RISK MANAGEMENT IN PRACTICE:
Ten Lessons From The Trenches

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ISPE Product Show
Track 1, Session 3
September 26, 2018

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

"Well he certainly does a very thorough risk analysis."

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

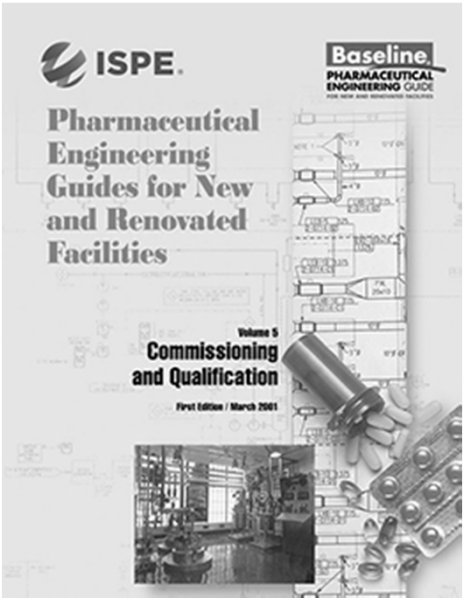
- ISPE
- ICH Q9
- ASTM E2500
- PDA

Guidances

ISPE - March 2001

Baseline Guide – Volume 5

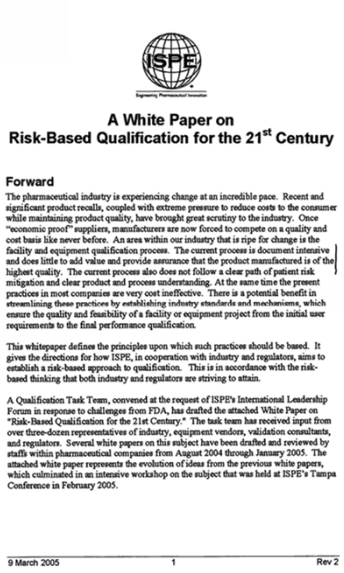
Commissioning and Qualification



Guidances

ISPE - March 2005

White Paper
Risk-Based Qualification



A White Paper on
Risk-Based Qualification for the 21st Century

Forward

The pharmaceutical industry is experiencing change at an incredible pace. Recent and significant product recalls, coupled with extreme pressure to reduce costs to the consumer while maintaining product quality, have brought great scrutiny to the industry. Once "economic proof" suppliers, manufacturers are now forced to compete on a quality and cost basis like never before. An area within our industry that is ripe for change is the facility and equipment qualification process. The current process is document intensive and does little to add value and provide assurance that the product manufactured is of the highest quality. The current process also does not follow a clear path of patient risk mitigation and clear product and process understanding. At the same time the present practices in most companies are very cost ineffective. There is a potential benefit in streamlining these practices by establishing industry standards and mechanisms, which ensure the quality and feasibility of a facility or equipment project from the initial user requirements to the final performance qualification.

This whitepaper defines the principles upon which such practices should be based. It gives the directions for how ISPE, in cooperation with industry and regulators, aims to establish a risk-based approach to qualification. This is in accordance with the risk-based thinking that both industry and regulators are striving to attain.

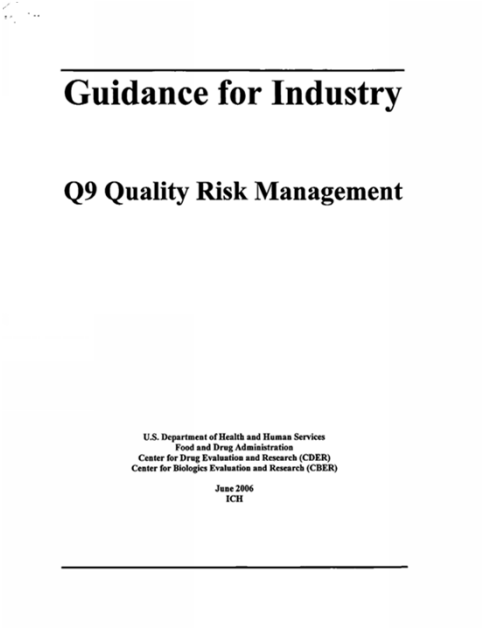
A Qualification Task Team, convened at the request of ISPE's International Leadership Forum in response to challenges from FDA, has drafted the attached White Paper on "Risk-Based Qualification for the 21st Century." The task team has received input from over three-dozen representatives of industry, equipment vendors, validation consultants, and regulators. Several white papers on this subject have been drafted and reviewed by staffs within pharmaceutical companies from August 2004 through January 2005. The attached white paper represents the evolution of ideas from the previous white papers, which culminated in an intensive workshop on the subject that was held at ISPE's Tampa Conference in February 2005.

9 March 2005 1 Rev 2

Guidances

ICH Q9 – June 2006

Quality Risk Management



Guidance for Industry

Q9 Quality Risk Management

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

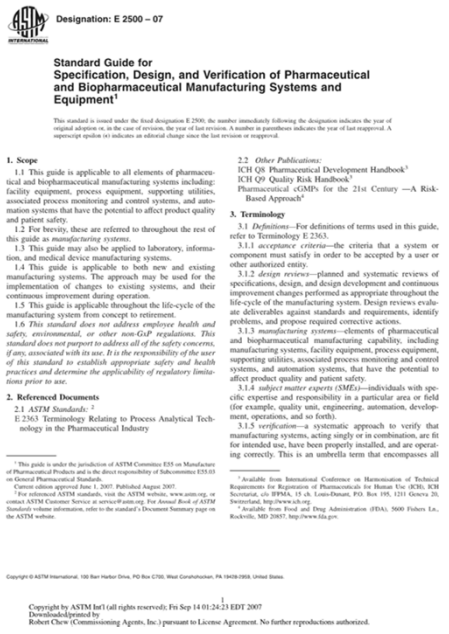
June 2006
ICH

Guidances

ASTM E2500 (2007)

Industry Consensus Standard

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



Designation: E 2500 – 07

Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment[1]

This standard is issued under the fixed designation E 2500; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide is applicable to all elements of pharmaceutical and biopharmaceutical manufacturing systems including: facility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems that have the potential to affect product quality and patient safety.

1.2 For brevity, these are referred to throughout the rest of this guide as *manufacturing systems*.

1.3 This guide may also be applied to laboratory, information, and medical device manufacturing systems.

1.4 This guide is applicable to both new and existing manufacturing systems. The approach may be used for the implementation of changes to existing systems, and their continuous improvement during operation.

1.5 This guide is applicable throughout the life-cycle of the manufacturing system from concept to retirement.

1.6 *This standard does not address employee health and safety, environmental, or other non-GxP regulations. This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:* [2]

E 2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

2.2 *Other Publications:*

ICH Q8 Pharmaceutical Development Handbook[3]

ICH Q9 Quality Risk Handbook[3]

Pharmaceutical cGMPs for the 21st Century —A Risk-Based Approach[4]

3. Terminology

3.1 *Definitions*—For definitions of terms used in this guide, refer to Terminology E 2363.

3.1.1 *acceptance criteria*—the criteria that a system or component must satisfy in order to be accepted by a user or other authorized entity.

3.1.2 *design reviews*—planned and systematic reviews of specifications, design, and design development and continuous improvement changes performed as appropriate throughout the life-cycle of the manufacturing system. Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions.

3.1.3 *manufacturing systems*—elements of pharmaceutical and biopharmaceutical manufacturing capability, including manufacturing systems, facility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems, that have the potential to affect product quality and patient safety.

3.1.4 *subject matter experts (SMEs)*—individuals with specific expertise and responsibility in a particular area or field (for example, quality unit, engineering, automation, development, operations, and so forth).

3.1.5 *verification*—a systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all

[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical Products and is the direct responsibility of Subcommittee E55.03 on General Pharmaceutical Standards.

Current edition approved June 1, 2007. Published August 2007.

[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

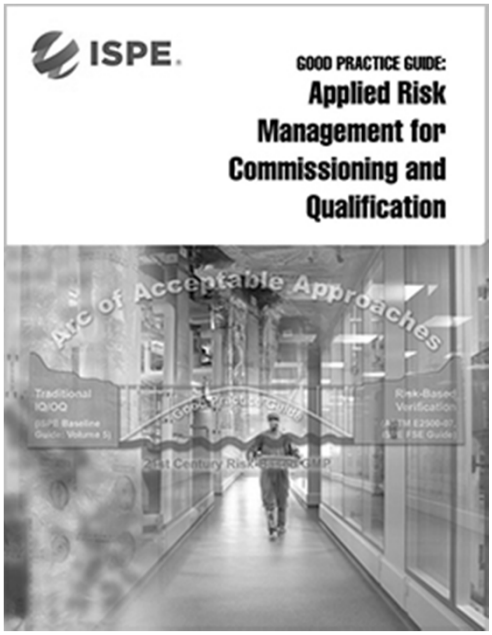
[3] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, c/o IFPMA, 15 ch. Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

[4] Available from Food and Drug Administration (FDA), 5600 Fishers Ln., Rockville, MD 20857, http://www.fda.gov.

Guidances

ISPE - October 2011

Good Practice Guide
Applied Risk Management for Commissioning and Qualification



Guidances

PDA Technical Report 54 (2012)

Implementation of Quality Risk Management

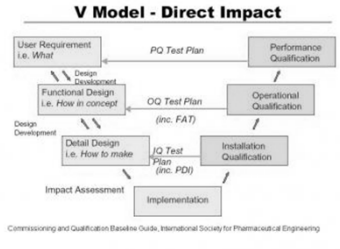
Guidance

PDA Technical Report 54-5 (2017)

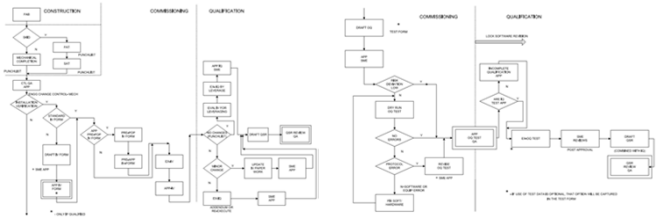
Quality Risk Management for the Design, Qualification and Operation of Manufacturing Systems

Risk Management at 15

Theory



And Practice



RISK MANAGEMENT IN PRACTICE

TEN LESSONS FROM THE TRENCHES

THE WAR STORIES

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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)

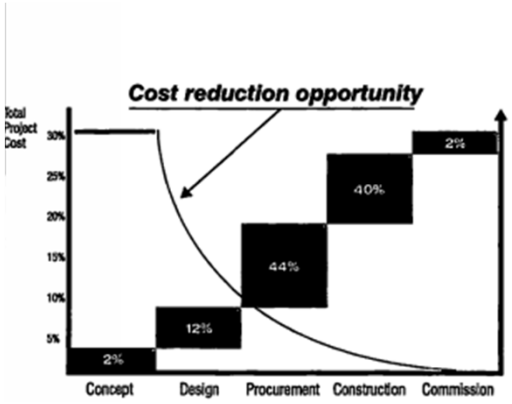
Tends to be a waste of time, money and resources

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…lets 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

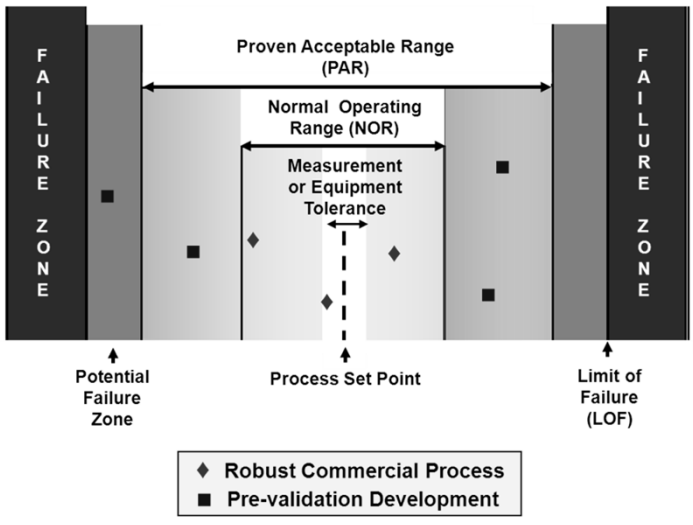
Once again … KISS

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



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

Automation / Alarms as Crutches

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”

The Curse of Global Standards

… 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

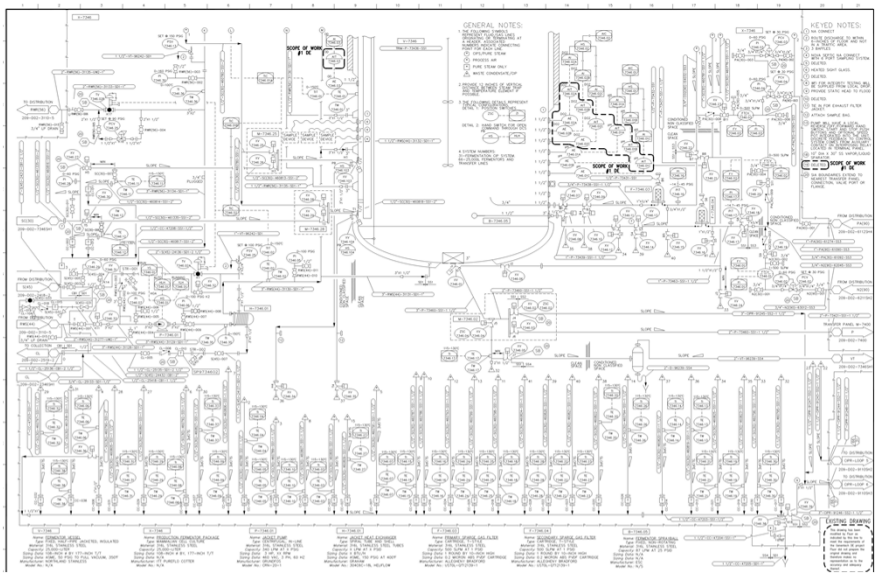
Fairly simple if you have only a few SOPs, very hard if you have hundreds or thousands

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



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…"

The Never-Ending Quest for Perfection

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

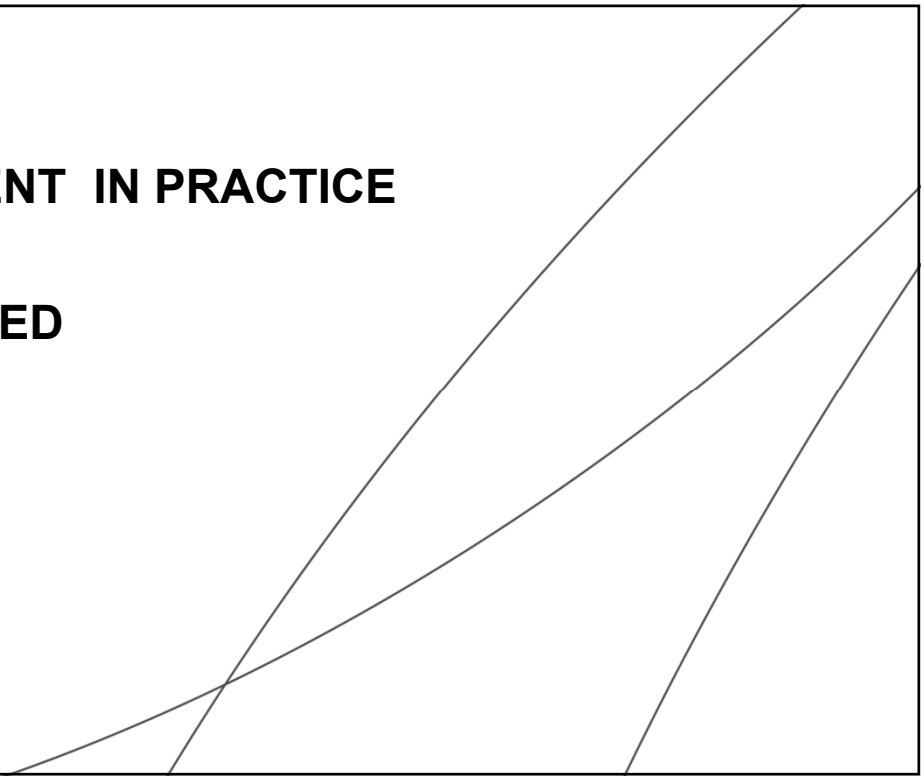
  but a lot of gray areas at the edges

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 unexpecting 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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