RISK MANAGEMENT IN PRACTICE:
Ten Lessons From The Trenches

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Agenda

– Quality risk management at 15
  How did we get here
– Ten lessons from the trenches
  Stories from wilds of pharma
– Where do we go from here
  Lessons learned
RISK MANAGEMENT IN PRACTICE

QUALITY RISK MANAGEMENT AT 15

HOW DID WE GET HERE
Risk Management at 15 - How did we get here?

The Old Paradigm

– Qualify everything

– If in doubt, qualify it – if it moves, qualify it

– Success is judged by the weight of the qualification reports

Risk Management at 15 - How did we get here?

The New Paradigm

– Use risk management (QRM)

– Identify the few critical items

– Qualify the hell out of these
Risk Management at 15 - How did we get here?

The Guidances

- ISPE
- ICH Q9
- ASTM E2500
- PDA

Guidances

ISPE - March 2001

Baseline Guide – Volume 5

Commissioning and Qualification
Guidances

ISPE - March 2005

White Paper
Risk-Based Qualification

Guidances

ICH Q9 – June 2006

Quality Risk Management
Guidances

ASTM E2500 (2007)

Industry Consensus Standard

Specification, Design and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

Guidances

ISPE - October 2011

Good Practice Guide

Applied Risk Management for Commissioning and Qualification
Guidances


Implementation of Quality Risk Management

Guidance


Quality Risk Management for the Design, Qualification and Operation of Manufacturing Systems
RISK MANAGEMENT IN PRACTICE

TEN LESSONS FROM THE TRENCHES

THE WAR STORIES
Front Load the Project

Late Risk Assessment

A risk assessment after you have built the plant – becomes a box checking exercise

We have to do it (the SOP says so)
We have to justify what we built (changing costs too much)

Tends to be a waste of time, money and resources

Front Load the Project

Early Risk Assessment

Great way to identify issues when they can still be fixed

Put off because resource intensive
Front Load the Project – the excuses

“…We don’t know if the project is going to be funded …just do a conceptual study with a couple of guys…”

“…risk assessments are too expensive and take too many people…let’s wait until we see if the project is going to fly..”

“…the manufacturing team is busy, just take the system from the other plant and write a URS for that…."

Front Load the Project

My first RPN of 1000 from a QRM Risk Assessment

RPN = severity x occurrence x detection

Risk assessment done just prior to process validation

Product had been in the clinic for seven years
Front Load the Project

Harvest of solid product involved cutting of plastic film

- particulates generated every batch – high frequency
- final product was an injectable – particulates high severity
- plastic particulates in a powder – low detectability

Fix – done in a panic
- expensive
- potential to delay filing

Severity Inflation

Is this risk a 4 or a 6 severity score?

- No one is every criticized for being too conservative

So if that risk is a 6 severity, then this next risk must be an 8 severity!

We want to be consistent in our scoring

And before you know it:

- Not following an SOP is an equivalent risk to a product recall
Severity Inflation

This would be amusing except that the results drive real activity with real impact on schedule, money and resources

Drives the focus to the wrong areas

If the URS is the only tool we have ..... 

“No one is paying attention to safety, so we’ll just hold the URS hostage”

“…shall fully comply with 21CFR211 & 212…”

“…will fully comply with OSHA Part 1910 …”

“…shall be easily cleanable…”

Think on how these could actually be tested ! ?
If the URS is the only tool we have ..... 

“...can be easily maintained...”
“...will comfortably fit in the manufacturing space...”
“...will ship 2 weeks after P.O....” 
“...payment will be net 90 days....”

If the URS is the only tool we have ....

**URS Guidelines**

KISS (keep it simple ...)

Think how you would test the requirement

If its not testable, it’s shouldn’t be there

Is this a wish, or a requirement?

If you would accept the equipment without ... it’s a wish

Once again ... KISS
Not All Important Things Are Critical

Typical process
Between equipment and process, there are hundreds of variables
Most are kept in tight control
Most have a wide proven acceptable range
Few vary enough to be critical to the process quality
These deserve our close attention
**Not All Important Things Are Critical**

Most things, if they go wrong enough will adversely effect product quality

Misunderstanding the nature of “critical”

Endless debate on critical versus non-critical

Focus on what actually drives variation in product quality

“If every thing is critical, you’re saying that nothing is critical”

**Automation / Alarms as Crutches**

The reality of risk assessments

Humans are the biggest source of risk (occurrence)

Human observation is often limited (detection)

Humans - often limiting factor to reducing RPN score

Only way to reduce is to automate or alarm
Automation / Alarms as Crutches

Automation

Reduce risk - making manual operation, a complex automation?

Is there a complexity risk that we are not good at quantifying?

Limited flexibility --- resistant to change

Alarms

Issues with alarm prioritization especially as complexity increases

Operators overwhelmed with false alarms and miss key ones

False alarms can become a compliance nightmare
The Curse of SOPs

The curse of standard operating procedures for non-standard things
... like projects

Very hard to write a good SOP

Even for a well understood and defined procedure

Many procedures not well defined

Hard to predict and encompass all of the small exceptions

The Curse of SOPs

Next to impossible to write an effective and useful SOP to govern messy things like risk management or projects

Our paradigm is that we have to have SOPs for everything

We either tie ourselves in knots trying to follow the SOP

Or we ignore the SOP and hope no one notices
The Curse of Global Standards

A bit of rust is observed on a waste water line going into a drain.

The site master specification is modified to require stainless for equipment and piping external surfaces in clean space.

After several corporate purchases and mergers, there is a need to align the global specifications.

The global master spec becomes “only 316L or better can be used in manufacturing areas.”

… next that a large tank is being bolted down using 316L nuts on 316L studs (the galling will make the next mechanic very unhappy).

We can:
- Take an exception to the specification (planned deviation)
- Fix the specification (but modifying a global standards could take years)
- Ignore the specification and use the proper bronze nut (deviation)
- Follow the specification and do the technically wrong thing (madness?)

No good path forward

All done with the best of intentions but.…
The Curse of CAPAs

A young start-up writes SOPs as needed
Maybe imports many from a big engineering firm that they use on their first big project
For the most part the SOPs are written to work together
But then there is an audit /deviation …they are under the gun for a fix
One easy fix is to put into a CAPA that the SOP will be modified
Often only that specific SOP that is modified, not the whole system

The Curse of CAPAs

Limited time and limited resources
No ones job to make sure that all the SOPs play nicely together
Fairly simple if you have only a few SOPs, very hard if you have hundreds or thousands
After a decade or two of CAPAs and modifications – there will be conflicts between the SOPs
Think of it as a complex building …… built without a blue-print
You will get something – but it may not be pretty
The Never-Ending Quest for Perfection

P&IDs and Red-lines

Typical P&ID has 1000's of pieces of information

They are never 100% correct

When you try an correct the last piece

- usually create a new error someplace else (CAD demons)

QA never accepts this
The Never-Ending Quest for Perfection

Qualification and Deviations
My first qualification
“We are just going to execute the entire qualification to shakeout…”
“…we don’t want any deviations…”
Then 2nd qualification to have a “clean run” on paper

Talking to a lead auditor
“…if I don’t see any deviations, that’s a red flag and I dig deeper…”

Commas or no commas
Colon versus semi-colon
Epic debates on proper risk scoring for risks that will not just not matter
The quest for perfect consistency across a project
All documents must look alike, and have the same wording ….?
The amount of effort needed to get to an acceptable product versus amount
needed to get to a perfect product (or nearly perfect…)

Perfection is the enemy of getting the project done...
and doesn’t help the patient
Strong QA

There is a need for strong QA and validation groups

…. But the SOP says all instruments must be….

  - Calibrated stopwatches
  - Qualified calculators
  - Calibrated volt-ohm meters

A strong QA can listen to reason and common sense

Strong QA

- Common view of Engineering and Quality as ancient enemies
- Much of the guidance/SOP is high level and vague
- Many things are clear black / white
  but a lot of gray areas at the edges
Strong QA

– Without strong QA the engineering group
  a) Go too far and gets themselves in trouble
  b) Tries to police themselves and get too conservative
– But isn’t conservative good?
  Conservative costs time, resources, and money
  Resources could be better used to address larger risks

RISK MANAGEMENT IN PRACTICE

LESSONS LEARNED
LESSONS LEARNED

“...if I had to do this project over again, I’d get rid of all this Quality Risk Management and just qualify everything. It would be simpler, faster and cheaper....”

After 15 years have we learned anything?
LESSONS LEARNED

• You can’t start quality risk management too early
• You can’t spend too much on front-end engineering & QRM
• Time spent on getting the URS’s right will payoff in the end
• If everything is critical, nothing is critical

LESSONS LEARNED

• An SOP for a non-standard practice is a bad idea
• It must be possible to change SOPs and standards (even global standards) to meet reality
• Perfection is the enemy of the reasonable (also of finishing the project)
• Keep QA close
LESSONS LEARNED

• Risk management when done early can be very cost effective, saving grief latter
• Risk management when done as a box checking exercise is generally a waste of time, resources and money
• QRM is a creative enterprise requiring thought and judgement
• QRM is filled with land mines for the unexpected and inexperienced engineer

CREDITS

My colleagues at Hyde and elsewhere who have shared their war stories

Others whose names have been changed to protect the guilty

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