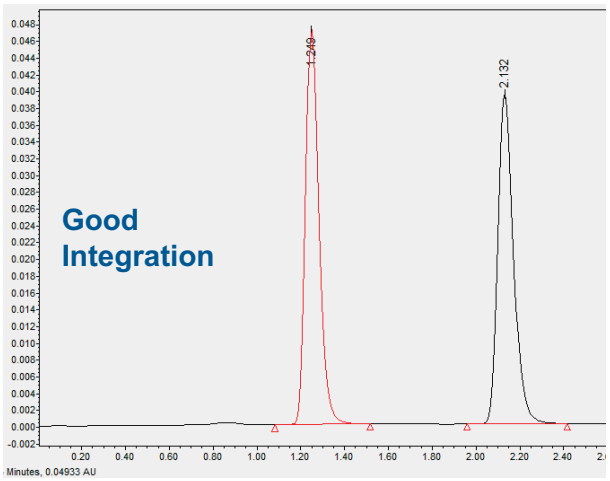
> NO!

Is Manual integration allowed?

> Is it ? In your lab? When? How you know if it has been done? How do you review it?

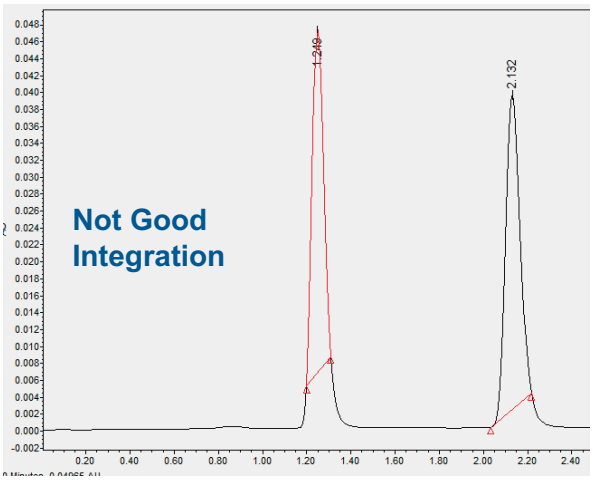
What Integration is Better?

Pass



Manual

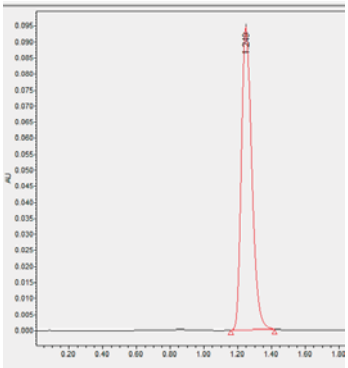
Fail



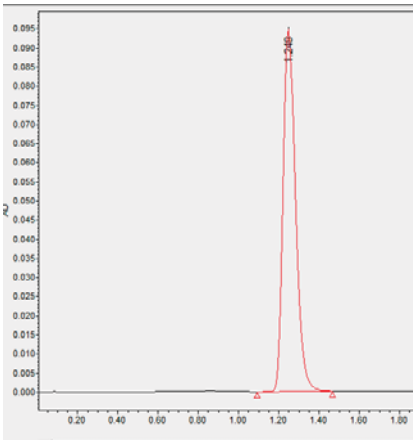
Processing Method

Manual integration isn't always bad and you can still use processing methods to manipulate integration

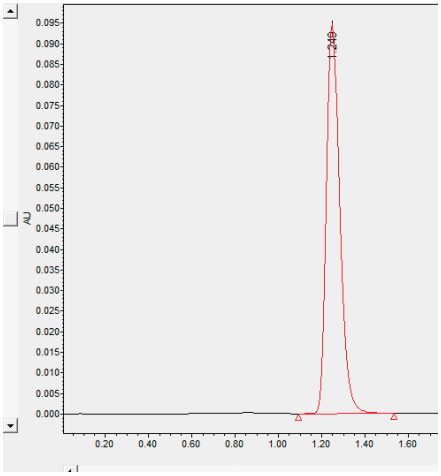
The history of integration is important



Version 1
Fail Criteria



Version 2
Fail Criteria



Version 3
Pass Criteria

Monitoring User Behaviour

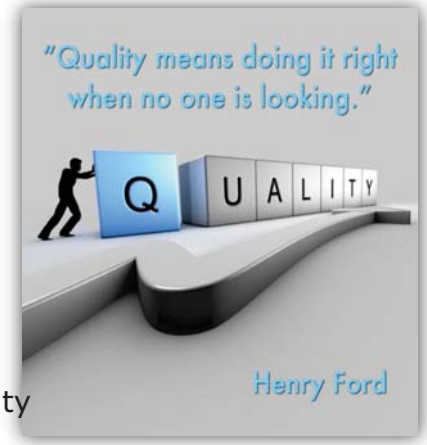
How can I make sure that analysts never make mistakes?

or if they do... that they don't try to hide them.

How can I hide bad data from my QA group?

How can I hide test/trial analyses or results from QA or regulators?

Culture of Compliance



Culture of Quality

Cultural Approaches to Test Failures?

I can't tell manufacturing they messed up

I don't make mistakes

I'll be fired if I admit my mistakes

It's probably my fault, I'd better change it

Manufacturing Error

Instrument Error

Software Error

Analyst Error

SOP Error

Quality Error

I have no time to do an OOS investigation

It was only a small mistake, I can easily correct it

I'll just write that out again

No one will notice if I'm clever

It's only a signature date

Management Culture

Throwing People into the Works : Charlie Wakeham (Waters Asia) and Thomas Haag (Novartis)

Human error can disrupt even the best planned and implemented IT system.

Implementing a Corporate Data Integrity Program : Mike Rutherford (Eli Lilly)

A well designed strategy is the cornerstone of any Data Integrity program

An Ounce of Prevention: Charlie Wakeham (Waters Asia) and Thomas Haag (Novartis)

The administrative and technical controls to mitigate risks to data integrity....

How Good Is Your Data? : Peter Boogaard (Industrial Lab Automation)

New methods can increase Data Integrity in your lab

Introducing the concept of "Data Stewards"

Big Brother Is Watching: Charlie Wakeham (Waters Asia) and Thomas Haag (Novartis)

Reinforce "right behaviour" with ongoing training and monitor effectiveness with Review Processes

Doing the Right Thing: Charlie Wakeham (Waters Asia) and Thomas Haag (Novartis)

Tools and Techniques encourage positive responses

A Special Interest Group (SIG) for Data Integrity: Mike Rutherford (Eli Lilly)

Rewarding the right behaviour

Company Culture is Important

It is important to find a balance between compliance and business goals because both are important

Don't inadvertently tempt individuals to try and avoid compliance because the compliant path is hard and complex

Help me Deal with Regulators

Can you please speak to this investigator and explain how this works?

Could you tell the auditor why we do it this way?

Can you write a response to this 483 observation we just received?

Can you guarantee I wont get any 483 observations in my next audit?

Please tell the FDA how this software works?

Please would you NOT tell the FDA how this software works?

Why you should not invite /demand your vendor takes part in your inspection

Vendors do not know your product, procedures or SOPs

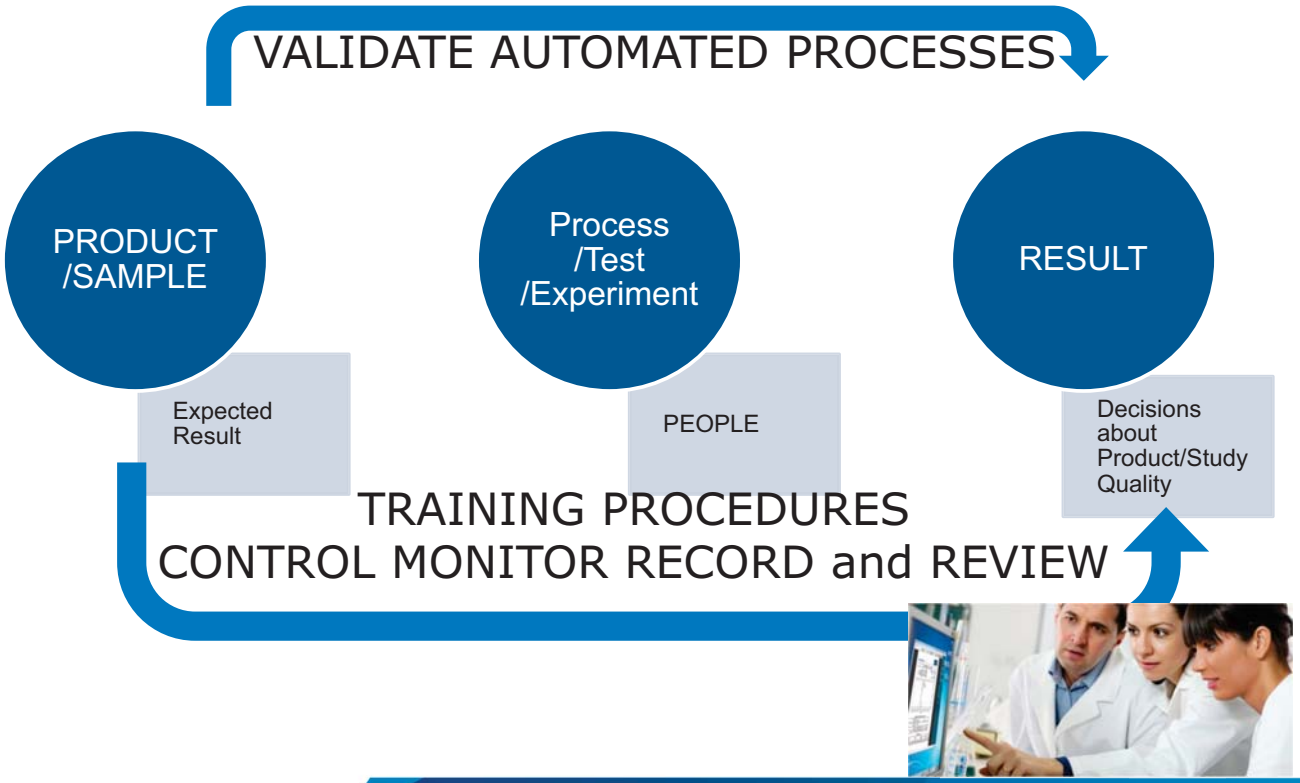
Vendors have not been trained in how to participate in audits at your company

Customers use the same software in different ways, may connect to LIMS or ELNs in unknown ways.

Calling the vendor indicates you do not know your equipment /tools

It could be very easy for your vendor to say something contrary to your procedures

Addressing Technical and Procedural Controls



THANK YOU!

HEATHER LONGDEN

SNR MANAGER INFORMATICS AND REGULATORY COMPLIANCE

1 508 244 7097

HEATHER_LONGDEN@WATERS.COM