

The Importance of Being Ernest – Risk Based Approach (RBA)

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The Leader in RBM

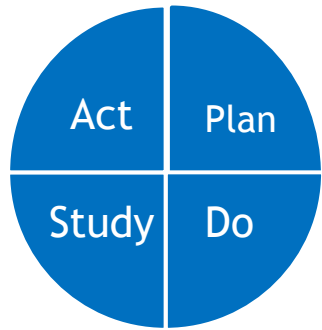
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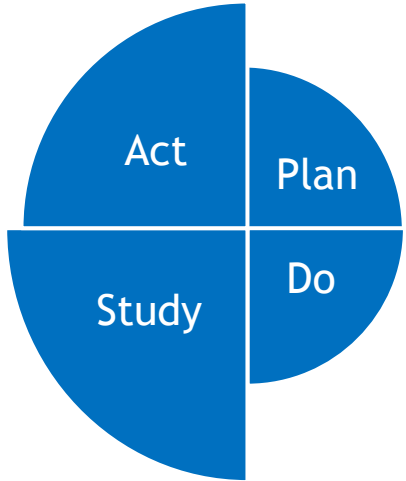
Topics

- ▶ Big Picture
 - ▶ Industry status
- ▶ Background to ICH E6 R2
 - ▶ Regulatory
 - ▶ Structural
 - ▶ Issues that led to changes
 - ▶ QbD
- ▶ Impact on programming/programmers
 - ▶ Validation
 - ▶ QTLs
 - ▶ RBM

Industry Approaches to Quality

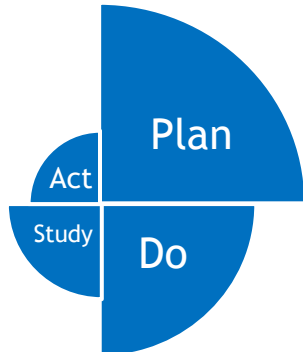


Typical
Manufacturing



Amazon

Amazon make big gambles which do not always succeed, but they study the failures points and change their approach (“Act”)

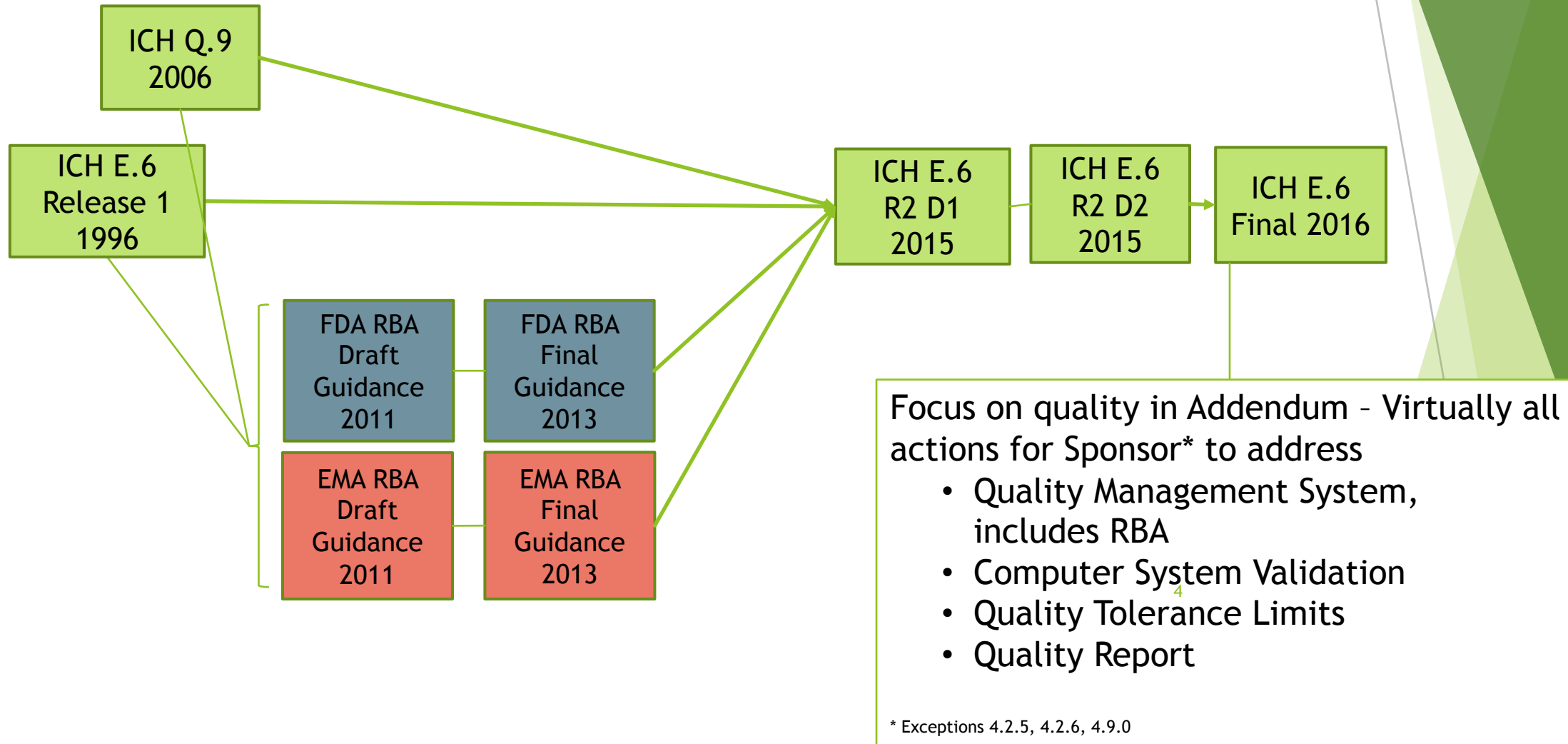


Pharma

Pharma tend to go back to “training” or the “Plan” with failures, which results in lots of plans. The “Do” part is not undertaken to the same level. “Study” only undertaken on SAP, so no analytics on failures except individual cases. Failure to “Study” also leads to a failure to “Act” as shown by Pharma not stopping “failed” drug developments

Plans
Monitoring
Central Monitoring
Training
Communication
PV
Data Management
Statistical Analysis
etc

What's led to ICH E.6 Addendum



Drivers for ICH E.6 Addendum changes

- ▶ Concerns over quality from Regulatory Authorities
 - ▶ Lack of trust for ICH-GCP statements in submission based on Audits
 - ▶ We claim “all trials conducted to ICH-GCP”, but results from inspections always show GCP issues
 - ▶ Upset over lack of transparency
 - ▶ Want defined quality
 - ▶ Transparency
 - ▶ Want “Quality by Design, sometimes feel it is by Accident”
 - ▶ Industry is too silo’d, this impacts Quality
 - ▶ Lack of demonstrable oversight
 - ▶ Do not understand risk
 - ▶ Poor “Root cause analysis”
 - ▶ “Stupidity of 100% SDV” as solution, CRA misses “helicopter” view of site
 - ▶ Pharma is wasting resources

QbD and Clinical Trials

1



2



Which image best represents the pharma industry approach to quality in Clinical Trials?

QbD and Clinical Trials



Current state

Pharmaceutical Products are of good quality
– Quality itself is not the issue

We need to get it
'Right First Time'
and then to **continue
to improve**

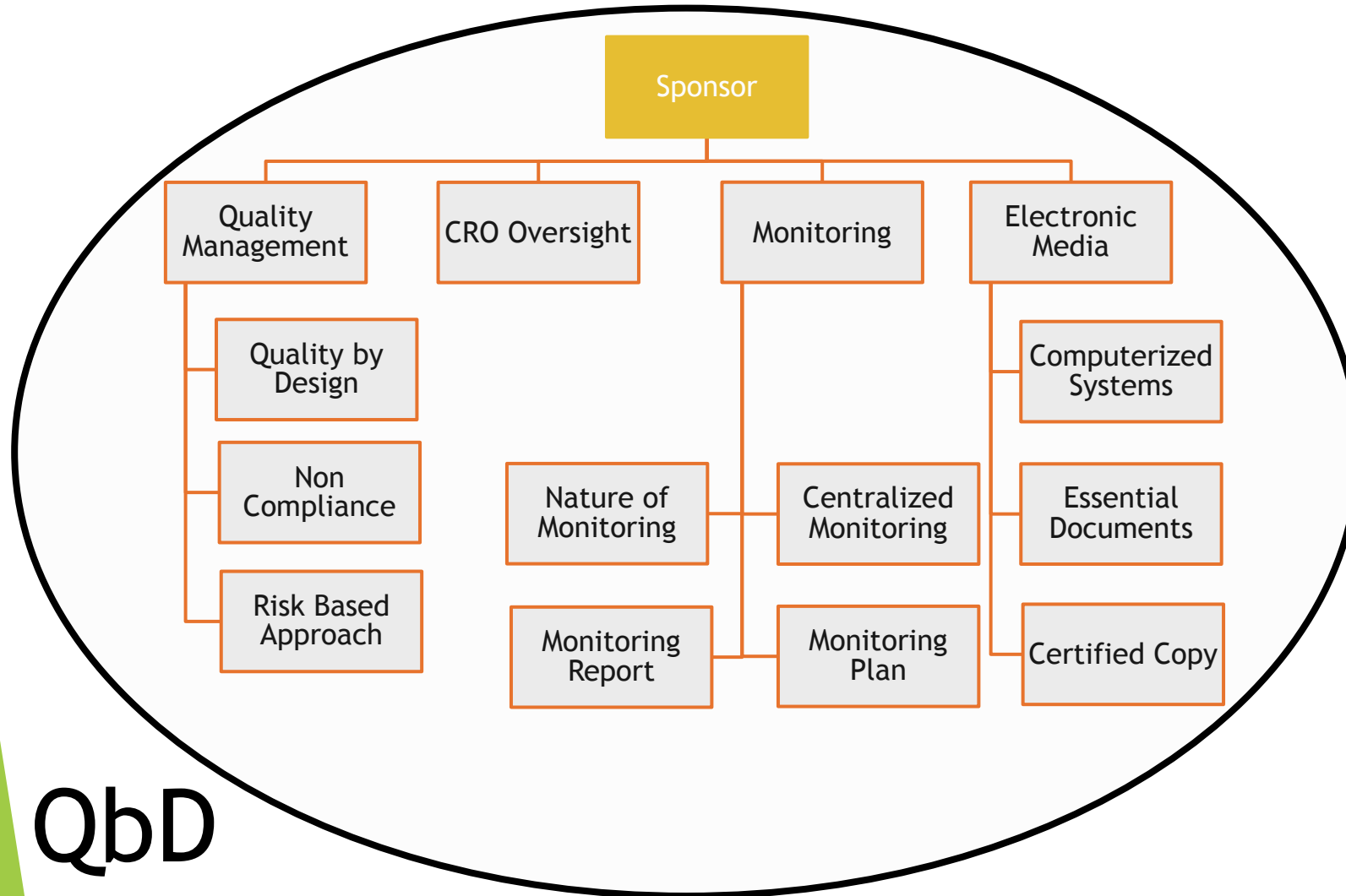
But pharmaceutical development and manufacturing **could be improved**

Pharma

Semicon

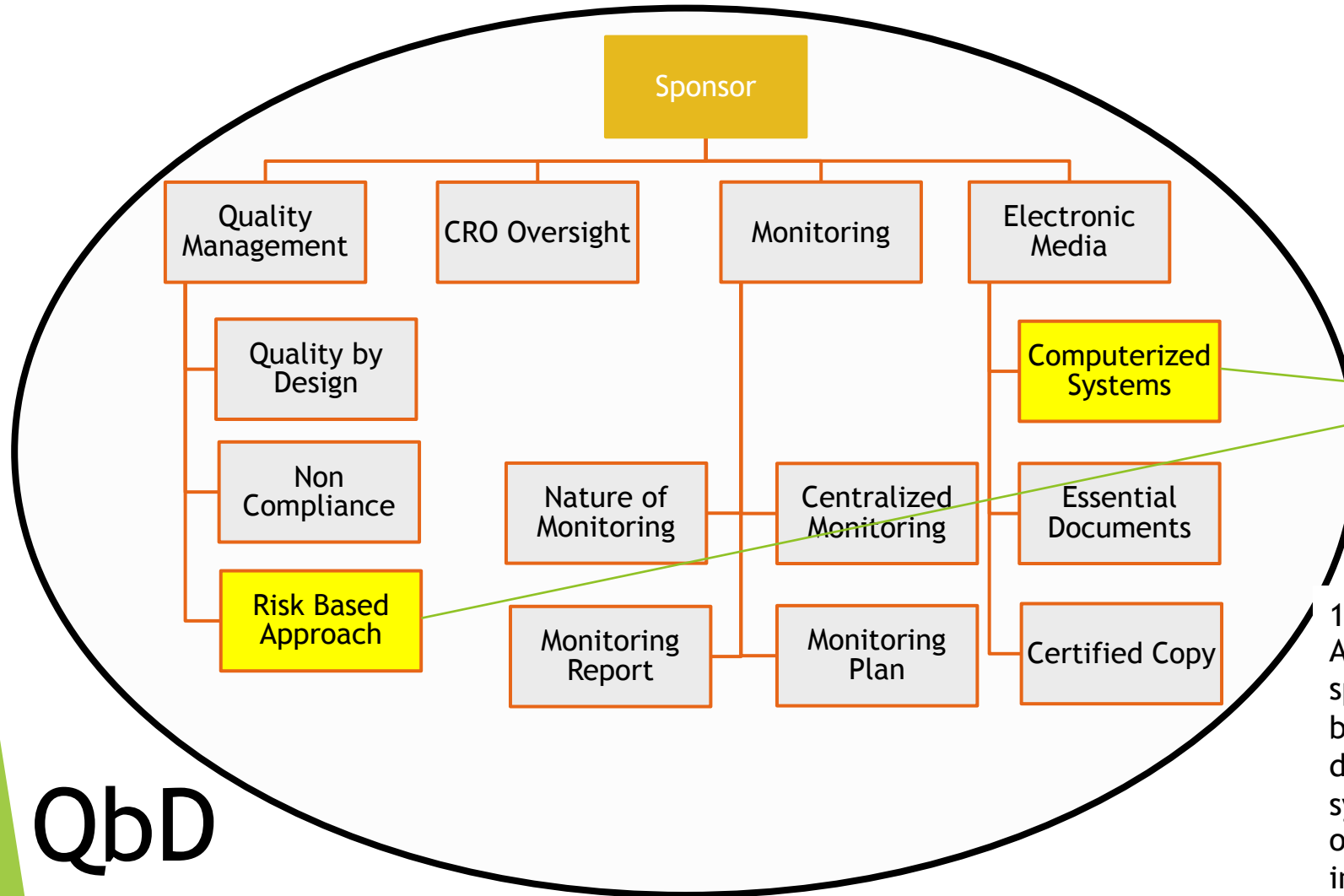
Sigma	ppm Defects	Yield	Cost of Quality
2 σ	308,537	69.2%	25-35%
3 σ	66,807	93.3%	20-25%
4 σ	6,210	99.4%	12-18%
5 σ	233	99.98%	4-8%
6 σ	3.4	99.99966%	1-3%

Sponsor requirements - New or Modified in ICH E.6



QbD

Sponsor requirements - Impact on Programmers



Are you taking a Risk Based approach to Validation of your programs

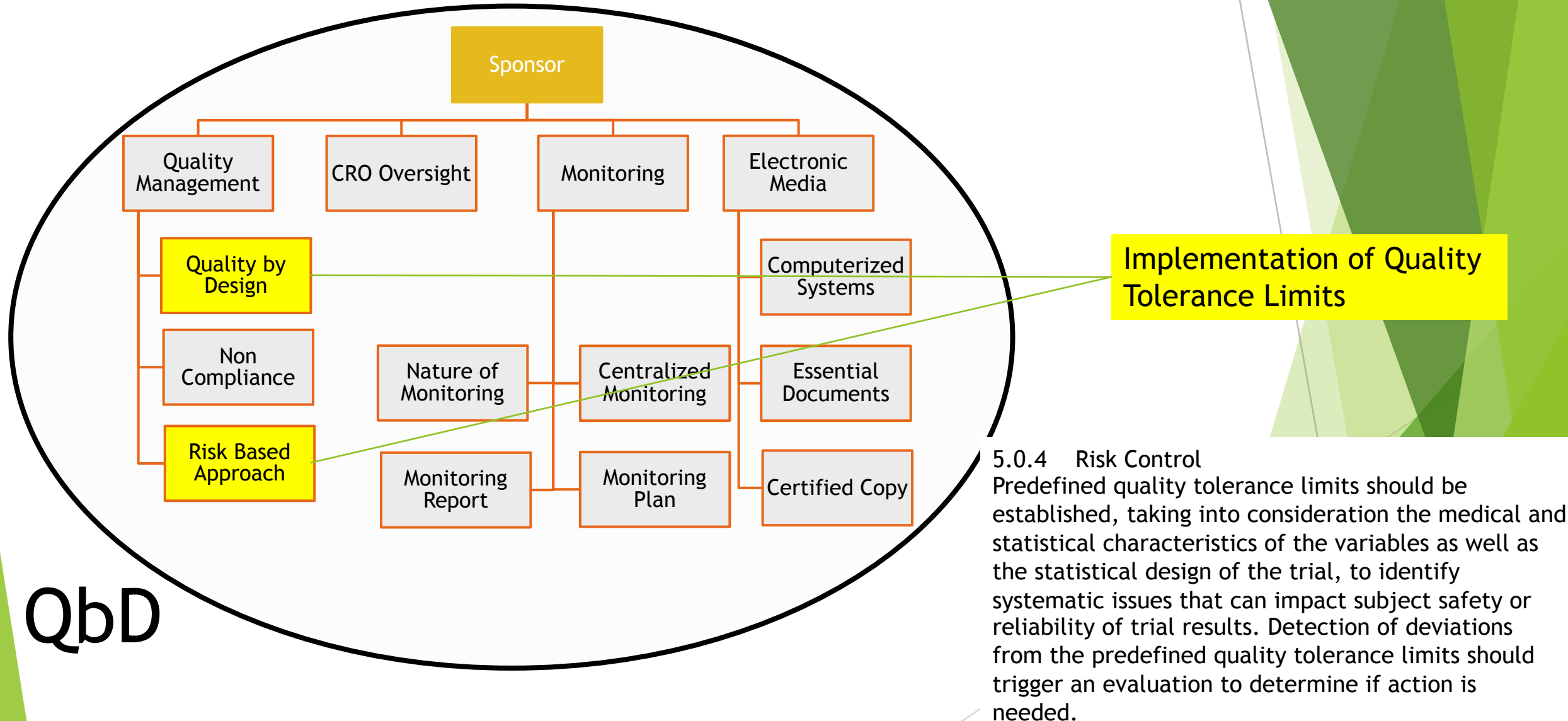
1.65 Validation of computerized systems
A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

QbD

CSV for ad hoc SAS (or other) programs

- ▶ All companies have some type of validation approach to validation
 - ▶ Duplicate programming
 - ▶ Code review
 - ▶ Other
- ▶ Few companies have a risk assessment for these programs
- ▶ Intention is to reduce workload from taking a blanket approach
- ▶ Focus on high risk areas

Sponsor requirements - Potential Impact on Programmers



ICH E.6 R2 section on QTL

5.0.4 Risk Control

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Shewhart



Deming



Statistical
Quality
Control
1930's

Total Quality
Control
1956

Statistical
Process
Control
1960's

Company
Wide Quality
Control
1968

Total Quality
Management
1985

Six Sigma
1986

Application
of statistical
methods,
control
charts and
acceptance
sampling, in
quality
control

Stress on
involving
other
departments
in addition to
production
.e.g.
Finance, HR,
etc

Inspired by
control
systems, use
of control
charts to
monitor
individual
industrial
process

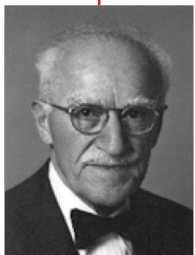
Japanese
style total
quality
control

Originating
with US
Department
of Defence

Statistical
quality
control as
applied to
business
strategy

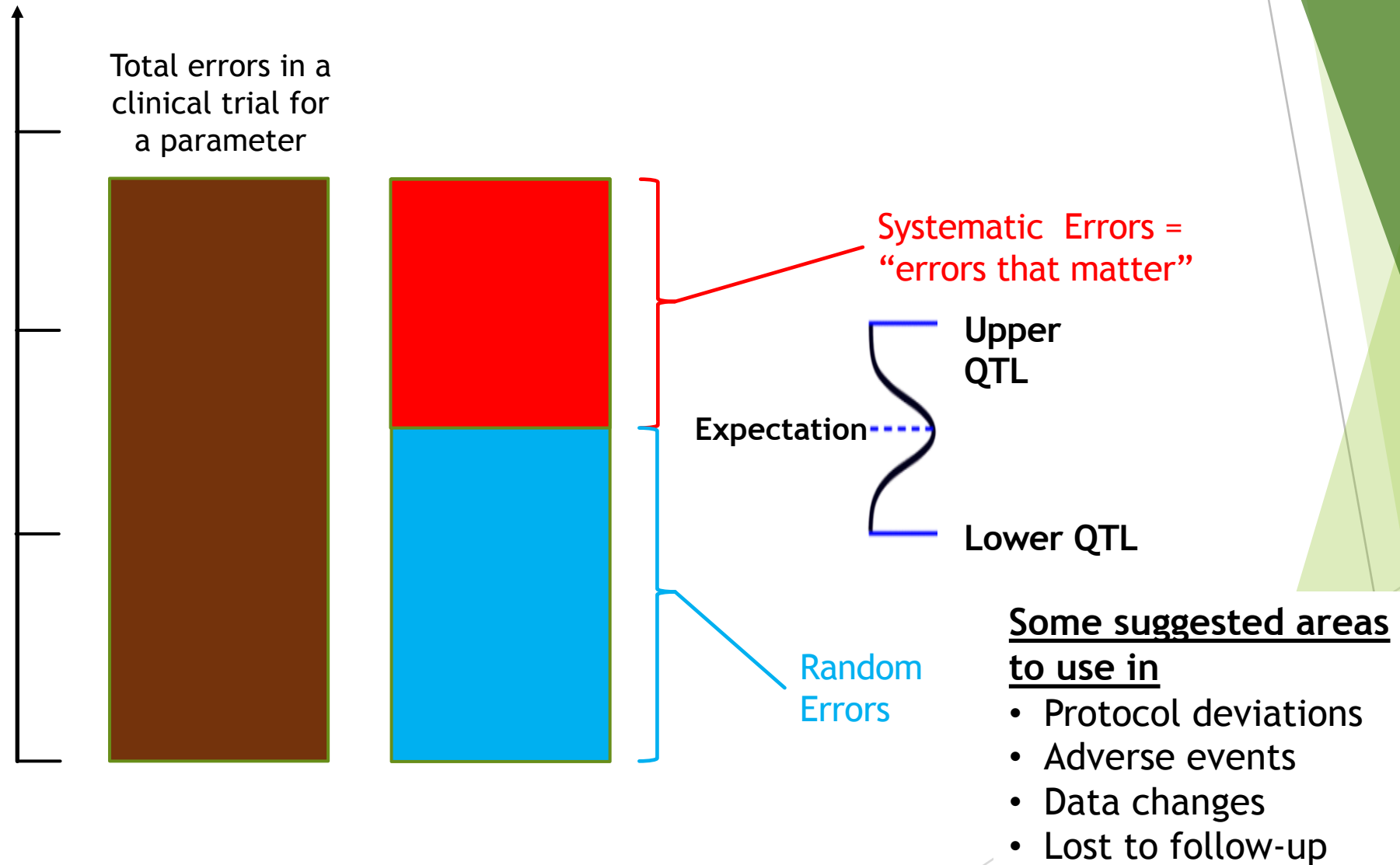
Tolerance Limits

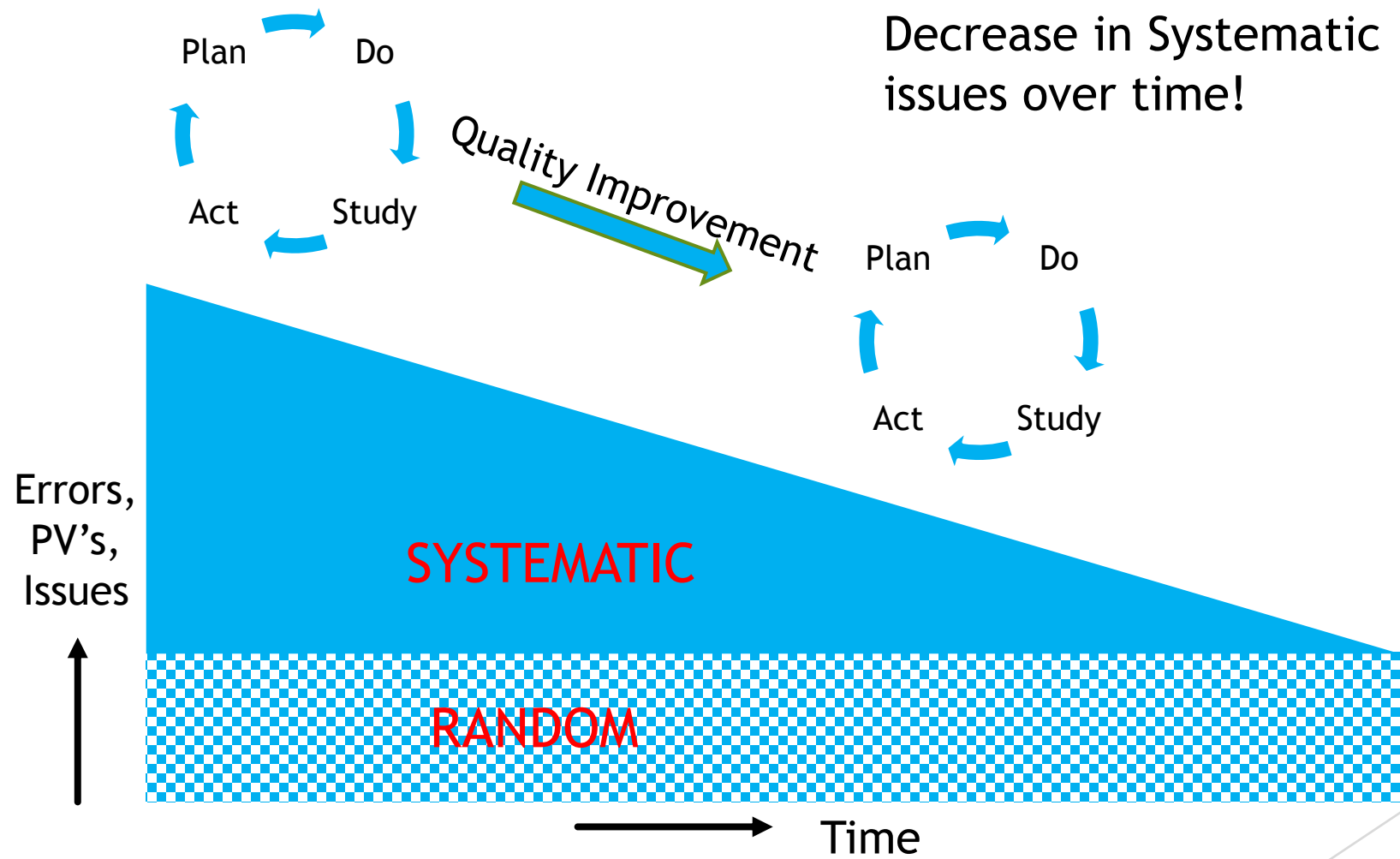
Juran



Quality by Design

Quality Tolerance Limits

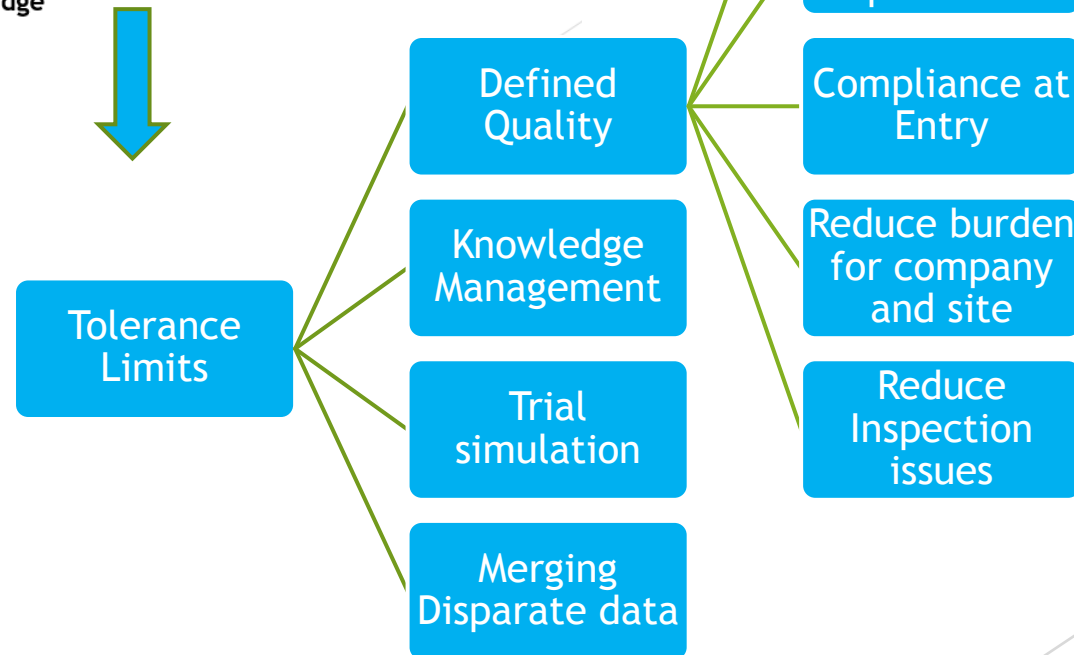
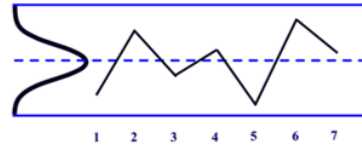
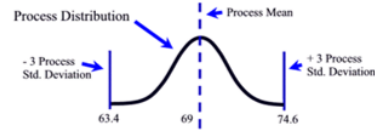




Tolerance Limits - Acceptable Defects: Rather than waste efforts on zero-defect goals, W Edwards Deming

What is a tolerance limit

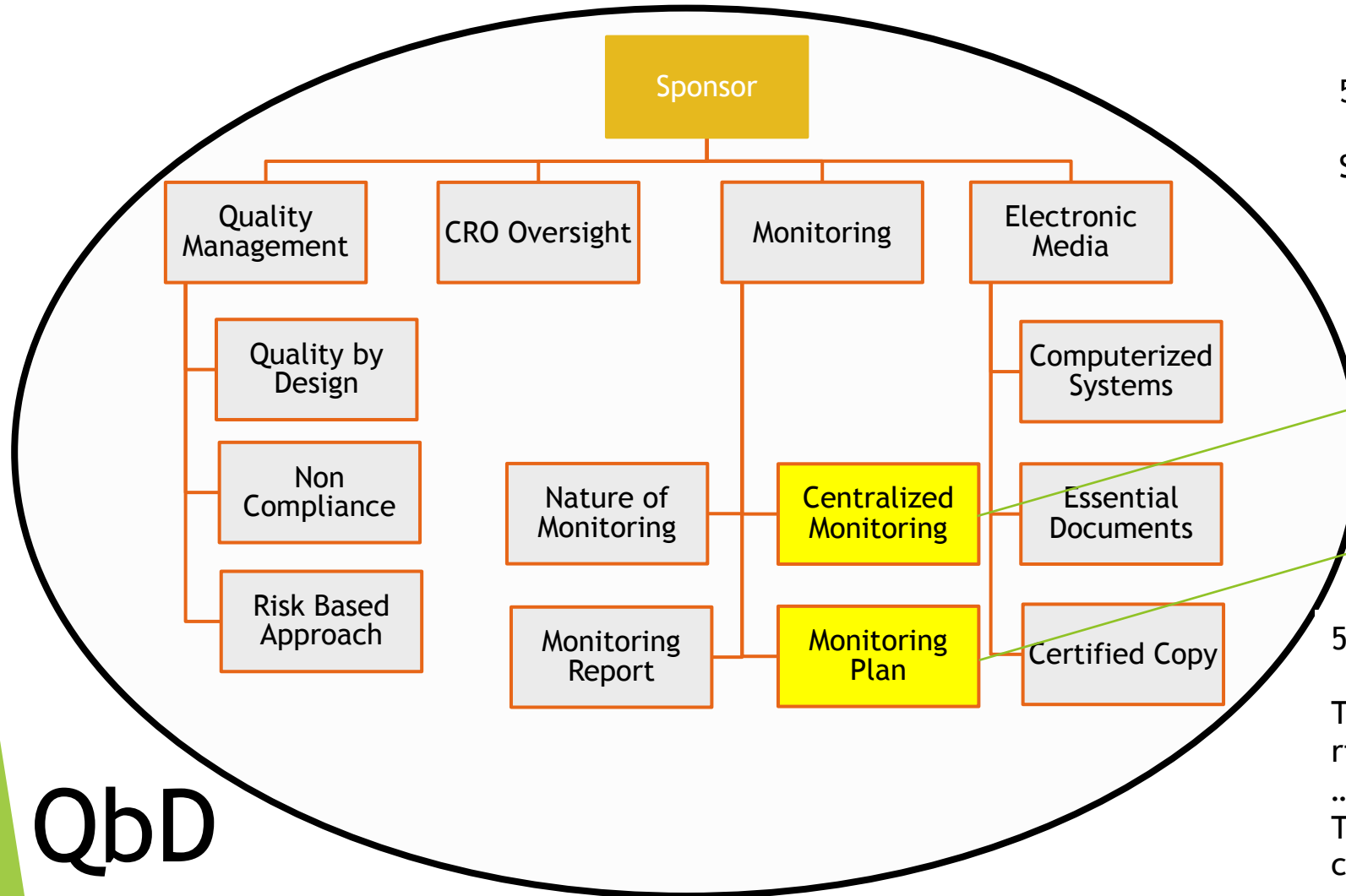
- A tolerance interval can be seen as a statistical version of a probability interval
 - One sided e.g. non compliance, PV
 - Two sided e.g. AE reporting, endpoint
- Used in engineering and manufacturing
- Standard part of the quality process
- Based on standard statistical methodology
 - Action limits
 - Warning limits
 - Control mechanisms when trending out of sequence
 - CUSUM
- Needs to be defined for Clinical Trials
- Base on Statistical and Medical knowledge



Summary: What can Tolerance Limits give us

Quality by Design

Sponsor requirements - Potential Impact on Programmers



5.18.3 Extent and Nature of Monitoring

Sections a)-e)

Are you involved in programming and modelling for Central Monitoring (RBM)
What is the strategy for Central Monitoring

5.18.3 Extent and Nature of Monitoring

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trial.

...
The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

QbD

Programming for RBM

- ▶ Key area is CSM (Central Statistical Monitoring)
 - ▶ More effective than SDV at detecting critical issues (see refs - Sheetz et al, Knepper et al)
 - ▶ More than just detection of potential fraud, also misconduct and other systematic issues
 - ▶ What checks (programmatic) to meet ICH E6 R2 Section 5.18.3

Section 5.18.3

... help distinguish between reliable data and potentially unreliable data

- a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations
- b) examine data trends such as the range, consistency, and variability of data within and across sites
- c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems
- d) analyze site characteristics and performance metrics
- e) select sites and/or processes for targeted on-site monitoring

Programming for RBM

- ▶ Programming and system checks accounts for almost 2 ½ times more data changes than SDV (see refs - Sheetz et al)
- ▶ SDV accounts for 25% cost of a clinical trial (when undertaking 100% SDV) (see refs - Sheetz et al)
- ▶ What is the cost of programming?
 - ▶ “Efficiency” is in the introduction to ICH E6 R2 - utilising programming more is an obvious way to meet the objective.
- ▶ What is your companies strategy for Monitoring, where does programming fit in?
 - ▶ Avoiding late queries

Assessing efficiency of methods (specificity and sensitivity)

- Best practise
 - Logical part of Plan Do Study Act cycle
 - Expected by Inspectors
 - Yellow should be high, Pink should be low - close to zero

Generic RBM system

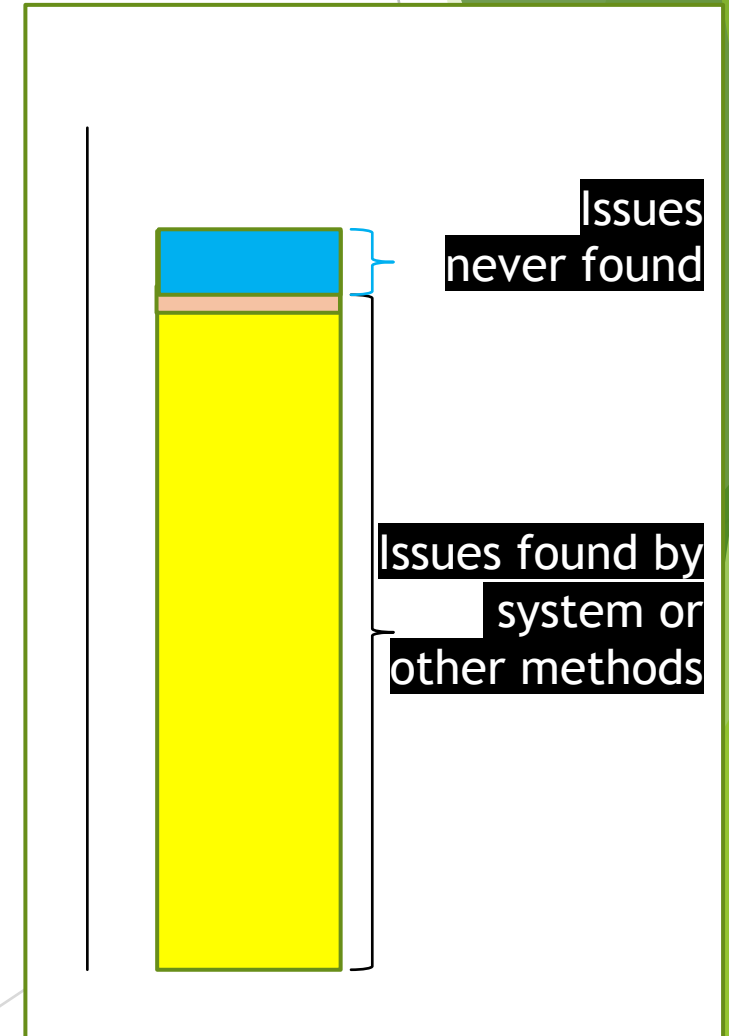
Result	Issue	Not an Issue
By program		
Flagged as Issue	30-40%	60-70%
Not Flagged as Issue	?	?

Tailored program - optimised for indication

Result	Issue	Not an Issue
By program		
Flagged as Issue	80%	20%
Not Flagged as Issue	?	?

Assessing efficiency of methods (specificity and sensitivity)

- No standard test data set available for everyone to use
 - Without this no method to compare products
- Companies unwilling to share data on fraud/misconduct
- Historical data
 - Yellow portion
 - Issues found from program
 - Pink portion
 - Discovered by routine onsite monitoring etc
 - Blue portion
 - Never found or from non standard areas e.g. from “routine” audits (not “for cause”)



Summary

- ▶ Implement a risk assessment for your SAS programming
 - ▶ Does not have to be complex, link to critical data assessment
 - ▶ Does not have to be on individual program, can group

Do not apply same solution to all programs

- ▶ Quality Tolerance Limits
 - ▶ Essential part of ICH E6 R2
 - ▶ Programming has critical part to play in defining expectation and variation from historical trial / project data
 - ▶ Incorporation into QMS

Summary (cont)

- ▶ Risk Based Monitoring
 - ▶ Central Statistical Monitoring and section 5.18.3
 - ▶ Monitoring Strategy - Role of Programming
 - ▶ Apply best practise
 - ▶ Assess how efficient and effective
- ▶ And if you do not follow RBA...



Q & A

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Confidential

The Leader in RBM

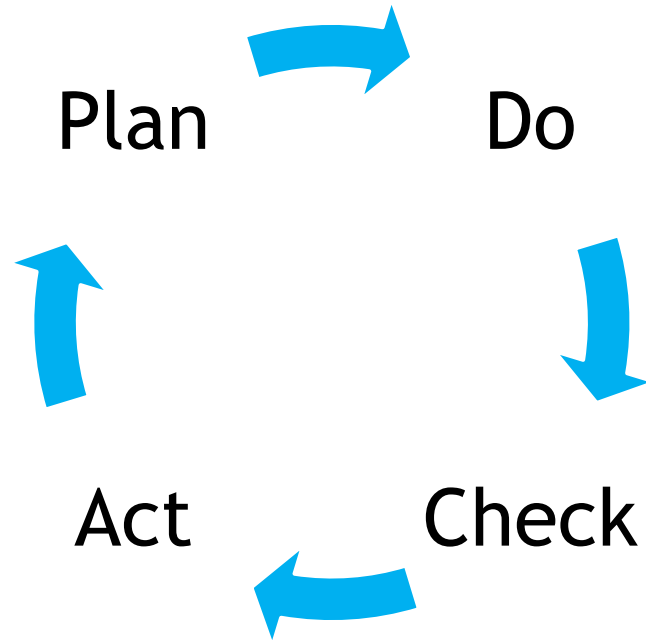
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References

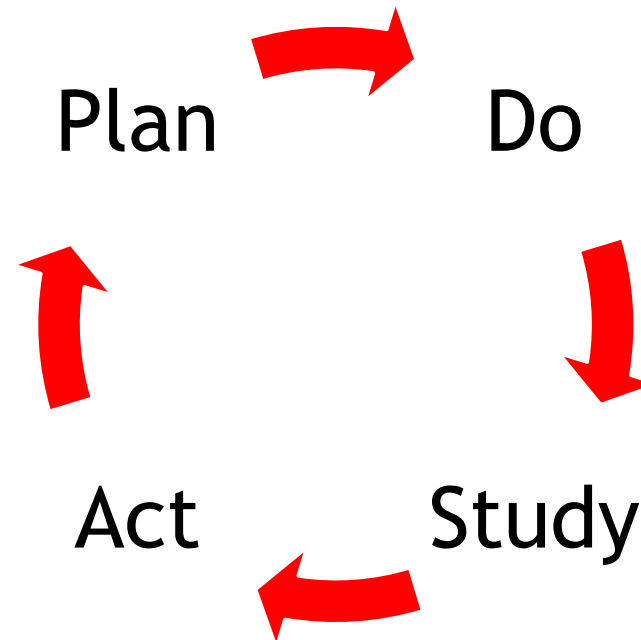
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#3- Cease dependence on inspection to achieve quality. Eliminate the need for massive inspection by building quality into the product in the first place.
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PDCA vs PDSA



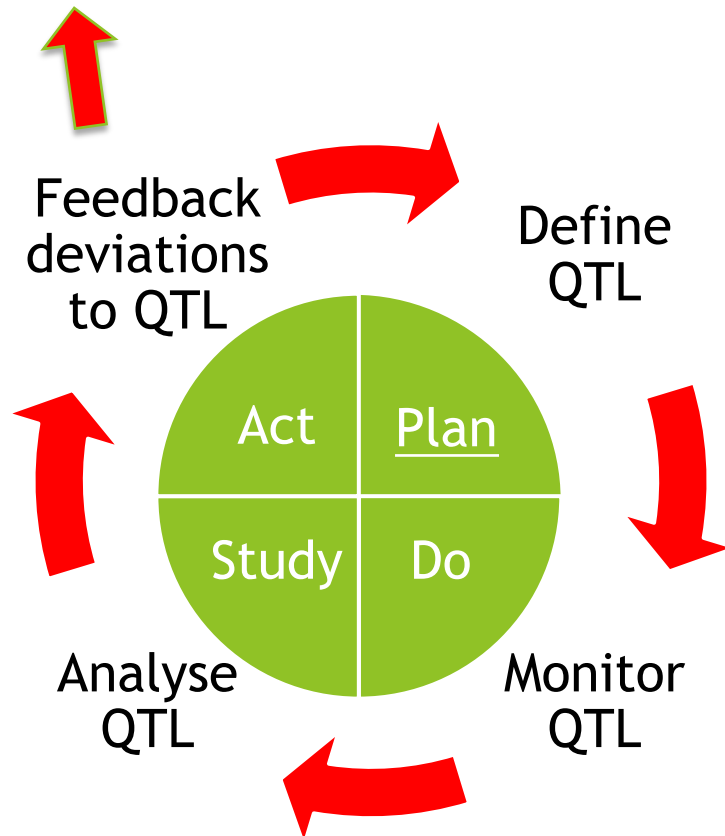
Deming –
Plan-Do-Study-Act

Shewhart –
Plan-Do-Check-Act



“Quality 101 - Deming - PDSA cycle”

Feedback into process improvement (QbD) to eliminate systematic errors



QbD Elements: Plan-Do-Study-Act

The “Plan-Do-Study-Act” framework succinctly encapsulates the key elements of QbD.

The “Plan” phase requires “design diligence.” The study design presented in the protocol must focus on proactive quality risk management and, specifically, scientific risk assessments: ensuring the safety of the study participants who will be recruited via carefully determined inclusion and exclusion criteria, the study’s scientific objectives, and the assessments and procedures that will generate the data collected. Operational plans will be created for site/country selection, quality, data monitoring, and safety. Define CQA (Critical Quality Attributes) and this should lead to selection of QTLs

In the “Do” phase of the cycle, training investigational sites, principal investigators, monitors, and clinical trial educators is the first step. Then you need to set up the process for overseeing trial execution, including prospective alerts, triggers, and risk mitigation plans that deliver against iterative project management plans.

The “Study” phase uses analytics to review the QTLs and metrics to examine the process (root cause analysis) for non random (systematic) errors.

The “Act” phase entails the final proactive (rather than reactive) step in QbD. It involves feeding the a fix for the root cause of any identified systematic errors. Reforecasting is conducted based on information gained to date and QA/quality management processes followed.