

ICH Q9 QUALITY RISK MANAGEMENT

Annex I: Methods & Tools

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- To guide through **Risk Management Methods and Tools**

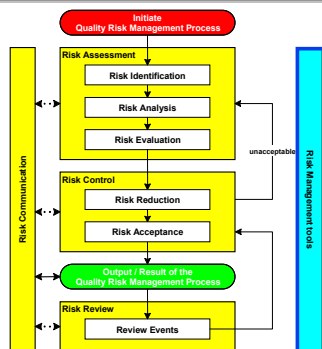
- Give an aid by providing key principles on the theory of the tools
- Give some examples and methods of use

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Chapter 5 & Annex I



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- The purpose of this annex is to provide a **general overview** of and references for **some** of the primary **tools** that **might be used** in quality risk management by **industry and regulators**.

- The references are included as an aid to gain more knowledge and detail about the particular tool.
- The list of tools is **not exhaustive**.
- It is important to note **that no one tool** or set of tools **is applicable to every situation** in which a quality risk management procedure is used.

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Use the appropriate tool(s)!

No one tool is
“all inclusive”!

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- **System Risk** (facility & people)

- > e.g. interfaces, operators risk, environment, components such as equipment, IT, design elements
- **System Risk (organisation)**
 - > e.g. Quality systems, controls, measurements, documentation, regulatory compliance
- **Process Risk**
 - > e.g. process operations and quality parameters
- **Product Risk (safety & efficacy)**
 - > e.g. quality attributes:
 - measured data according to specifications

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EXAMPLE

Choose the right tool for the task: An example

A possible aid where to use methods / tools	general → detail			
	System Risk (facility & people)	System Risk (organisation)	Process Risk	Product Risk (safety & efficacy)
Risk ranking & filtering	X	X	X	
Failure mode effect analysis		X	X	
Hazard analysis and critical control points		X	X	
Process mapping			X	
Flow charts			X	X
Statistical tools				X
Check sheets	X			X

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Annex I: Methods & Tools

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Annex I.1

Basic Risk Management Facilitation Methods

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I.1: Basic risk management facilitation methods

- Flowchart
- Check Sheets
- Process mapping
- Cause and Effect Diagrams (Ishikawa / fish bone)

They might be helpful to support risk identification

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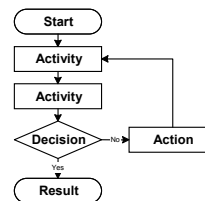
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I.1: Basic risk management facilitation methods

Flowcharts



- Pictorial representations of a process
- Breaking the process down into its constituent **steps**

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I.1: Basic risk management facilitation methods

Check sheets

Common Questions for Investigating an Out-of-Control Process		
☐ Yes ☐ No	Are there differences in the measurement accuracy of instruments/methods used?	
☐ Yes ☐ No	Are there differences in the methods used by different personnel?	
☐ Yes ☐ No	Is the process affected by the environment e.g., temperature, humidity?	
☐ Yes ☐ No	Has there been a significant change in the environment?	
☐ Yes ☐ No	Is the process affected by predictable conditions? Example: tool wear.	
☐ Yes ☐ No	Were any untrained personnel involved in the process at the time?	
☐ Yes ☐ No	Has there been a change in the source for input to the process? Example: raw materials, information.	
☐ Yes ☐ No	Is the process affected by employee fatigue?	
☐ Yes ☐ No	Has there been a change in policies?	

- Present information in an **efficient, clear format**
- May be accomplished with a simple listing of items

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I.1: Basic risk management facilitation methods

Process mapping

- The indicators may be selected based on **unit operations**
- Shows how they are **interrelated**

Potential Areas of Use(s) / outcomes

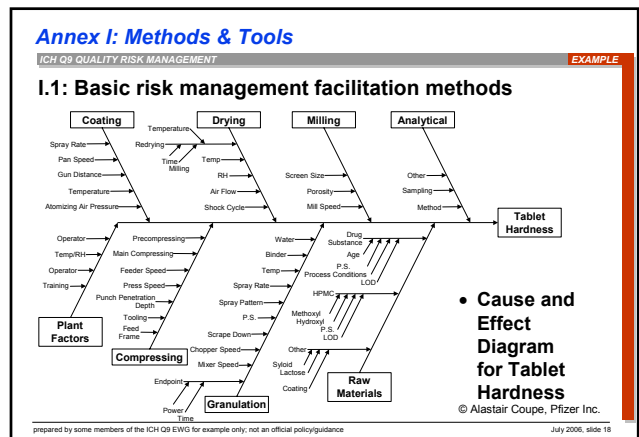
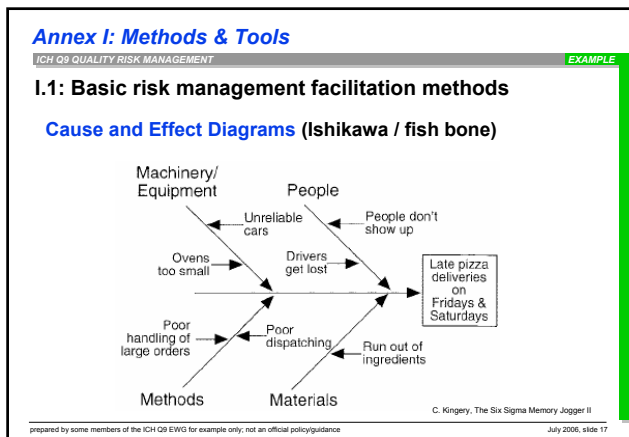
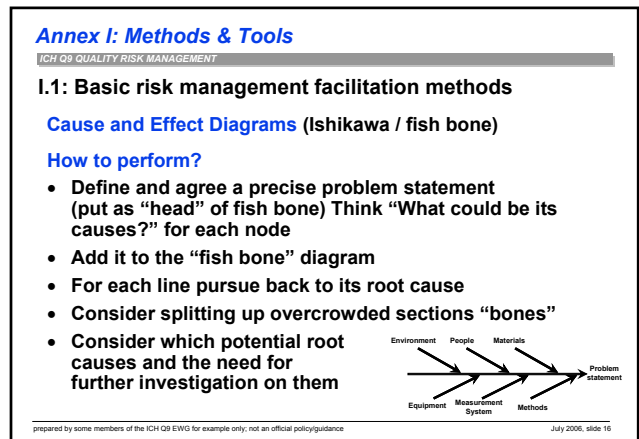
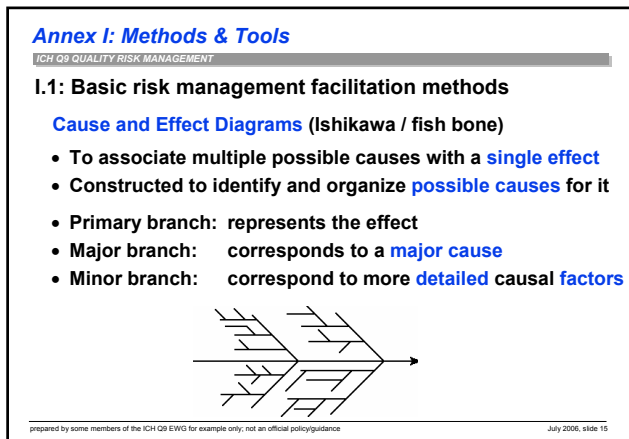
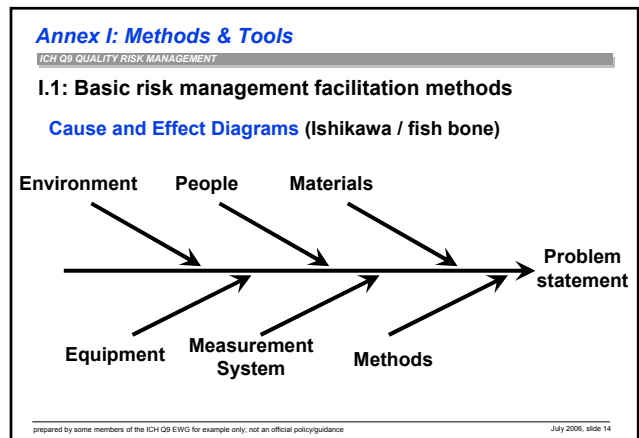
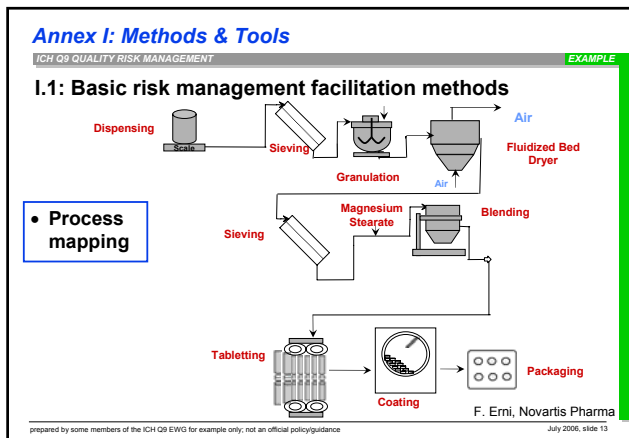
- Provides a clear and simple **visual representation** of involved steps
- Facilitates understanding, explaining and systematically **analyzing complex processes** and associated risks
- A **pre-requisite** for the use of some other tools

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Failure Mode Effects Analysis (FMEA)

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(see IEC 60812)

- Evaluation of **potential failure modes** for processes
- The likely **effect on outcomes** and/or product **performance**
- Once failure modes are established, **risk reduction** can be used to eliminate, reduce or control the potential failures
- FMEA relies on **process understanding**
- Summarize the important modes of failure, factors causing these failures and the likely effects of these failures

How to perform?

Break down large complex processes into **manageable steps**

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[illegible]

RNP: Risk Priority Number C. Kingery, The Six Sigma Memory Jogger II

Potential Areas of Use(s)

- **Prioritize risks**
- **Monitor the effectiveness of risk control activities**
- **Equipment and facilities**
- **Analyze a manufacturing process to identify high-risk steps or critical parameters**

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How to perform?

1. Establish a team
2. Identify the known and potential failure modes:
Develop lists of known problems and brainstorm other potentials...
e.g.
 - > Product not meeting specification
 - > Process not meeting yield requirements
 - > Malfunctioning equipment
 - > Software problems

Newly identified failure modes should be added at any time

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How to perform?

- ### 3. Characterise the severity, probability and detectability
- An *equal* number of levels is sometimes helpful
 - > Some preference to 3, 4, 5, 6 or 10 levels
 - > But: an even number of levels avoids the mid point
 - Use different scales
 - > Linear: 1, 2, 3, 4
 - > Exponential: 1, 2, 4, 8
 - > Logarithmic: 1, 10, 100, 1000
 - > Self made: 1, 3, 7, 10
- The aim is to come up with a method of prioritising

Multiplying different scales will differentiate the outcome

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How to perform?

4. Define actions
5. Revisit the ranking
6. Define residual risk
7. Perform a short summary
 - > Scope
 - > Data from the assessment & control
(e.g. No. of identified failure modes)
 - > Level of accepted risk without actions i.e. residual risk
(e.g. Risk priority Number < 50)
 - > Recommended actions, responsibilities and due dates
(including approval, if appropriate)
 - > Person in charge for follow-up of FMEA

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EXAMPLE

Severity (Consequences of failure)

- **10 Extreme**
 - Predicted to cause severe impact to quality (Product out of specifications, no Expert Statement possible)
- **7 High**
 - Predicted to cause significant impact on quality (Failure to meet specifications, no Stability data, Expert Statement possible)
- **3 Moderate**
 - Predicted to cause minor impact on quality (Failure to meet specifications, Stability data available)
- **1 Low**
 - Predicted to have no/minor impact on quality of the product (Quality within specifications)

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EXAMPLE

Probability (Likelihood failure will happen)

- **8 Regular failures**
 - Expected to happen regularly
- **4 Repeated failures**
 - Expected to happen in a low frequency
- **2 Occasional failures**
 - Expected to happen infrequently
- **1 Unlikely failures**
 - Unlikely to happen

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EXAMPLE

Detectability (Ability to find the failure)

- **4 Normally not detected**
 - Failure very likely to be overlooked, hence not detected (no technical solution, no manual control)
- **3 Likely not detected**
 - Failure may be overseen (manual control, spot checks)
- **2 Regularly detected**
 - Failure will normally be detected (manual control, routine work with statistical control)
- **1 Always detected**
 - Failure can and will be detected in all cases (monitoring, technical solution available)

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EXAMPLE

FMEA: Quantitation of Risk : Severity

10	Dangerously High	Failure could lead to death or permanent injury to the customer. Financial: >\$1,000,000
9	Extremely high	Failure could lead to injury to the customer. Failure would create non-compliance with registered specifications. Failure likely to lead to recall. Financial: \$1,000,000
8	Very High	Failure could lead to adverse reaction for customer. Failure would create non-compliance with GMP regulations or product registrations. Failure possible to lead to recall. Financial: \$500,000
7	High	Failure leads to customer perception of safety issue. Failure renders individual unit(s) unusable. Failure causes a high degree of customer dissatisfaction. Recall for business reasons possible but Authority required recall unlikely. Financial: \$100,000
6	Moderate	Failure causes a high degree of customer dissatisfaction and numerous complaints. Failure unlikely to lead to recall. Financial: \$50,000
5	Low	Failure likely to cause isolated customer complaints. Financial: \$10,000
4	Very Low	Failure relates to non-dosage form issues (like minor packaging problems) and can be easily overcome by the customer. Financial: \$5,000
3	Minor	Failure could be noticed by the customer but is unlikely to be perceived as significant enough to warrant a complaint.
2	Very Minor	Failure not readily apparent to the customer. Financial: <\$1,000
1	None	Failure would not be noticeable to the customer. Financial: none

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EXAMPLE

FMEA: Quantitation of Risk : Probability

10	Very High: Failure is almost inevitable	More than one occurrence per day or a probability of more than three occurrences in 10 units ($C_{pk} < 0.33$ or $< 1\sigma$).
9		One occurrence every three to four days or a probability of three occurrences in 10 units ($C_{pk} \sim 0.33$ or $\sim 1\sigma$).
8	High: Repeated failures	One occurrence per week or a probability of 5 occurrences in 100 units ($C_{pk} \sim 0.67$ or $\sim 2\sigma$).
7		One occurrence every month or one occurrence in 100 units ($C_{pk} \sim 0.83$ or $\sim 2.5\sigma$).
6	Moderate: Occasional Failures	One occurrence every three months or three occurrences in 1,000 units ($C_{pk} \sim 1.00$ or $\sim 3\sigma$).
5		One occurrence every six months to one year or one occurrence in 10,000 units ($C_{pk} \sim 1.17$ or $\sim 3.5\sigma$).
4		One occurrence per year or six occurrences in 100,000 units ($C_{pk} \sim 1.33$ or $\sim 4\sigma$).
3	Low: Relatively few Failures	One occurrence every one to three years or six occurrences in 1,000,000 units ($C_{pk} \sim 1.67$ or $\sim 5\sigma$).
2		One occurrence every three to five years or 2 occurrences in 1,000,000,000 units ($C_{pk} \sim 2.00$ OR $\sim 6\sigma$).
1	Remote: Failure is unlikely	One occurrence in greater than five years or less than two occurrences in 1,000,000,000 units ($C_{pk} > 2.00$ OR $> 6\sigma$).

For batch failures use the time scale for unit failures use the unit scale.

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EXAMPLE

FMEA: Quantitation of Risk: Detection

10	Absolute Uncertainty	The product is not inspected or the defect caused by the failure is not detectable.
9	Very Remote	Product is sampled, inspected, and released based on Acceptable Quality Level (AQL) sampling plans.
8	Remote	Product is accepted based on no defects in a sample.
7	Very Low	Product is 100% manually inspected in the process.
6	Low	Product is 100% manually inspected using go/no-go or other mistake-proofing gauges.
5	Moderate	Some Statistical Process Control (SPC) is used in the process and product is final inspected off-line.
4	Moderately High	SPC is used and there is immediate reaction to out-of-control conditions.
3	High	An effective SPC program is in place with process capabilities (C_{pk}) greater than 1.33.
2	Very High	All product is 100% automatically inspected.
1	Almost Certain	The defect is obvious and there is 100% automatic inspection with regular calibration and preventive maintenance of the inspection equipment.

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EXAMPLE

Severity / Probability / Detection (SPD)

Ranking	Severity (S)	Probability (P)	Detection (D)
1	Negligible effect on final product performance as designed	Never happened and is unlikely to occur	Can always detect failure before it reaches customer
3	Reasonable expectation that the patient/user will experience inconvenience e.g. can't open container		High confidence will detect both random and systematic errors >99%
4	Reasonable expectation that the patient/user will experience temporary discomfort not requiring medical intervention e.g. pain on injection, brief fever	Low volume production: Never occurred but likely to or Seen once on a similar product. High volume production: Problem occurred once in 2 years	Confident systematic errors will be detected > 95% Little chance of random error detection <95%
6	Reasonable expectation that the fault will cause patient/user non-permanent medical condition requiring medical intervention e.g. infection requiring antibiotics	Low volume production: Occurred once in 5 years High volume production: Occurred more than once per year	
8	Reasonable expectation that the fault will cause patient/user permanent injury e.g. paralysis, coma	Problem occurs occasionally more than 3 times per year	No confidence that a random or remote error will be detected e.g. <95%
10	Reasonable expectation that the fault will cause patient/user death	Occurs frequently >1% of batches/vials/events	Virtually impossible to detect failure before it reaches customer

PhD R.C. Mendon, Menson & Associates, Inc
ICH EWG London, March 2004

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA) Drying Process

- **Severity (S)**
 - > Link to end product functional failure
 - > Medical Department involvement
- **Probability (P)**
 - > Use historical data
 - > Similar processes products
- **Detection**
 - > Method validation studies
 - > Historical data

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA) Drying Process

Ranking	Severity (S)	Probability (P)	Detection (D)
10	Death	More than once a day	Impossible to detect
9	↓	3 – 4 times a day	Remote
8	Permanent injury	Once a week	Very slight
7	↓	Once a month	Slight
6	Temporary injury	Once in three month	Low
5	↓	Once in half – one year	Medium
4	Reported/ dissatisfied	Once a year	Moderately high
3	↓	Once in 1 – 3 years	High
2	Notice/ no report	Once in 3 – 5 years	Very High
1	↓	Less than once in 5 years	Virtually certain

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA) Drying Process

Process	Potential Failure Mode	Potential Cause	S	P	D	RPN
1. Set up	contamination	disheveled gown of operator insufficient cleaning of equipment				
2. Start drying	contamination degradation of product	damage of inlet-air filter damage of thermometer				
3. Maintain temperature	long drying time high Loss On Drying (LOD) low LOD non-uniformity of LOD	unstable supply-air volume damage of timer high dew-point uneven temperature distribution				

RPN: Risk Priority Number = S*P*D

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA) Drying Process

Process	Potential Failure Mode	Potential Cause	S	P	D	RPN
1. Set up	contamination	disheveled gown of operator	3	5	8	120
		insufficient cleaning of equipment	7	2	8	112
2. Start drying	contamination	damage of inlet-air filter	7	3	6	126
	degradation of product	damage of thermometer	7	3	3	63
3. Maintain temperature	long drying time	unstable supply-air volume	2	4	5	40
	high LOD	malfunction of timer	2	2	2	8
	low LOD	high dew-point	3	3	3	27
	non-uniformity of LOD	uneven temperature distribution	3	5	3	45

Existing controls: IPC of LOD and degradation product after drying process
RPN: Risk Priority Number = S*P*D

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA) Drying Process

Process	Potential Cause	RPN	Recommended Action	S	P	D	RPN
1. Set up	disheveled gown of operator	120	use long gloves and goggles	3	2	8	48
	insufficient cleaning of equipment	112	change cleaning procedure	7	2	4	56
2. Start drying	damage of inlet-air filter	126	change maintenance period	7	2	6	84
	damage of thermometer	63	change calibration period	7	2	3	42
3. Maintain temperature	unstable supply-air volume	40	—	2	4	5	40
	malfunction of timer	8	—	2	2	2	8
	high dew-point	27	—	3	3	3	27
	uneven temperature distribution	45	—	3	5	3	45

Take action when RPN is over 100

RPN: Risk Priority Number = S*P*D

Take action when severity is over 5

Remaining critical parameters after taking action; further controls required

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

• Risk Evaluation

> Prepare a risk profile: **Consequences**

class	rating	Consequences
ii	marginal	Patient: no side effects, but patient can observe the defect Availability: interruption: < 4 weeks GMP: issue, investigation reports, market complaints etc. Business: loss: 100 – 1.000 k€ image: local scope Employees, neighbourhood: minor injuries, affect inside the site area Environment: only site area affected
ii	negligible	Patient: no side effects Availability: interruption: < 2 weeks GMP: corrective actions possible, deviation report etc. Business: loss: < 100 k€ image: no effects Employees, neighbourhood: no effects Environment: no effects

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

• Risk Evaluation: Risk Profile

		PROBABILITY					
		Very unlikely F	Unlikely E	Rare D	Occasional C	Moderate B	Frequent A
CONSEQUENCES	Catastrophic iv						
	Critical iii						
	Marginal ii						
	Negligible i						
		risk protection level					
		Accepted					

> For high risks, which are not acceptable, risk reduction measures have to be taken as a high priority

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

How to perform?

3. Summary (Risk Evaluation)

- > The effects are rated in terms of their **consequences** and the causes are assessed in terms of their **probabilities**
 - a) qualitative or b) quantitative
- > Based on these results a **risk profile** is completed.
- > In this **profile the risks** are compared with the **risk protection level**, which determines the accepted probability for defined consequences
- > Use as an aid to prioritise **actions**!

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

• QRM for facilities, equipment and utilities **Assess an existing compressed air system**

- > Old approach: **60 "risks"** should have been solved in detail
- > Initial RM-Approach:
 - > 4 sessions in total 16 people
 - > 153 potential risks discussed
 - > 34 Cases beyond the action limit
 - > **30 Corrective** actions have been performed (- 50%)
- > Review of RM-Approach after inspection
 - > Did you consider this hazard?
 - yes: show and explain rationale
 - yes, but start discussion for a yes/no decision
 - no: revisit initial risk assessment

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

Experiences

- Ease of applicability
 - > Prospective tool
 - > Good tool for operators to use
 - > Can be used to identify critical steps for validation
 - > More objective than Fault Tree Analysis
 - > Covers minor risks

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

Experiences

- Limitations
 - > Can be time and resource consuming
 - > Mitigation plans must be followed up
 - > Not a good tool for analysis of complex systems
 - > Compound failure effects cannot be analyzed
 - > Incorporating all possible factors requires a thorough knowledge of characteristics and performance of the different components of the system
 - > Successful completion requires expertise, experience and good team skills
 - > Dealing with data redundancies can be difficult

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ICH Q9 QUALITY RISK MANAGEMENT

Annex I.3

Failure Mode, Effects and Criticality Analysis (FMECA)

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I.3: Failure Mode, Effects and Criticality Analysis (FMECA)

(IEC 60812)

- Extended to incorporate an investigation of the degree of **severity** of the consequences, their respective **probabilities** of occurrence and their **detectability**
- The product or process **specifications** should be established
- Identify places where **additional preventive actions** may be necessary to minimize risks

Potential Areas of Use(s)

- Utilized on failures and risks associated with manufacturing processes

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Annex I.4

Fault Tree Analysis (FTA)

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I.4: Fault Tree Analysis (FTA)

(IEC 61025)

- Assumes **failure** of the functionality of a product or process
- Identifies all potential **root causes** of an assumed failure or problem that it is thought to be important to prevent
- **Evaluates system** (or sub-system) failures one at a time
- Can combine multiple causes by identifying causal chains

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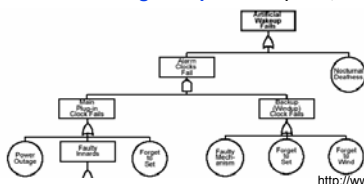
ICH Q9 QUALITY RISK MANAGEMENT

I.4: Fault Tree Analysis (FTA)

How to perform?

Results are represented pictorially in the form of a **tree of fault modes**. At each level in the tree, combinations of fault modes are described with **logical operators** (AND, OR, etc.)

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<http://www.sverdrup.com/safety/fta.pdf>

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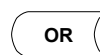
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I.4: Fault Tree Analysis (FTA)

Basic symbols: Basic Flow



- Fault in a box indicates that it is a result of previous faults



- Connects preceding fault with a subsequent fault that could cause a failure



- Connects two or more faults that must occur simultaneously to cause the preceding fault

Source: Overview of Risk Management Techniques, Robert C. Merson, PhD (2004).

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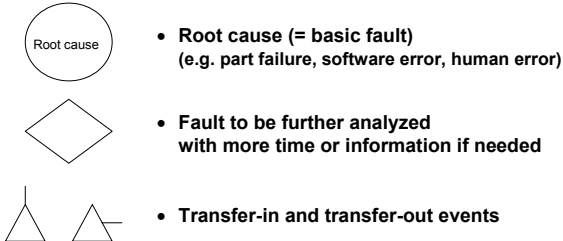
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EXAMPLE

I.4: Fault Tree Analysis (FTA)

• Basic symbols: End Points & Connector



Source: Overview of Risk Management Techniques, Robert C. Merson, PhD (2004).

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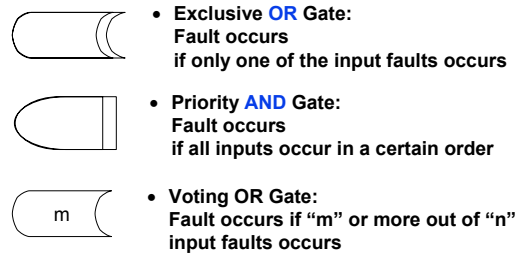
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EXAMPLE

I.4: Fault Tree Analysis (FTA)

• Additional Symbols



Source: Overview of Risk Management Techniques, Robert C. Merson, PhD (2004).

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I.4: Fault Tree Analysis (FTA)

Potential Areas of Use(s)

- Establish the pathway to the **root cause** of the failure
- While investigating **complaints or deviations** to fully understand their root cause
- Ensure that intended improvements will fully resolve the issue and not lead to other issues
- Evaluating how multiple factors **affect a given issue**

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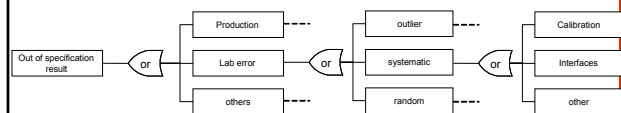
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EXAMPLE

I.4: Fault Tree Analysis (FTA)

• Investigation of laboratory failures



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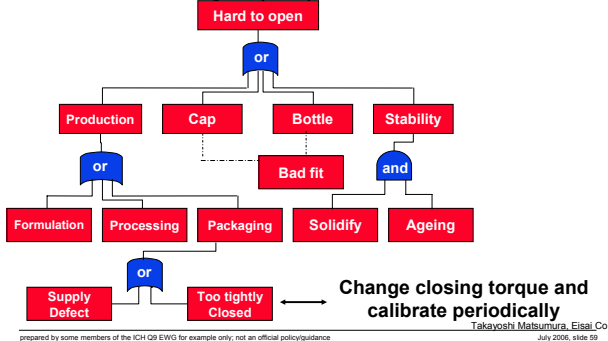
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EXAMPLE

I.4: Fault Tree Analysis (FTA)



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I.4: Fault Tree Analysis (FTA)

Experiences

- Better as a retrospective tool
- Visually focused: aid for showing linkages
- Limitations
 - > Only as good as input
 - > Time and resource consuming (needs FMEA as a complement)
 - > Need skilled leader to focus on what is really important
 - > Need significant amount of information
 - > Human errors may be difficult to predict
 - > Many potential fault trees for a system
 - Some more useful than others
 - Need to evaluate contribution

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EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

I.4: Fault Tree Analysis (FTA)

FTA

- Assumes failure of the functionality of a product
- Identifies the root cause of functional failure
- Top down

FMEA

- Assumes component failure
- Identifies functional failure as a result of component failure
- Bottom up

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Annex I.5

Hazard Analysis and Critical Control Points (HACCP)

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ICH Q9 QUALITY RISK MANAGEMENT

I.5: Hazard Analysis and Critical Control Points (HACCP)

“A systematic, proactive, and preventive method for assuring product quality, reliability, and safety”

WHO: <http://www.who.int/medicines/library/gsm/trs908/trs908-7.pdf>
Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals, WHO Technical Report Series No 908, Annex 7, WHO, Geneva, 2003

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I.5: Hazard Analysis and Critical Control Points (HACCP)

How to perform?

- Conduct hazard analysis: identify preventive measures for each step of the process
- Determine critical control points (CCP's)
- Establish target levels and critical limit(s)
- Establish system to monitor the CCP's
- Establish corrective actions to be taken, if CCP is out of control
- Establish verification procedures, that HACCP works effectively
- Establish documentation of all procedures and keep records

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See WHO

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I.5: Hazard Analysis and Critical Control Points (HACCP)

Potential Areas of Use(s)

- To identify and manage risks associated with **physical, chemical and biological hazards** (including microbiological contamination)
- Useful when process understanding is sufficiently comprehensive to support identification of **critical control points** (critical parameters / variables)
- Facilitates monitoring of **critical points** in the manufacturing process

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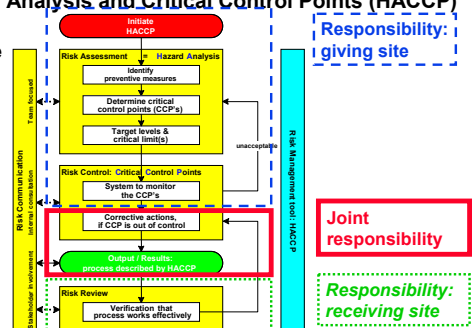
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EXAMPLE

I.5: Hazard Analysis and Critical Control Points (HACCP)

- Site change or Technical transfer



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EXAMPLE

I.5: Hazard Analysis and Critical Control Points (HACCP)

- Analyse a tablet process step because a systematic, proactive, and preventive risk assessment method helps to adjust parameters of the machine

Automatic machine without constant operator control

Quality hazard	Critical Control Point (CCP)	Target level	Critical limits	Comments
influence on specification of appearance	speed	400'000	<400'000	fix parameter to adjust
influence on specification of hardness	compression force	15 kN	13-18kN	in function with the weight of the tablet, thickness and hardness
influence on specification of assay	weight variation	200 mg	180-220 mg	+/- 10 %

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EXAMPLE

I.5: Hazard Analysis and Critical Control Points (HACCP)

Comments	System to monitor CCP	Possible corrective actions, if CCP is out of control	Keeping records
fix parameter to adjust	by equipment (autoimmunisation)	< content uniformity out of range	online Batch Record
in function with the weight of the tablet, thickness and hardness	by equipment (autoimmunisation)	automatic ejection of tablet	online Batch Record
+/- 10 %	IPC on weight	rejection (100% mass control)	analytical data in Batch Record
	compression force	automatic ejection of tablet	online Batch Record
release limit for stability must be	stability studies	critical limit: min 50 N	stability studies
optimisation during production	IPC of appearance	adjust machine parameters	online Batch Record

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I.5: Hazard Analysis and Critical Control Points (HACCP)

Experiences

- Benefit
 - > Teamwork in cross functional groups
 - > Use very similar principles in Qualification & Validation
 - > Critical control points (CCPs) are similar to critical process parameters
- Limitations of the model
 - > Has to be combined with another tool (e.g. FMEA, statistical tools)
 - > Not good for complex processes
 - > Assumes you know the processes
 - > Most CCPs should be addressed for risk control activities
 - > May need to use other models for quantifying risk

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ICH Q9 QUALITY RISK MANAGEMENT

Annex I.6

Hazard Operability Analysis (HAZOP)

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I.6: Hazard Operability Analysis (HAZOP)

(IEC 61882)

- A theory that assumes that risk events are caused by deviations from the design or operating intentions
- Identify potential deviations from normal use

How to perform?

A systematic brainstorming technique for identifying hazards using so-called "guide-words" applied to relevant parameters:

- > No, More, Other Than, None

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I.6: Hazard Operability Analysis (HAZOP)

Concept

- Focus team discussions by applying "deviations" to specific nodes
- Deviations are generated by applying Guidewords to process parameters
- Examine the process by discussing causes of each deviation
 - > Identify consequences
 - > Evaluate risk and safeguards
 - > Make recommendations, if necessary
- Include all parts of the process

Source: Hazard and Operability Studies in Solid Dosage Manufacture. Nail L. Maxson. (2004).

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I.6: Hazard Operability Analysis (HAZOP)

Potential Areas of Use(s)

- Manufacturing processes
- Equipment and facilities
- Evaluating process safety hazards
- Primarily as starter of a HACCP
- Operator error ("use error")

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I.6: Hazard Operability Analysis (HAZOP)

Guidewords	Explanation	Remarks
NO, NOT, NONE	The total absence of the function	No part of the function is active, but also nothing else happens
MORE	Quantitative increase or	This applies to quantities & properties such as flow, temperature, and also for functions such as heating and reacting.
LESS	Quantitative decrease	
AS WELL AS	Qualitative increase or	All desired functions & operations are achieved. Additionally, something else happens. Only a few functions are achieved, some not.
PARTIALLY	Qualitative decrease	
REVERSE	The logical reverse of the desired function	This applies mainly to functions, e.g., reverse flow or reversible chemical reaction. It can also be applied to materials, e.g., poison instead of antidote, or D- instead of L- optical isomer.
OTHER	Total exchange	The original function is not performed. Something totally different happens.

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Nail L. Maxson, (2004).

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EXAMPLE

I.6: Hazard Operability Analysis (HAZOP)

Deviation	Causes	Consequences	Safeguards	Recommend
High temperature in blender	Steam heating control malfunction	• Feed material #1 reaches decomposition temperature • Violent reaction with toxic gas generation • Personnel exposure/injury • Equipment damage	• Diverse high temp. interlock on blender • Blender vented	• Test interlock on quarterly basis • Add steam heating control to monthly PM

Nail L. Maxson, (2004).

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I.6: Hazard Operability Analysis (HAZOP)

Experiences

- Ease of applicability of the model?
 - > Simplifies decision making
 - > Allows uniformity of analysis across sites
 - > Process steps guided ("guide words", if available)
- Limitations of the model
 - > Applies to specific situations only
 - > May need to use other models for quantifying risk
 - > Not a structured approach
 - > Not designed for quantifiable risk assessment
 - > Complex output

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Annex I.7

Preliminary Hazard Analysis (PHA)

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I.7: Preliminary Hazard Analysis (PHA)

(ISO14971)

- Analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that can cause harm
- In estimating their probability of occurrence for a given activity, facility, product or system

How to perform?

- Identification of the possibilities that the risk event happens
- Qualitative evaluation of the extent of possible injury or damage to health that could result
- Identification of possible remedial measures

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EXAMPLE

I.7: Preliminary Hazard Analysis (PHA)

The steps

- Risk Matrix Form
 - > List known potential hazards
 - Literature
 - Previous projects
 - Reportable events
 - Complaints
- Severity rankings
- Frequency codes and estimates risk codes
- Once established should remain same for similar product classes

Hazards Arising From Product Design				
Hazard	Investigation/Controls	Sev	Freq	Imp (SxF)

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EXAMPLE

I.7: Preliminary Hazard Analysis (PHA)

Hazards Arising From Product Design				
Hazard	Investigation/Controls	Sev	Freq	Imp
Wrong Material	SOPs, Crosscheck	Sev	Rem	I
Lack of stability	Stability studies	Min	Occ	I

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I.7: Preliminary Hazard Analysis (PHA)

Potential Areas of Use(s)

- Analyzing existing systems
- Prioritizing hazards
- Evaluate the types of hazards for the general product type, then the product class and finally the specific product
- Early in the development: little information on design details or operating procedures will often be a precursor to further studies
- For product, process and facility design
- Further assessed with other risk management tools

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ICH Q9 QUALITY RISK MANAGEMENT

Annex I.8

Risk ranking and filtering

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I.8: Risk ranking and filtering

Compare and prioritize risks

How to perform?

- Requires evaluation of multiple diverse quantitative and qualitative factors for each risk
- Involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk
- These factors are combined into a single relative risk score that can then be compared, prioritized and ranked

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I.8: Risk ranking and filtering

Potential Areas of Use(s)

- To prioritize manufacturing sites for inspection/audit by regulators or industry
- Helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool
- Useful when management needs to evaluate both quantitatively and qualitatively assessed risks within the same organizational framework

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk assessment: Risk identification

- > recurring quality relevant problems within production and/or processes

Risk assessment: Risk analysis

Footnote on an analysis of

- > Production problems 1999-2002
- > Complaints 2000-2002
- > Investigation Reports 2000-2002
- > Recalls 2000-2002
- > Additional information from manufacturer considered

J. Knöbel, S. Marner, Roche

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EXAMPLE

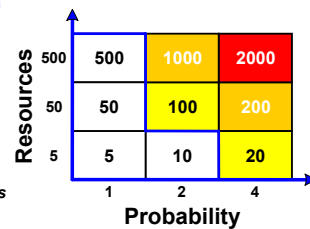
I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk assessment: Risk evaluation

Three columns based on a classical approach by multiplying factors

- Probability
- 1: rare quality events
 - 2: infrequent quality events
 - 3: frequent quality events



Based on J. Knöbel, S. Marner, Roche

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk assessment: Risk analysis

Analyze production problems

Site	Product name	Type of recurrent problem/defect
A	ABC	Broken units
B	ACB	Broken tablets
C	BAC	Melt backs during lyophilization
A	CAB	Foreign particles

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EXAMPLE

I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk assessment: Risk evaluation

Risk evaluation added to production problems

Site	Product name	Type of recurrent problem/defect	Probability	Resources	Risk (Probability multiplied with Resource)
A	ABC	Broken units	4	500	2000
B	ACB	Broken tablets	2	500	1000
C	BAC	Melt backs during lyophilization	4	50	200
A	CAB	Foreign particles	2	50	100

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EXAMPLE

I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk assessment: Risk Control

Risk control actions added to production problems

Site	Product name	Type of recurrent problem/defect	Corrective actions instituted to date	Probability	Resources	Risk (Probability multiplied with Resources)
A	ABC	Broken units	Task force headed by investigations in B initiated	4	500	2000
B	ACB	Broken tablets	Investigating process improvements together with production	2	500	1000
C	BAC	Melt backs during lyophilization	Project initiated	4	50	200
A	CAB	Foreign particles		2	50	100

J. Knöbel, S. Marner, Roche

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk assessment: Risk analysis

Analyze process problems

Process	Products concerned
Printing of Variable Data	ABC
	ACB
	BAC
	CAB
	CBA
Blister: blister foil peels off	ABC
	ACB
	BAC
	CAB

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk assessment: Risk evaluation

Risk evaluation added to process problems

Process	Products concerned	Probability	Resources	Risk (Probability multiplied with Resources)
Missing prints of Variable Data	ABC	4	500	2000
	ACB	4	50	200
	BAC	4	50	200
	CAB	4	5	20
	CBA	4	500	2000
Blister: blister foil peels off	ABC	2	500	2000
	ACB	2	50	100
	BAC	2	50	100
	CAB	2	50	100

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EXAMPLE

I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk assessment: Risk Control

Risk control actions added to process problems

Process	Products concerned	Corrective actions instituted to date	Probability	Resources	Risk (Probability multiplied with Resources)
Missing prints of Variable Data	ABC	Project started; corrective measures under discussion	4	500	2000
	ACB		4	50	200
	BAC		4	50	200
	CAB		4	5	20
	CBA		4	500	2000
Blister: blister foil peels off	ABC	Task force established	2	500	2000
	ACB		2	50	100
	BAC		2	50	100
	CAB		2	50	100

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EXAMPLE

I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk communication

- Providing stakeholders with the update of the overview of Risk control step

Risk Review

- Regularly the responsible person updates the overview to support line/senior management decisions

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EXAMPLE

I.8: Risk ranking and filtering

Risk Matrix (1)

		Severity			
		Low	Medium	High	
Probability	High				Risk Class ONE Risk Class TWO Risk Class THREE
	Medium				
	Low				

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Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

I.8: Risk ranking and filtering

Risk Matrix (2)

		Detection			
		Low	Medium	High	
Risk Classification	ONE				HIGH priority MEDIUM priority LOW priority
	TWO				
	THREE				

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ICH Q9 QUALITY RISK MANAGEMENT

Annex I.9

Supporting statistical tools

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ICH Q9 QUALITY RISK MANAGEMENT

I.9: Supporting statistical tools

- Control Charts (for example):
 - Shewhart Control Charts (see ISO 8258)
 - Control Charts with Arithmetic Average and Warning Limits (see ISO 7873)
 - Acceptance Control Charts (see ISO 7966)
 - Cumulative Sum Charts (ISO 7871)
 - Weighted Moving Average
- Design of Experiments (DOE)
- Pareto Charts
- Process Capability Analysis

Aid for:
- Effective data assessment
- Aid in determining the significance of the data set(s)

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ICH Q9 QUALITY RISK MANAGEMENT

I.9: Supporting statistical tools

Control charts (ISO 7870)

- Indicates the range of variability that is built into a system
- Shows statistically determined upper and lower control limits drawn on either side of the process average
- The bounds of the control chart are marked by **upper and lower control limits**
 - Calculated by applying statistical formulas to data
 - Data points that fall outside these bounds represent variations due to special causes
 - Can be found and eliminated
- Improvements require changes in the process

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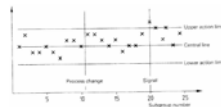
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I.9: Supporting statistical tools

Control charts

Potential Areas of Use(s)

- Monitoring critical parameters
- Provides information to determine
 - Process capability
 - Variability
 - Control
- Some charts are dealing with warning limits or trend analysis



Example

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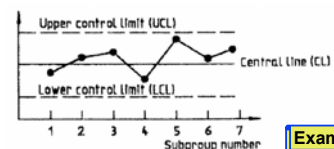
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I.9: Supporting statistical tools

Control Chart: Shewhart Control Charts (ISO 8258)

- Use warning limits
- Analysis trend patterns



Example

Potential Areas of Use(s)

- Statistical control of the process

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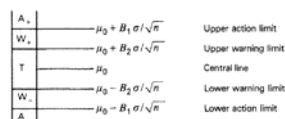
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ICH Q9 QUALITY RISK MANAGEMENT

I.9: Supporting statistical tools

Control Charts with Arithmetic Average and Warning Limits (ISO 7873)

- A control chart with **warning and action limits**



Potential Areas of Use(s)

- Enable a base period of quality measure
- Provide a basis for the construction of relationships between a process and product quality
- Producing recommendations for the adjustment of the process
- Can be applied with process Analytical technology tools

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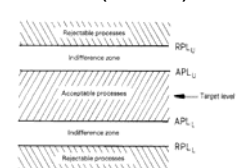
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ICH Q9 QUALITY RISK MANAGEMENT

I.9: Supporting statistical tools

Control Chart: Acceptance Control Charts (ISO 7966)

- Chart with a **central line** within an **acceptable process zone**
- Ideal the average should be the target value



Potential Areas of Use(s)

- During regular batch manufacturing can give guidance for determine sample size, action limits and decision criteria
- Ongoing improvements under process robustness/six sigma program can be initiated

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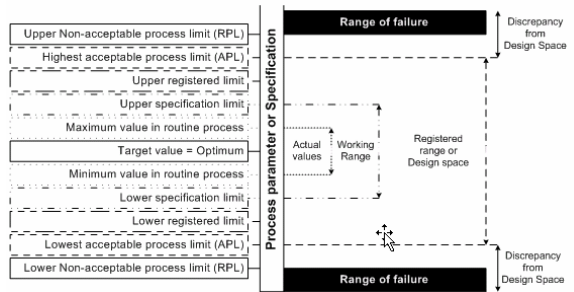
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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Compilation of limits and ranges



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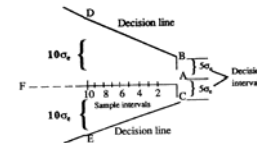
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I.9: Supporting statistical tools

Control Charts: Cumulative Sum Charts (ISO 7871)

- Sum of deviations from the mean or predefined value and plot against time or number of occurrences (e.g. V-mask)



- Determines if a monitored process is changing
- They will detect shifts of .5 sigma to 2 sigma in about half the time of Shewhart charts with the same sample size

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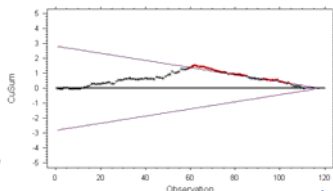
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I.9: Supporting statistical tools

Control Charts: Cumulative Sum Charts (ISO 7871)

Potential Areas of Use(s)

- Analyze process parameters or analytical results (e.g. PAT)
- Allow the detection of slight discrepancies in a process before a trend is visible using other control charts



Example

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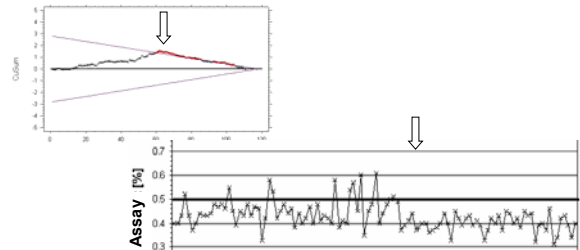
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EXAMPLE

I.9: Supporting statistical tools

Control Charts: Cumulative Sum Charts (ISO 7871)



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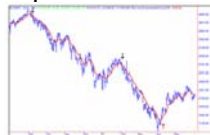
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I.9: Supporting statistical tools

Control Chart: Weighted Moving Average

- A simple, or arithmetic, moving average is calculated by adding the closing results of the security for a number of time periods and then dividing this total by the number of time periods



Potential Areas of Use(s)

- Analyze process parameters or analytical results (e.g. PAT)
- Allow the detection of slight discrepancies in a process before a trend is visible using other control charts

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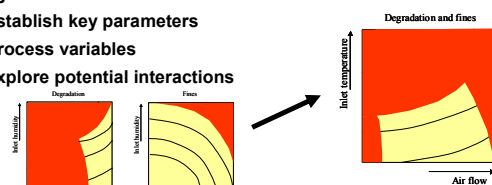
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ICH Q9 QUALITY RISK MANAGEMENT

I.9: Supporting statistical tools

Design of Experiments (DoE)

- Design experiments based on statistical considerations
- Analyze data and results to determine
 - establish key parameters
 - process variables
 - explore potential interactions



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I.9: Supporting statistical tools

Design of Experiments (DOE)

Potential Areas of Use(s)

- Research and development area
- Retrospective evaluation of established parameters (Proven Acceptable Ranges)
- Systematically choosing certain combinations of variables it is possible to separate their individual effects
- A special variant: focus on optimizing design parameters to minimize variation BEFORE optimizing design to hit mean target values for output parameters

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EXAMPLE

I.9: Supporting statistical tools

Design of Experiments (DOE) in a submission

- Type of experimental design used e.g. full/ fractional factorial
- Justification of the selection of factors and responses
- As an appendix
 - > Number and levels of factors under study
 - > The experimental matrix with the values of the responses for each combination of factors
- Graphical representation
 - > Coefficient plot of the relative significance of the factors under study and interactions between them

Reflection paper on...PAT: EMEA/INS/277260/2005, March 20, 2006

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EXAMPLE

I.9: Supporting statistical tools

Design of Experiments (DOE) in a submission

- Statistical evaluation of the model derived from DoE (e.g. ANOVA table)
- Graphical representation of the relationship of the significant factors under study with the responses (e.g. response surface and contour plots) providing a clear overview of the conclusions.
- The Design Space (based on real test results and/or on the model) as defined in ICH Q8 should be described
- Verification of the model derived from DoE

Reflection paper on...PAT: EMEA/INS/277260/2005, March 20, 2006

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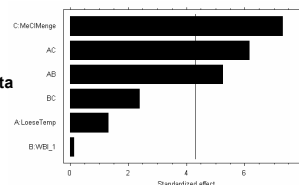
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ICH Q9 QUALITY RISK MANAGEMENT

I.9: Supporting statistical tools

Pareto Charts

- Created by plotting the cumulative frequencies of the relative frequency data in descending order
- The most essential factors for the analysis are graphically apparent, and in an orderly format



Potential Areas of Use(s)

- Identify those factors that have the greatest cumulative effect on a system
- Few important factors in a process: Screen out the less significant factors

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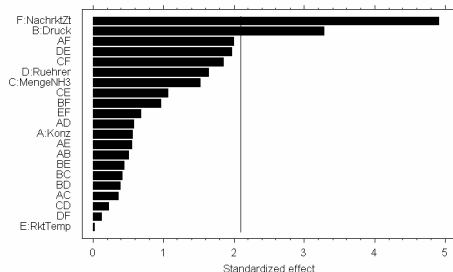
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EXAMPLE

I.9: Supporting statistical tools

Pareto Chart



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I.9: Supporting statistical tools

Process Capability Analysis

- Estimate the potential percent of defective product

Cp value	cp=0.5	cp=1	cp=3
graphical view of different cp values			
values statistically out of limit	13,58 %	0,27 %	approx. 0
values in the limit	86,42 %	99,73 %	> 99,99999 %
Result:	process statistically out of control	process statistically under control	

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I.9: Supporting statistical tools

Process Capability Analysis

Potential Areas of Use(s)

- Monitor / measure process variability
- Analyze data retrospectively
 - > Annual Product Review
- Determine the relationship between process variability and specification
- Requirement: Process specific data
- Tool for both regulator and industry

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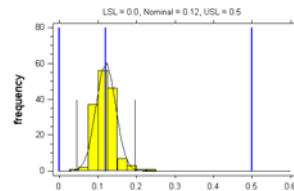
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I.9: Supporting statistical tools

Histogram

- A simple, graphical view of accumulated data
 - > including its dispersion and central tendency
- Provide the easiest way to evaluate the distribution of data



Process compatibility

Example

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I.9: Supporting statistical tools

Scatter diagrams (x/y-diagram)

- To depict the influence that one variable has on another
- Usually displays points representing the observed value of one variable corresponding to the value of another variable
- How to perform: plot two parameters x and y in a two dimensional way

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Others

Combination of tools

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Combination of Tools

Probabilistic Risk Assessment (PRA)

- Integrating various reliability modelling tools such as Fault Tree, Event Tree Block Diagram, FMEA to numerically quantify risks
- Determine what quality risk scenarios can occur, what is the likelihood and the consequences given they occur.
- Estimates of the parameters used to determine the frequencies and probabilities of the various events
- It involves the development of models that delineate the response of systems and operators to accident initiating events.

<http://www.relexsoftware.com/resources/riskassess.asp>

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ICH Q9 QUALITY RISK MANAGEMENT

Combination of Tools

Probabilistic Risk Assessment (PRA)

How to perform?

- To identify an undesired top event e.g. "loss of life" or "loss of mission"
- Trace out all quality risk that could lead to this events.
- Conducted through the use of event trees (fault trees)
- At the lowest level: basic events are assigned probabilities
- Propagated up the logic to reach a probability

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Examples of combination of tools

Another way to proceed

1. Define the scope of an analysis
Collect all relevant data surrounding the system
Subject to determine the need for additional information
2. Describe the desired and controlled conditions of the process
3. Using a structured approach identify the risk by reviewing the direct and indirect causal areas
4. Using assessment tools (e.g. statistical) assess the hazard

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Examples of combination of tools

Another way to proceed

1. Define the scope of QRM
2. Choose team and team leader
3. Identify hazards and assess hazard scenarios
4. Build the risk profile to visualize the risks:
 - set the risk tolerance boundary
 - plot the risks
5. Develop risk reduction actions
6. Accept risk reduction actions
7. Implement risk reduction actions
8. Follow up on success

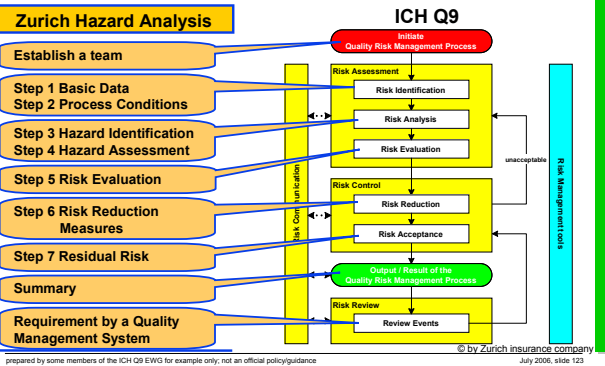
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EXAMPLE



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EXAMPLE

Examples of combination of tools

“Zurich Hazard Analysis” Methodology A systematic approach managing quality risks

- **Step 1 Basic Data**
 - > Define the scope carefully
 - > Collect all relevant data about the system
 - > Determine the need for additional data
- **Step 2 Process Conditions**
 - > Describe the desired, quality function of the system

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EXAMPLE

Examples of combination of tools

“Zurich Hazard Analysis” Methodology

- **Step 3 Hazard Identification**
 - > Systematic approach by reviewing all critical areas
 - > An optimal method doesn't exist as it depends on the particular system being analysed
- **Step 4 Hazard Assessment**
 - > The effects are rated in terms of their **consequences** and the causes are assessed in terms of their **probabilities**
 - > Based on these **results** a risk profile is created
 - > In this profile the risks are compared with the **risk protection level**: define the accepted level

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EXAMPLE

Examples of combination of tools

“Zurich Hazard Analysis” Methodology

- **Step 5 Risk Evaluation**
 - > The effects are rated in and the result completes the risk profile
 - > In this profile the risks are compared with the risk protection level
- **Step 6 Risk Reduction Measures**
 - > Measures to be taken for every unacceptable risk to **reduce the consequences and the probability or both**
 - > Prioritise actions



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EXAMPLE

Examples of combination of tools

“Zurich Hazard Analysis” Methodology

• Step 7 Residual Risk

- > The residual risk is acceptable if the risk protection level is achieved
- > Current scientific knowledge and techniques must be considered in coming to this decision as well as the authorities

• Communicate results (Risk Communication)

- > Summarise the relevant risks
- > Low risks may be neglected

• Maintain Risk Management (Risk Review)

- > Updated regularly especially in any change

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Conclusion

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CONSIDERATIONS

Simple explanations of some tools

• Failure Mode Effects Analysis (FMEA)

- > Break down large complex processes into manageable steps

• Failure Mode, Effects and Criticality Analysis (FMECA)

- > FMEA & links severity, probability & detectability to criticality

• Fault Tree Analysis (FTA)

- > Tree of failure modes combinations with logical operators

• Hazard Analysis and Critical Control Points (HACCP)

- > Systematic, proactive, and preventive method on criticality

• Hazard Operability Analysis (HAZOP)

- > Brainstorming technique

• Preliminary Hazard Analysis (PHA)

- > Possibilities that the risk event happens

• Risk ranking and filtering

- > Compare and prioritize risks with factors for each risk



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Annex I: Methods & Tools

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Overview: Some risk management tools...

Supporting statistical tools

- Control Charts
- Design of Experiments (DOE)
- Pareto Charts
- Probabilistic Risk Assessment (PRA)
- Process Capability Analysis

The results from using statistical methods
can not be better than your data

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Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT

Conclusion on Methods and Tools

- Provides a **general overview** of and **references** for some of the primary tools
- Might be used in QRM by **industry and competent authorities**
- This is **not an exhaustive list**
- No one tool or set of tools is **applicable to every** situation in which a QRM procedure is used

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Conclusion: ICH Q9 makes suggestions for improvements of Quality

*This Annex is intended to **identify opportunities** for the use of quality risk management principles by industry and regulators (e.g., for both inspections and submissions).*

*However, the **selection of particular risk management tools** is completely **dependent upon specific facts and circumstances**.*

*These examples are provided for **illustrative purposes** and only suggest potential uses of quality risk management.*

*This Annex is **not intended to create any new expectations** beyond the current regulatory requirements.*

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Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT

It is not always necessary to use formal risk management tools in a QRM process, however in the right circumstances they can be very powerful



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Annex II: Potential Applications

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Quality Risk Management

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Annex II: Potential Applications

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

Purpose of this part

- To guide through **Potential Applications for Quality Risk Management**
- Provision of some concrete, non exhaustive examples

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

Introduction

- This Annex is intended to identify **potential uses** of quality risk management principles and tools **by industry and regulators**.
- However, the **selection of particular risk management tools** is completely dependent upon specific facts and circumstances.
- These examples are provided for **illustrative purposes** and only **suggest potential uses** of quality risk management.
- This Annex is **not** intended to **create any new expectations** beyond the current regulatory requirements.

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Annex II: Potential Applications

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Potential Applications for Quality Risk Management

Quality Risk Management as Part of...

- II.1 Integrated Quality Management
- II.2 Regulatory Operations
- II.3 Development
- II.4 Facilities, Equipment and Utilities
- II.5 Materials Management
- II.6 Production
- II.7 Laboratory Control and Stability Studies
- II.8 Packaging and Labelling

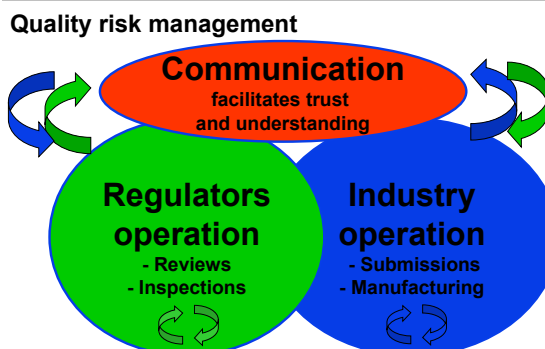
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Annex II: Potential Applications

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CONSIDERATIONS



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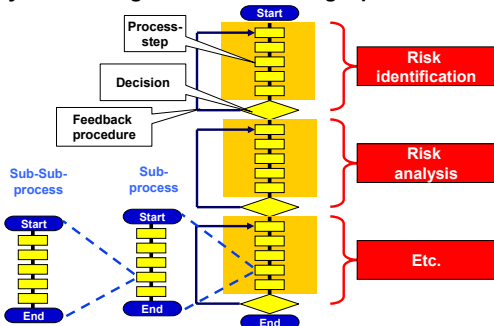
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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

Quality Risk Management is not a single process



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Probability and Severity

- Given the broad concept of risk can **probability** and **severity** be more narrowly defined?
- Probability has two major meanings
 - > Frequency of "successes" divided by the number of trials
 - > Degree of belief
- Severity is even more difficult to qualify as it often has different variable attributes around a quantifiable outcome
- Examples...

G. Claycomb, FDA, Sept. 2005

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Which consequence is more severe?

- 300 lives lost in single, fiery plane crash
- 300 lives lost on country roads over a weekend
- 300 lives *potentially* lost from cancer within the next 20 years

Even in a narrow context,

e.g., "microbial contamination", severity potentially spans:

- > Product spoilage...
- > Mild malaise...acute illness...(acute) death
- > Chronic illness...premature death

G. Claycomb, FDA, Sept. 2005

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Simple Probability Statements?

A common understanding of probability is elusive!

For example:

What does a "30% chance of rain tomorrow" mean?

- > 30% of the days like tomorrow will have at least a trace of rain.
- > 30% of the area will have rain tomorrow.
- > 30% of the time tomorrow, it will rain.

See Gigerenzer, et. al (2005)

G. Claycomb, FDA, Sept. 2005

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Challenges for potential applications

Problem:

What is the risk of a rain shower now?

- Answer 1:
 - > Set up a new department with 5 employees
 - > Develop a computer program for this risk ("weather forecast")
 - > 10 external meetings, 2 conferences, 5 publications,...
 - > Verify with experimental data
 - > Revisit your program on an annual basis
 - > ...
- Answer 2:
 - > Look out of a window

S. Rönninger, Sept. 2005

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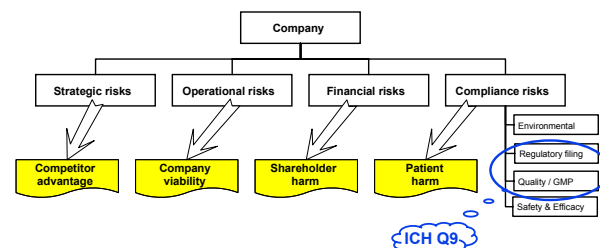
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EXAMPLE

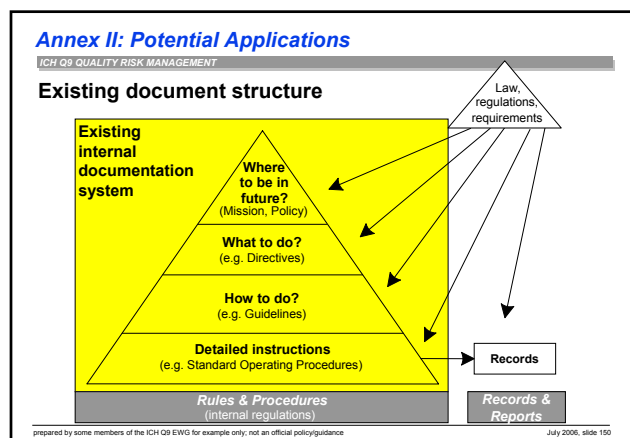
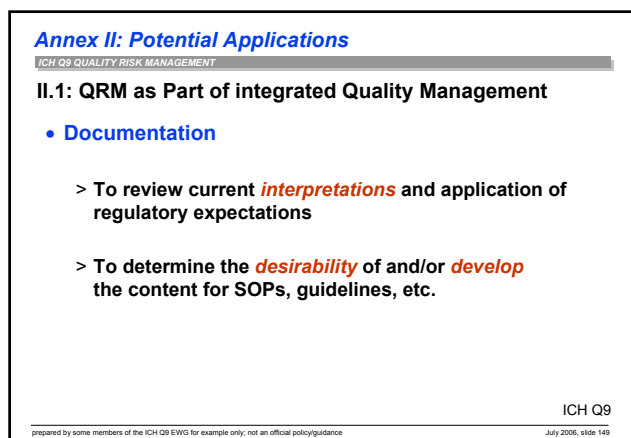
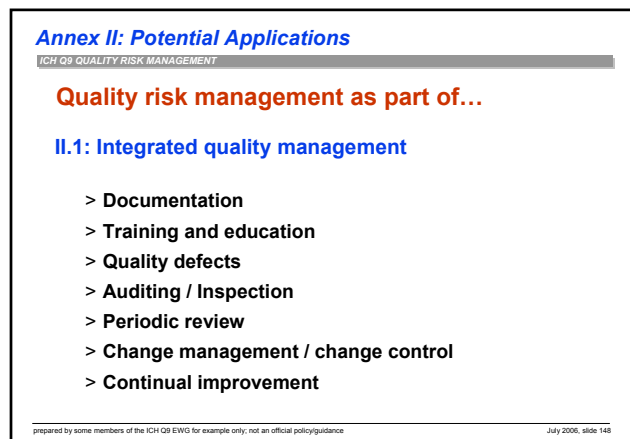
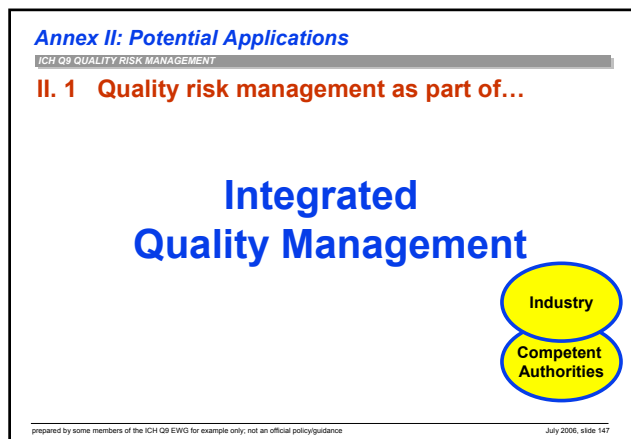
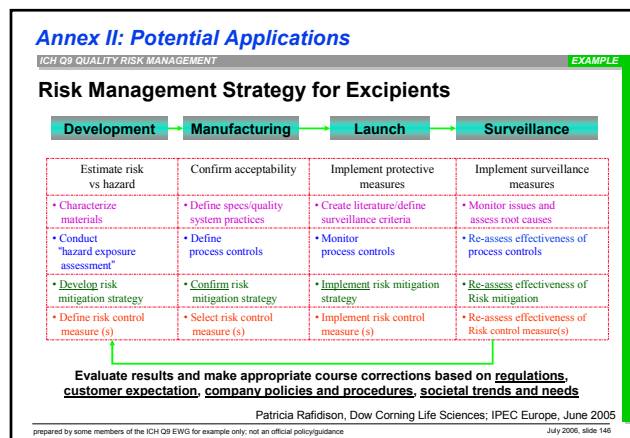
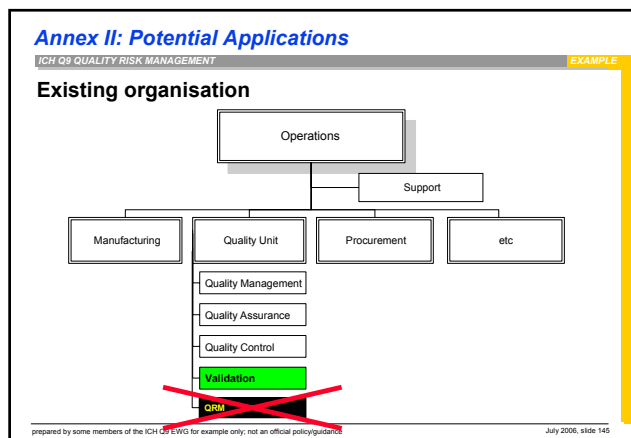
Managing risks in a company



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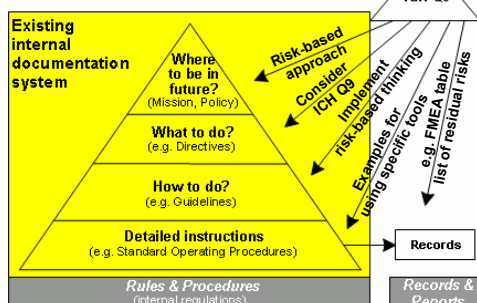


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Include ICH Q9



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Application of documentation system

- A topic for any quality management system might be a “**risk-based approach**” for decision making
- Include **consideration of ICH Q9 guideline** in the “directive on Quality Unit-activities” as a requirement
- During periodic review of regulations, policies, guidelines and standard operating procedures (SOP) etc. think about **implementing the ICH Q9 principles**
- Share examples of **specific tools and their use** as a means of sharing best practice

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.1: QRM as Part of integrated Quality Management

- **Training and education**
 - > To **determine the appropriateness** of initial and/or ongoing training sessions
 - Based on **education, experience and working habits**
 - A periodic assessment of previous training (**effectiveness**)
 - > To **identify** the training, experience, qualifications and physical **abilities**
 - > To perform an operation reliably and with no adverse **impact on the quality of the product**

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.1: QRM as Part of integrated Quality Management

- **Quality defects**
 - > To provide the basis for identifying, evaluating, and communicating the **potential quality impact** of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc.
 - > To facilitate risk **communications**
 - > To determine **appropriate action** to address significant product defects, in conjunction with regulatory authorities (e.g., recall)

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Assess the history of known quality defects

- **Vision**
 - > Robust Processes, non-recurrent Q-problems
- **Target**
 - > **Continuous improvement** to resolve known problems e.g. from CAPA, inspections/audits, non robust processes
 - > Preventatively work towards the achievement of a **high reliability, productivity, quality** of all that we do
 - > Manage dedicated projects to **support site / departments / process / products**

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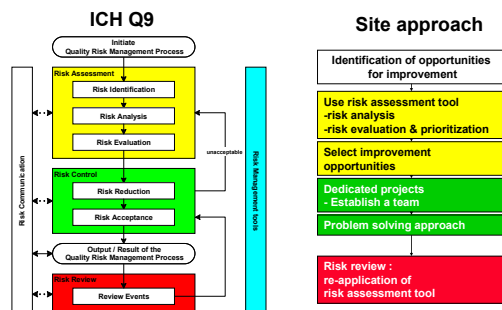
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EXAMPLE

Assess the history of known quality defects



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EXAMPLE

Assess the history of known quality defects

- Approach
 - > Increase the knowledge of weaknesses for all processes at the site and evaluate the related risks
 - > Tackle individual issues by problem solving methods e.g. root cause analysis, statistics, tools
- Tool
 - > Risk Assessment tools: select dynamic tool to identify which are the most significant problems in order to allow identification of priorities (e.g. FTA, FMEA, etc.)
 - > SixSigma type Project approach for problem solving teams on each identified priority

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Assess the history of known quality defects

The project approach

- Teamwork (inter-departmental teams) possibly using a **facilitator**
 - > Select methodology
 - > Commit resources appropriate to the project, priority and size
- Problem solving structure
 - > Problem Finding & Setting
 - > Problem Analysis
 - > Problem solution identification
 - > Sharing with management (communication)
 - > Decision making & implementation

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.1: QRM as Part of integrated Quality Management

Deviation / Investigation Report

- The event triggers a review of quality risk management decisions
 - > to control or accept risk related to a process
 - > to ensure these decisions are still valid based on the new learning
- In detail this could include:
 - > Initiate Quality Risk Management process: Product and process information
 - > Define the problem: Detailed description of the discrepancy



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Deviation/ Investigation Report

- Risk assessment: Risk analysis
 - > Assessment of effects of the discrepancy
Examples if applicable:
 - Product quality
 - Drug safety
 - Registration files / Marketing authorisation
 - Systems in place
 - Availability of goods: potentially insufficient stock levels
 - > Identification of the root cause



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Annex II: Potential Applications

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EXAMPLE

Deviation/ Investigation Report

- Risk assessment: Risk evaluation
 - > Consequences for other products / batches
 - > Systems failure
 - > Evaluation of
 - Performed
 - Foreseen actions
 - Measurements
 - ...



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Deviation/ Investigation Report

- Risk Control: Risk Reduction/ Mitigation
 - > Corrective actions to resolve the discrepancy
 - > Corrective actions to avoid a recurrence in the future
- Risk Control: Risk Acceptance
 - > Conclusions of measures taken
 - > Decisions on disposition of the material
 - > Define Follow up actions (if applicable)
 - > Management summary (if applicable)
 - > Date and signature
 - responsible manager
 - approval of QU



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Deviation/ Investigation Report

- Risk Communication
 - > Frequent interactions (e.g. short daily meeting)
 - > Informal meetings
 - > Scheduled regular meetings (minutes)



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EXAMPLE

Deviation/ Investigation Report

- Risk Review
 - > Follow up of action items
 - > Summary and evaluation
- e.g. Annual Product Review



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

One page: Deviation/ Investigation Report

No: _____		product - year / sequence no.		Deviation Report		My logo	
Risk Initiation: init. manager: Location: Tel. no.:		Risk Initiation: Product: Step: Batch No. / Pos. No.:		page /			
Risk Identification: Description of the discrepancy		Risk Analysis: Assessment of effects of the discrepancy (incl. root cause) ☐ Master batch record ☐ Cleaning ☐ Instruments ☐ Maintenance ☐		Affected amount (e.g. kg, No bottles)		Risk Reduction: Planned actions: 1. _____	
Risk Evaluation: Assessment by responsible: 1. Influence on quality of product / batch ☐ yes ☐ no ☐ unknown, expected 2. Deviation from registration ☐ yes ☐ no ☐ unknown, expected 3. Other affected batch / lot / cleaning ☐ yes ☐ no ☐ unknown, expected 4. Effects on other products or systems ☐ yes ☐ no ☐ unknown, expected 5. Any other deviations occurred? ☐ yes ☐ no ☐ unknown		Risk Acceptance: Date / Signature (responsible manager):		Risk Acceptance: Date / Signature (responsible manager):		Risk Acceptance: Quality Assurance Name: Tel. no.: Date / Signature:	
Risk Acceptance: Decision of Quality Unit: 1. Registration affected? ☐ yes ☐ no 2. Release of the lot / batch: ☐ yes ☐ no ☐ conditional use 3. Initiation of an Investigation Report: ☐ yes ☐ no		Risk communication: Distribution: Original batch documentation / logbook ☐ Quality Unit ☐ Operational Unit (Production, Quality, Technical or Laboratory, etc.)					

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Complaint/ Issue Management

- Initiate Quality Risk Management process
 - > Information on the complaint/ issue
 - > Product information
- Risk identification: Define the problem
 - > Detailed description of the complaint/ issue
 - > Risk to patient? Recall needed?
 - > Risk communication:
to central coordination unit



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Complaint/ Issue Management

- Risk assessment: Risk analysis
 - > Assessment of effects of the discrepancyExamples if applicable:
 - > Lot tracing
 - > Product quality
 - > Patient impact
 - > Registration/ Marketing authorisation
 - > Systems in place
 - > Availability of stock:
potentially insufficient stock levels..
- > Identification of the root cause
- > Risk communication: to expert team



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Complaint/ Issue Management

- Risk assessment: Risk evaluation
 - > Consequences for other batches/ products
 - > Systems failure
 - > Evaluation of
 - > Available data
 - > Performed actions
 - > Foreseen actions
 - > Measurements
 - > ...
 - > Risk communication: to central coordination unit; involve management, if appropriate



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Complaint/ Issue Management

- Risk Control: **Risk Reduction/ Mitigation**
 - > Corrective actions to resolve the discrepancy
 - > Corrective actions to avoid a recurrence in the future
- Risk Control: **Risk Acceptance**
 - > Conclusions of measures taken (management sign off)
 - > Decisions on disposition of the material
 - > Define follow up actions (if applicable)
 - > Management summary (if applicable)
 - > Date and signature of minutes
 - > *Risk communication: management to decide "next steps"*



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Complaint/ Issue Management

- Output/ result: **Risk Communication**
 - Internal**
 - > Sites / Affiliates
 - > Informal meetings
 - > Address in regular meetings
 - > Training sessions
 - External**
 - > Communicate with Competent Authorities (e.g. Field Alert, incident summary)
 - > "To whom it may concern" – letters
 - > Pharmacies



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Complaint/ Issue Management

- Risk Review
 - > Follow up of action items
 - > Summary and evaluation
e.g. Product Quality Review, Annual Product Review, follow-up report



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.1: QRM as Part of integrated Quality Management

- Auditing / Inspection
 - > To define the **frequency and scope** of audits
 - > Taking into account factors such as:
 - > Existing legal requirements
 - > Overall compliance status and history of the **company**
 - > Robustness of a company's **quality risk management** activities
 - > **Complexity** of the site, manufacturing process, product and its therapeutic significance
 - > **Compliance status** and history
 - > Results of **previous audits/inspections**
 - > Number and significance of **quality defects** (e.g. recall)
 - > Results of previous audits/inspections
 - > Major **changes** of building, equipment, processes, key personnel
 - > **Experience** with manufacturing of a product (e.g. frequency, volume, number of batches)
 - > **Test results** of official control laboratories

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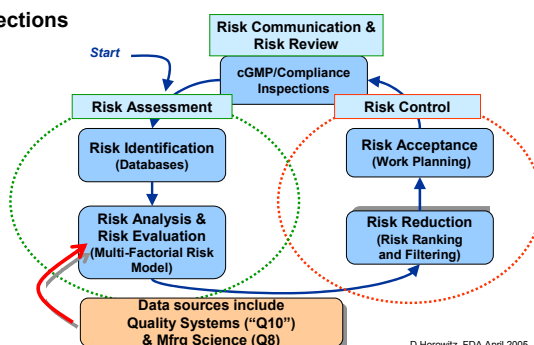
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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Inspections



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Scheduling audits: A framework

How industry might be able to set up a **risk-based evaluation** scheme to assess the need to **audit**.

A similar approach could be used by competent authorities (CA) for scheduling **inspections**.

1. **Brainstorm**
to create a list of manufacturers / traders to be audited
2. **Evaluate all sources of audit reports**
from competent authorities, competent companies or third parties conducted according local and/or other GMP-standards (e.g. PIC/S, WHO respective VFA, APIC)

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EXAMPLE

Scheduling audits: A framework

3. Evaluate risk factor

according to criteria based on managing risk for patients, which can (easily) be evaluated and maintained:

- > **Severity:** Compliance: effects safety & efficacy
- > **Severity:** Patient interest: effects availability
- > **Probability:** Complexity: Drug(medicinal)product, API etc.
- > **Detectability:** Audit History frequency of audit/inspections

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EXAMPLE

Scheduling audits: A framework

4. Weighting on to protection of patient

	very high	high	medium	low
Compliance	10	6	3	1
Availability	6	4	2	1
Complexity	8	4	2	1
Frequency	6	4	2	1

See list on following slides:

- In case of different activities take the highest ranking!
- In case their is nothing known, take the highest ranking!

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Scheduling audits: A framework

- **Compliance (Severity)**
patient risk: addressing safety & efficacy

Factor	Impact	Examples
		Based on own experience and/or availability of data (e.g. PIC/S, WHO)
10	Very high or Not known	No compliance status available or Last year a recall caused by this manufacturer/trader or strong indication for counterfeit
6	Moderately high or May represent major health risk	Result of the last audit/inspection: "not satisfactory" (critical) or Inadequate response to observations
3	Not fully satisfactory or No major health risk	Result of the last audit/inspection: "not fully satisfactory" or Result of last audit/inspection indicates some deficiencies
1	Satisfactory	Result of the last audit/inspection: "satisfactory" or Adequate response to all observations of the previous audit/inspection

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Scheduling audits: A framework

- **Compliance (Severity)**
patient risk: addressing availability

Factor	Impact	Example
6	Key partner in supporting market	Manufacturer/trader of top 5 medicines for the company / market [e.g. based on indication, volume] or No alternative supplier available
4	Major partner in supporting market	Manufacturer/trader of important medicines for the company / market [e.g. based on indication, volume] or Alternative supplier available
2	Minor partner in supporting market	Manufacturer/trader of limited medicines for the company / market [e.g. based on indication, volume] or Alternative suppliers available
1	Partner in supporting market	Manufacturer/trader of medicine(s) for the company / market [e.g. based on indication, volume] or Commodity

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Scheduling audits: A framework

- **Complexity (Probability)**

Factor	Impact	Example
8	Product directly used by patient or Manufactured in highly complex processes	Manufacturing/trading sterile products, aseptic production, sterile API or Sterile Packaging material or products required to be manufactured under strict separation regimes e.g. penicillin, cytotoxic products
4	Directly use on the patient and complex process or Manufactured in complex processes or maintained by complex services	Manufacturing/trading non-sterile finished products, Bulk non-sterile drug product or Storage & distribution: "key Warehouse", products with special storage / transport requirements
2	Compounds not directly used by patients or Services not executed to patients	Manufacturing/trading non-sterile API / API-BioTech products / lyophilized Excipients or Packaging material: any other or Operations limited to packaging only or Storage & distribution: Warehousing only
1	Compounds only used during manufacturing processes	Manufacturing/trading Starting materials / Raw materials / Excipients

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Scheduling audits: A framework

- **History (Detectability)**

Factor	Impact	Example
6	Compliance status out-of-date or not known or Defects in the Quality systems are definitely not known	Never audited/inspected by any recognized competent company/authority or Last audit/inspection: more than 5 years ago or Request of an audit (e.g. by reviewers)
4	Compliance status could be affected by time or changes or Defects in the Quality systems might not been known	Last audit/inspection: three to four years ago or Change in site owner (i.e. as a result of a merger, acquisition, or takeover) or global reorganization or Evaluation/information may be outdated
2	Compliance status has a good reputation by compliance history or Defects in the Quality systems might be possible	Last audit/inspection: two to three years ago or Evaluation/information is not current
1	Compliance status have been assessed recently or Defects in the Quality systems have been assessed	Last audit/inspection: up to 2 years ago

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EXAMPLE

Scheduling audits: A framework

5. Multiply the factors
6. Sort by overall risk factor
7. Announce audits on a predetermined figure e.g. 96

Risk Initiation			Risk assessment				
Name of Manufacturer / Supplier	City	Country	Overall risk factor	SE Compliance status	SE Strategic Intent	PE Compliance	SE Audit history
				[3,5,10]	[2,4,6]	[2,4,6]	[2,4,6]
VIA	nn	zzz	1440	5	6	8	6
WNO	nn	yy	320	10	4	2	4
STU	pp	yyx	240	5	6	8	1
STU	nn	zzv	160	10	1	8	2
CCD	ll	xx	144	3	4	2	6
HE	nn	yy	144	5	6	8	1
DEF	bb	yy	80	5	4	2	2
POGR	ff	xyx	40	10	6	1	1
ABC	nn	yy	40	3	1	4	4
GHI	cc	zz	40	3	1	4	4
JKL	dd	xy	24	1	6	4	1
WEER	pp	yyz	16	1	4	4	1
AABB	kk	yyz	12	3	2	1	2
EDF	oo	zzv	12	1	1	2	6
XXZ	ll	zzz	12	1	6	1	2

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Scheduling audits: A framework

Why "96"?

Conclude to schedule an audit when,

- > Compliance/Severity: Safety & Efficacy = medium (3) or more
- > Compliance/Severity: Availability = major (4) or more
- > Complexity: Probability = indirect use for patient (2) or more = 3 years ago (4) or more
- > History: Detectability

This would result in $3 \times 4 \times 2 \times 4 = 96$

EFPIA TG foreign inspections Feb.06

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Scheduling audits

- Result: an overview
 - > Updating once a year for planning

Weighted factors

Indication for priority

Do not trust in the values only

Risk Initiation			Risk assessment				
Name of Business Partner	City	Country	Overall risk factor	SE Compliance status	SE Strategic Intent	PE Compliance	SE Audit history
				[3,5,10]	[2,4,6]	[2,4,6]	[2,4,6]
VIA	nn	zzz	1440	5	6	8	6
WNO	nn	yy	320	10	4	2	4
STU	pp	yyx	240	5	6	8	1
STU	nn	zzv	160	10	1	8	2
CCD	ll	xx	144	3	4	2	6
FRE	mm	yy	120	5	1	4	6
DEF	bb	yy	80	5	4	2	2
POGR	ff	xyx	40	10	6	1	1
ABC	nn	yy	40	3	1	4	4
GHI	cc	zz	40	3	1	4	4
JKL	dd	xy	24	1	6	4	1
WEER	pp	yyz	16	1	4	4	1
AABB	kk	yyz	12	3	2	1	2
EDF	oo	zzv	12	1	1	2	6
XXZ	ll	zzz	12	1	6	1	2

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.1: QRM as Part of integrated Quality Management

• Periodic review

- > To select, evaluate and interpret **trend** results within the product quality review
- > To interpret **monitoring data** e.g. to support an assessment of the need for revalidation, changes in sampling etc.

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.1: QRM as Part of integrated Quality Management

• Change management / change control

- > To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing
- > To evaluate the impact of the changes on the availability of the final product
- > To evaluate the impact on product quality of changes
- > To determine appropriate actions preceding the implementation of a change

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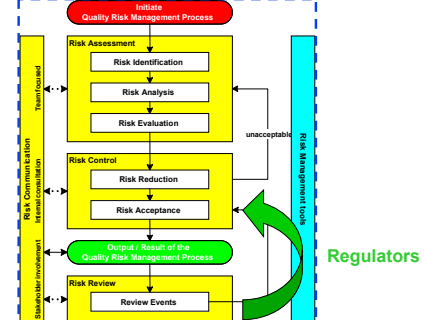
Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Responsibilities in case of Change Control

Industry



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ICH Q9 QUALITY RISK MANAGEMENT

II.1: QRM as Part of integrated Quality Management

- **Continual improvement**
 - > To facilitate continual improvement in processes throughout the product lifecycle

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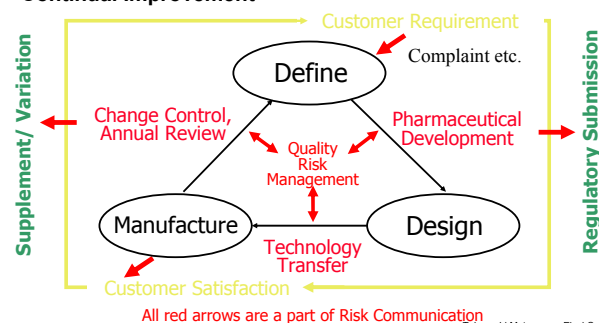
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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Continual Improvement



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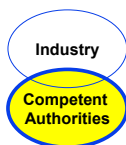
Takayoshi Matsumura, Eisai Co.
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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II. 2 Quality risk management as part of...

Regulatory operations
Inspection and assessment activities



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.2: QRM as Part of regulatory operations

Inspection and assessment activities

- To assist with **resource allocation** including e.g.
 - > Inspection planning
 - > Inspection frequency
 - > Intensity of assessment and inspection
 - > (see "Auditing" section in Annex II.1)
- To evaluate the **significance** of e.g.
 - > Quality defects
 - > CAPA following a recall
 - > Inspectional findings

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Scheduling Inspections

- **Target:**
Develop criteria, which can (easily) be evaluated/maintained by members of the department responsible for the audit plan....

**See previous section II.1:
auditing / inspection**

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ICH Q9 QUALITY RISK MANAGEMENT

II.2: QRM as Part of regulatory operations

Inspection and assessment activities

- To determine the **appropriateness and type** of post-inspection regulatory follow-up
- To evaluate **information submitted** by industry including pharmaceutical development information
- To evaluate **impact of proposed variations or changes**
- To identify risks which should be **communicated**
 - > between inspectors and assessors
- To facilitate **better understanding**
 - > how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT))

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ICH Q9 QUALITY RISK MANAGEMENT

II. 3 Quality risk management as part of...

Development



See also next chapters
using the intention to be applicable for development

II.4: Facilities, Equipment and Utilities

II.5: Materials Management

II.6: Production

II.7: Laboratory Control and Stability Studies

II.8: Packaging and Labelling

Note: Process understanding and criticality may be applied only to new products

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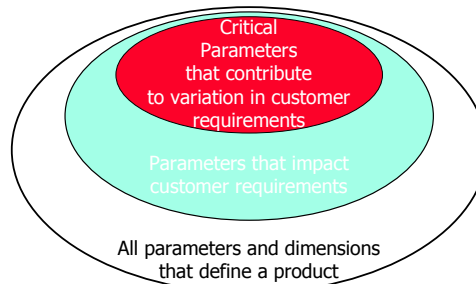
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ICH Q9 QUALITY RISK MANAGEMENT

CONSIDERATIONS

About development



T. Matsumura, Eisai Co.

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ICH Q9 QUALITY RISK MANAGEMENT

II.3: QRM as part of development

- To design a **quality product** and its **manufacturing process**
 - > to consistently deliver the intended performance of the product (see ICH Q8)
- To enhance **knowledge of product performance** over a wide range of
 - > material attributes (e.g. particle size distribution, moisture content, flow properties)
 - > processing options
 - > process parameters

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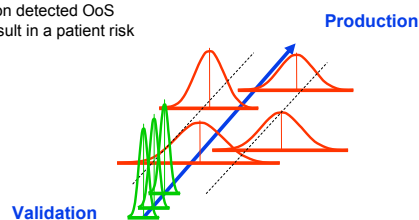
Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Quality by design: "Special Cause" or "Common Cause"

Note: Non detected OoS could result in a patient risk



- Consequence: Frequent, major OOS
 - Corrective actions eliminate "Special Cause"
- Result: Unstable process**

Based on A. Hussain, FDA, September 2004

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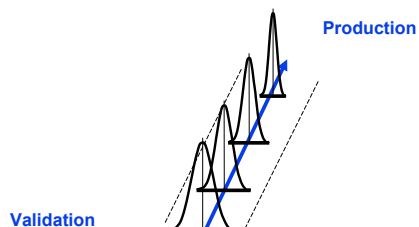
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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Quality by design: "Special Cause" or "Common Cause"



- Reduce "Common Cause" Variability
 - Consequence: On the continuous improvement path
- Result: Stable & Capable**

A. Hussain, FDA, September 2004

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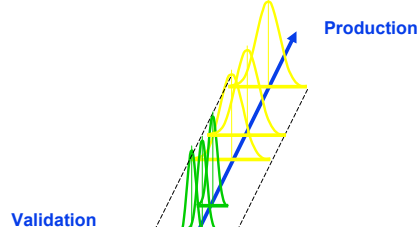
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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Quality by design: "Special Cause" or "Common Cause"



- Consequence: Minor, occasional OoS
 - Reduce "Common Cause" Variability
- Result: Stable- Yes; Capable?**

A. Hussain, FDA, September 2004

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ICH Q9 QUALITY RISK MANAGEMENT

II.3: QRM as part of development

- To assess the **critical attributes** of
 - Raw materials
 - Solvents
 - Active Pharmaceutical Ingredient (API)
 - Starting materials
 - Excipients
 - Packaging materials
- To establish **appropriate specifications**, identify **critical process parameters** and establish **manufacturing controls**

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ICH Q9 QUALITY RISK MANAGEMENT

II.3: QRM as part of development

- To **decrease variability** of quality attributes:
 - reduce product and material defects
 - reduce manufacturing defects
- To assess the need for **additional studies** (e.g., bioequivalence, stability) relating to scale up and technology transfer
- To make use of the “**design space**” concept (see ICH Q8)

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EXAMPLE

P2 of CTD as part of a regulatory submission



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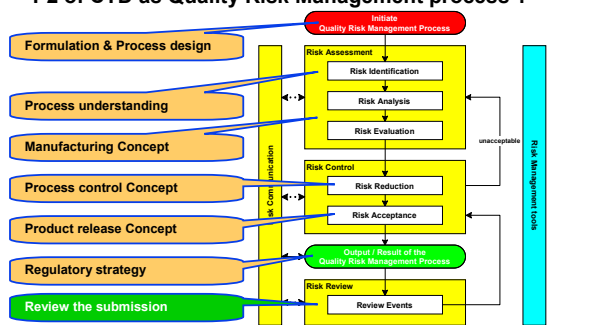
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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

P2 of CTD as Quality Risk Management process ?



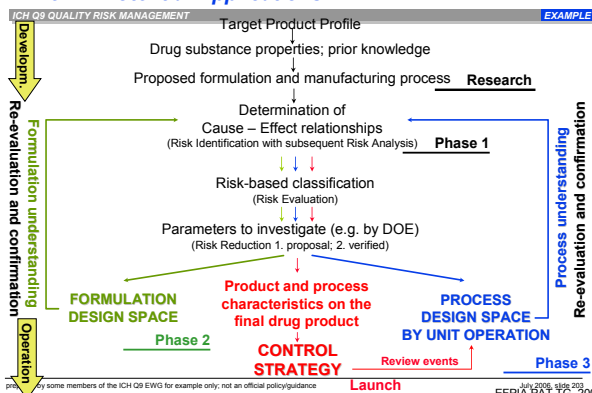
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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Risk Management approach to focus on critical attributes

Unit operation		Dispensing	Granulation	Drying	Blending	Tableting	
Quality Attributes	Dissolution						Significant influence
	Disintegration						
	Hardness						
	Assay						Initial assessment
	Content Uniformity						
	Degradation						Prior knowledge
	Stability						
	Appearance						
	Identification						First & Second review cycle
	Water						
	Microbiology						Formulation and Process understanding

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FFPIA PAT 1.0, 2006

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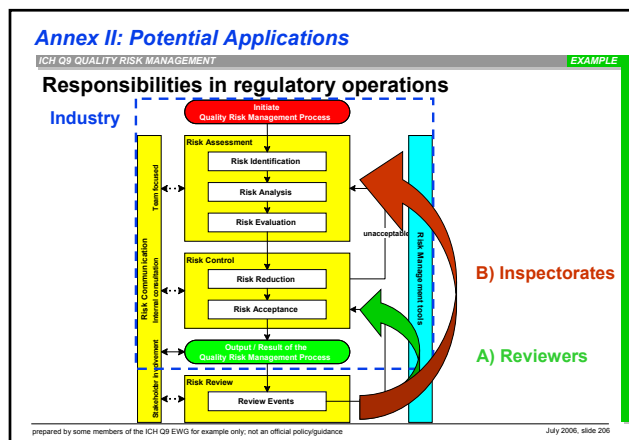
ICH Q9 QUALITY RISK MANAGEMENT

Risk to patient → **Unit operation** → **low Process understanding Control Strategy**

Unit operations	Dispensing (Raw Material Properties)	Granulation	Drying	Blending (Magnesium Stearate)	Tableting	Packaging
Disintegration	Particle size API	Power consumption	Prior knowledge	Not critical to quality	Not critical to quality	Prior knowledge
Disintegration	Particle size API	Water amount and feed rate	Prior knowledge	Not critical to quality	Not critical to quality	Prior knowledge
Hardness	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	NIR measurement	Prior knowledge
Assay	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	NIR measurement	Prior knowledge
Content uniformity	Prior knowledge	Power consumption	Not critical to quality	Not critical to quality	NIR measurement	Prior knowledge
Degradation	Prior knowledge	Water amount and feed rate	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge
Stability	Prior knowledge	Prior knowledge	Control water content	Prior knowledge	Prior knowledge	Prior knowledge
Appearance	Prior knowledge	Prior knowledge	Not critical to quality	Prior knowledge	Not critical to quality	Prior knowledge
Identification	NIR of raw material	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge
Water	Prior knowledge	Control water content	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge
Microbiology	Specification of starting material	Purified water used	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

QRM as part of development provide risk-based knowledge to manufacturer

Past Parameters and range

Future We have additional dimensions

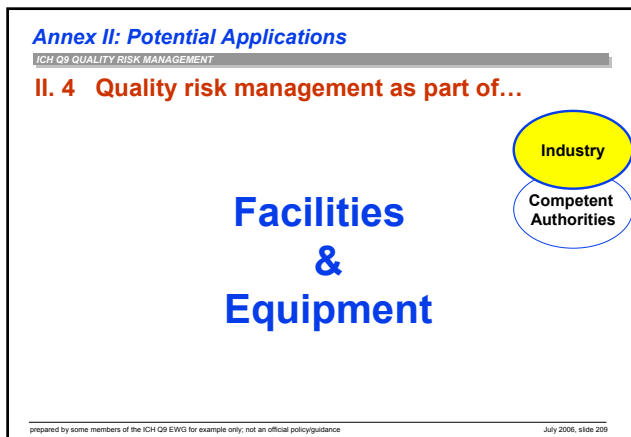
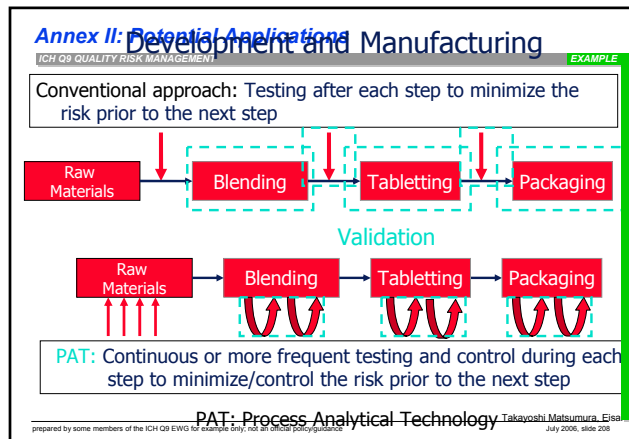
- Open question: How to challenge information for submission?

Answer the questions in ICH Q9 Chapter 4:

- > What might go wrong?
- > What is the likelihood (probability) it will go wrong?
- > What are the consequences (severity)?

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- Annex II: Potential Applications**
- ICH Q9 QUALITY RISK MANAGEMENT
- II.4: QRM for facilities, equipment and utilities**
- Design of facility / equipment**
- To determine appropriate ...**
- Zones**
 - when designing buildings and facilities, e.g.,
 - > flow of material and personnel
 - > minimize contamination
 - > pest control measures
 - > prevention of mix-ups
 - > open versus closed equipment
 - > clean rooms versus isolator technologies
 - > dedicated or segregated facilities / equipment
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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Assessing Facility Needs for the Manufacture of Certain Medicinal Products Using a Risk Based Approach

- Options for facility dedication / segregation
 - A physically separate or segregated **building**
 - A separate **area** which may comprise of one or more rooms within a multi-purpose facility with its own air-locked personnel/ material accesses and HVAC systems.
 - One or more rooms (**Suite**) within a multi-purpose facility or dedicated area that is dedicated to a specific product or product range, and is identified accordingly

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Assessing Facility Needs for the Manufacture of Certain Medicinal Products Using a Risk Based Approach

- Options for equipment dedication / segregation
 - Equipment** that is dedicated to a specific product or product range, and identified accordingly
 - A totally enclosed cabinet (**Containment Isolator**) that is specifically designed to contain a specific product or product range, and is identified accordingly
 - An equipment **change part** (e.g. sieve, filter, etc) that is dedicated to a specific product or product range, and is identified accordingly

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Facility Needs: **Risk Assessment of Severity of Harm**

Risk Assessment: Product Properties		
Risk Identification	Risk Analysis	Risk Evaluation
API physical-chemical Properties during the step of the manufacturing process - Particle size, surface area, solubility	How do these properties impact potential risk of migration?	Low: little risk of migration (e.g. solutions, wet cakes, waxes, oils) Medium: some risk of distribution/migration (e.g. dry powders) High: easy distribution/migration (e.g. micronized material)
Medicinal Product dosage form during the step of the manufacturing process Intermediate-physical form - Liquid, powder, single units,	What is the impact of the matrix or coating with regard to API?	Low: API tightly bound within a matrix (e.g. liquid coated tablets, filled capsules, semi-solids) Medium: Limited surface (e.g. Pellets, uncoated tablets, aerosols) High: High surface or API unbound (Powder, Granules, ...)
Decontamination and inactivation capability	Which kind of cleaning or inactivation procedures is required?	Low: easily soluble, standard cleaning procedures (e.g. cleaning with water only). No inactivation required. Medium: Product specific procedures (e.g. cleaning with solvents or detergents). High: Specialized procedures required (e.g. high temperature cleaning, and/or chemical inactivation)

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Facility Needs: **Risk Assessment of the process 1/2**

Risk Assessment: Process		
Risk Identification	Risk Analysis	Risk Evaluation
Process Design - Flows - Open/Closed systems - Utilities	What is the impact of the process design?	Low: Process is designed to eliminate potential root causes of cross contamination (e.g. Simple, robust and logical process) Medium: Process is designed to minimise potential sources of cross contamination (e.g.) High: Process is designed with few controls for containing potential sources of cross contamination (e.g. Open handling, manual operations).
Batch Related Process Steps - Normal operation - Changeover - Cleaning - Exceptions (e.g. spillage)	What is the impact of each batch-related process step?	Low: Little risk of dispersion of material as a result of the process step (e.g. solution mixing) Medium: Some risk of dispersion of material as a result of the process step (e.g. granulation) High: High risk of dispersion of material as a result of the process step (e.g. micronisation).

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Facility Needs: **Risk Assessment of the process 2/2**

Risk Assessment: Process		
Risk Identification	Risk Analysis	Risk Evaluation
Production Scale & Volume - Batch size - Changeover frequency - Sequencing	What is the quantity and changeover frequency?	Low: small scale quantities, easily containable process. (e.g. clinical trial materials and orphan drugs) Medium: Medium volumes, with infrequent changeovers High: large volumes, frequent changeovers
Supporting Activities - Maintenance - Waste Handling	What is the impact of supporting activities?	Low: Little or no risk of dispersion of material as a result of the support activity (e.g. bag in – bag out technology) Medium: Some risk of dispersion of material as a result of the support activity (e.g. granulation) High: High risk of dispersion of material as a result of the support activity (e.g. manual dust removal and filter change)

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs a **Process Risk Control**

- Consider the need improve the situation by one or more of the following options:
 - Improve the formulation
 - Minimise the release of material at source using the most appropriate equipment and technology.
 - Contain any residual material or product by means of facility, air handling, and other techniques.
 - Assure adequate cleaning and/or inactivation.
 - Instigate a specific monitoring program

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs: **Risk Control**

• Examples of Process Risk Controls 1/2

Risk Assessment: Product Properties			
Risk Identification	Risk Analysis	Risk Evaluation	Risk Control Examples
API physical-chemical Properties during the step of the manufacturing process - Particle size, surface area, solubility	How do these properties impact potential risk of migration?	Low: little risk of migration (e.g. solutions, wet cakes, waxes, oils) Medium: some risk of distribution/migration (e.g. dry powders) High: easy distribution/migration (e.g. micronized material)	API powder handling (e.g. pre-dispensed supply, container design)
Medicinal Product dosage form during the step of the manufacturing process Intermediates-physical form - Liquid, powder, single units,	What is the impact of the matrix or coating with regard to API?	Low: API tightly bound within a matrix (e.g. liquid, coated tablets, filled capsules, semi-solids) Medium: Limited surface (e.g. Pellets, uncoated tablets, aerosols) High: High surface or API unbound (Powder, Granules,...)	Adjust formulation, API into matrix as early as possible in the process (e.g. to minimise dust generation)

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs: **Risk Control**

• Examples of Process Risk Controls 2/2

Risk Assessment: Product Properties			
Risk Identification	Risk Analysis	Risk Evaluation	Risk Control Examples
Decontamination and inactivation capability	Which kind of cleaning or inactivation procedures is required	Low: easily soluble, standard cleaning procedures (e.g. cleaning with water only) No inactivation required Medium: Product specific procedures (e.g. cleaning with solvents or detergents) High: Specialized procedures required (e.g. high temperature cleaning, and/or chemical inactivation)	Develop, validate and implement adequate processes Measure & control efficiency Disposable tools Dedicated equipment/product contact parts

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs: **Risk Control**

• Examples of Process Risk Controls 1/3

Risk Assessment: Process			
Risk Identification	Risk Analysis	Risk Evaluation	Risk Control Examples
Process Design - Flows - Open/Closed systems - Utilities -	What is the impact of the process design? bb	Low: Process is designed to eliminate potential root causes of cross contamination (e.g. Simple, robust and logical process) Medium: Process is designed to minimise potential sources of cross contamination (e.g.) High: Process is designed with little consideration of containing potential sources of cross contamination (e.g. Open handling, manual operations)	Containment (e.g. Isolators), Equipment design, automatization Disposable tools Dedicated equipment/product contact parts Process design and optimization

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs: **Risk Control**

• Examples of Process Risk Controls 2/3

Risk Assessment: Process			
Risk Identification	Risk Analysis	Risk Evaluation	Risk Control Examples
Batch Related Process Steps - Normal operation - Changeover - Cleaning - Exceptions (e.g. spillage)	What is the impact of each batch-related process step?	Low: Little risk of dispersion of material as a result of the process step (e.g. solution mixing) Medium: Some risk of dispersion of material as a result of the process step (e.g. granulation) High: High risk of dispersion of material as a result of the process step (e.g. micronisation)	WIP/CIP systems Reduce potentially exposed personnel Material flow & handling Plan for potential failures (FMEA)
Production Scale & Volume - Batch size - Changeover frequency - Sequencing	What is the quantity and changeover frequency?	Low: small scale quantities, easily containable process Medium: Medium volumes, with infrequent changeovers High: large volumes, frequent changeovers	Campaigning

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs: **Risk Control**

• Examples of Process Risk Controls 3/3

Risk Assessment: Process			
Risk Identification	Risk Analysis	Risk Evaluation	Risk Control Examples
Supporting Activities - Maintenance Waste Handling	What is the impact of supporting activities?	Low: Little or no risk of dispersion of material as a result of the support activity (e.g. bag in - bag out technology) Medium: Some risk of dispersion of material as a result of the support activity (e.g. granulation) High: High risk of dispersion of material as a result of the support activity (e.g. manual dust removal and filter change)	Closed systems for materials Monitoring and Alarm controls for HVA/C/Dedusting systems Waste handling Backup systems Plan for potential failures (FMEA)

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs: **Risk Control: Operational solutions**

• A number of different technical solutions are possible:

- > Product Campaign in multi-product facility with campaign/extended cleaning
- > Appropriately Dedicated Equipment
- > Containment in multi-product area
- > Closed Processes
- > Dedicated suite (airlock, dedicated HVAC)
- > Dedicated area
- > Dedicated building

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs: Risk Acceptance profile



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs: Conclusion

This approach takes into account the risk based criteria:

- the potential **safety risk to patients** from cross contamination, different scales and/or stages of production
- the **physical form** of the product at each stage of products and factors which may affect ease of removal or deactivation
- the appropriate **technical means** to minimise and demonstrate effective ongoing control of the identified objective risk to patient safety
- the controls and supporting evidence necessary to support the alternative **use of facilities and equipment** previously used for materials identified with high potential for adverse medical effects at low levels

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

QRM for facilities, equipment and utilities

Zone concept for API:

Risk management of Contamination and Cross-contamination (zone concept) for API

- Initiate the Risk Management Process
 - > Defining **problem or question**
 - Where will protection be required?
 - What kind of protection will be adequate?
 - > Defining the **assessment information and conclusions**
 - Managing risk based on a **critical point** approach



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Zone concept for API

• Risk assessment: Risk identification and analysis

- > After the critical point:
Design chemical operations to prevent cross contamination by/of the API
- > Before the critical point:
Protection has to be considered
- > Rationale: Ability of a final purification, filtration and/or crystallisation step of removing trace levels of incidental (cross-)contamination
- > Notes: Consider industrial hygiene and safety conditions



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Zone concept for API

• Risk assessment: Risk evaluation

> Risk associated with different products

- Contamination by particulate matter
e.g. from equipment, environmental
- Microbiological contamination
e.g. API susceptible to microbiological growth?
- Cross-contamination
e.g. inadequate cleaning and/or material flow, air-handling, use of closed systems



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Zone concept for API

• Risk assessment: Risk evaluation

Risk associated with simultaneous operations

- plant design
(multi-purpose, dedicated, closed systems)
- requirements for special product categories
(e.g. highly toxic)

Risk to product from exposure to work environment

- exposure time, interfaces
(e.g. drums/containers)



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Zone concept for API

- Risk control
 - > A decision-making activity focused on controlling risks

Where will protection be required?

What kind of protection is adequate?

What to do?

- Minimize interfaces
- Segregate production facilities
- Closed systems
- control people and material movement



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Zone concept for API

- Risk control: Risk reduction
 - > Physical and technical solutions
 - closed systems
 - endless bag system
 - closed sampling
 - > Intermittently closed product handling (hybrid solutions)
 - glove boxes
 - enclosed room or cabin
 - > Open product handling
 - air flow controlled sampling



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Zone concept for API

- Risk control: Risk reduction
 - > Patient impact
 - Occurrence of harm
 - Detection of harm
 - > Procedural/ structural/ logistical solutions
 - gowning procedures
 - operational monitoring
 - optimising material flow
 - standardized drums/ containers
 - ...



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Zone concept for API

- Risk control: Risk Acceptance
 - No additional risk control activities are necessary
 - Supported by the decision maker(s).
 - Includes acceptance of risks that have not been identified
- > Design appropriate levels of protection
- > Accept the critical point of the process
- > Appropriate monitoring may be performed



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Zone concept for API

- Risk communication
 - > Internal:
 - "GMP-Master plan" to demonstrate that the risk management process is used
 - Capital investment plan can be supported or even changed by the quality risk management process
 - > External:
 - e.g. Site Master File



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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

Zone concept for API

- The review phase
 - > Audits / Inspections
 - > Regularly assessment of complaints/ deviations on (cross-) contamination topics



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.4: QRM for facilities, equipment and utilities

Design of facility / equipment

To determine appropriate ...

- **Product contact materials** for equipment and containers
 - > Selection of stainless steel grade, gaskets, lubricants, etc.
- **Utilities**
 - > steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water, etc.
- **Preventive maintenance** for associated equipment
 - > Inventory of necessary spare parts, etc.

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

• Design of facility / equipment

Risk criteria for Facility qualification (DQ/IQ/OQ/PQ)

- > **Probability:** Equipment has **contact with product full surface (vessel) / partial (gasket) / no contact**
- > **Severity:** possible source for **contamination** (e.g. Process validation) or **cross contamination** (e.g. Cleaning validation)
yes / no
- > **Severity:** **Product quality** affected? Impact on patient?
yes / no
- > **Detectability:** Knowledge of this attribute may affect the **release decision**

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

• Design of facility / equipment

Master Qualification Plan of a new facility: Document reduction initiative

* total number of documents	7306
* after classification / risk assessment:	
* Number of documents - plant	3682
* Number of documents - equipments	1782
* Number of documents - IT-System	119
	5583
* after integration of plant to one qualification project:	
* Number of documents - plant	882
* Number of documents - equipment	1782
* Number of documents - IT-System	119
	2783
Document consolidation equals risk reduction via constancy, easy maintenance/training reduces non compliance risk to patient	
Reduction in the number of documents:	62%

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ICH Q9 QUALITY RISK MANAGEMENT

II.4: QRM for facilities, equipment and utilities

• Hygiene aspects in facilities

- > To **protect the product** from environmental hazards including chemical, microbiological, physical hazards
 - > determining appropriate clothing and gowning
 - > hygiene concerns
- > To **protect the environment** from hazards related to the product being manufactured
 - > personnel, potential for cross-contamination

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II.4: QRM for facilities, equipment and utilities

- **Calibration/preventive maintenance**
 - > To set appropriate calibration and maintenance schedules
- **Qualification of facility/equipment/utilities**
 - > To differentiate **scope and efforts** and decisions based on the intended use
 - > multi-versus single-purpose
 - > batch versus continuous production
- **Cleaning of equipment and environmental control**
 - > To determine acceptable (specified) cleaning validation **limits**

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EXAMPLE

II.4: QRM for facilities, equipment and utilities

- **Potency Scale – max. daily dose (severity)**
 - > 10 < 1mg
 - > 6 1-10mg
 - > 4 10-100mg
 - > 2 100mg-1000mg
 - > 1 >1000mg
- **Solubility Scale – in cleaning medium (probability)**
 - > 5 low solubility
 - > 4 slightly soluble
 - > 3 moderately soluble
 - > 2 soluble
 - > 1 highly soluble
- **Interactions Scale (detectability)**
 - > 9 serious - patients life threatened
 - > 4 moderate patient feels adverse effect
 - > 1 low none – patient does not notice

Cleaning validation

P. Gough, D. Begg Ass.

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II.4: QRM for facilities, equipment and utilities

- Computer systems and computer controlled equipment
 - > To select the design of computer hardware and software
 - Modular
 - Structured
 - Fault tolerance
 - > To determine the extent of validation
 - Identification of critical performance parameters
 - Selection of the requirements and design
 - Code review
 - The extent of testing and test methods
 - Reliability of electronic records and signatures

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Computer systems and computer controlled equipment
 - Which risks could be considered?
 - > Patient risk
 - > Compliance risk
 - > Application risk
 - > Business risk (influenced by other than Q-risks)
 - > Infrastructure risk

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EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Risks on Comp. systems & comp. controlled equipment
 - Patient risk

Category	Questions	Choices
Patient harm	Will the failure of the system result in	A: Death
		B: Serious harm but not death
		C: Minor harm
		D: No effect on patient health
Secondary assurance of safety	Is/are there down stream processes to the subject system that could assure safety of the product.	A: Yes
		B: No

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Risks on Comp. systems & comp. controlled equipment
 - Compliance risk

Category	Questions	Choices
Business process regulation	Is the business process subject to predicate rule requirements?	A: Yes
	OR Is the business process regulated by an agency?	B: No
Degree of Exposure	Are the data or records made available to regulatory agencies?	A: Yes, submitted B: Yes, may be inspected C: No

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EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Risks on Comp. systems & comp. controlled equipment
 - Application risk 1/2

Category	Questions	Choices
Complexity	How many technology enablers are interfaced to the system?	A: 0
		B: 1
		C: more than 1
	What is the technology category for the system?	A: firmware
		B: standard software packages
		C: configurable software packages
		D: configurable software package with custom additions
		E: fully custom software

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Risks on Comp. systems & comp. controlled equipment
 - Application risk 2/2

Category	Questions	Choices
Experience	What is our experience with the technology?	A: New technology
		B: Mature technology but new to us
		C: Mature technology previously used by us
		D: Technology approaching obsolescence
Security	Is the application capable of limiting access at the individual authorized user level?	A: Yes B: No

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Risks on Comp. systems & comp. controlled equipment
Business risk 1/3

Category	Questions	Choices
Position in Value Chain	Identify where in the value chain the system is used	A: Discovery Research
		B: GLP Research
		C: Development GMP
		D: Development GCP
		E: API Manuf.
		F: Form. Manuf. & Pack
		G: Marketing / Dem. Manag.
		H: Prod. Plann. & Log.
		I: Supp. Proc. HR
		K: Supp. Proc. Informatics
		L: Supp Proc Finance
Number of users (Usage)	Estimate the number of users of the system	A: 1
		B: 2 to 20
		C: 21 to 100
		D: more than 100

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EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Risks on Comp. systems & comp. controlled equipment
Business risk 2/3

Category	Questions	Choices
Frequency of Usage (Usage)	Estimate how frequently the system users operate or interface with the system	A: < yearly B: monthly C: daily
Location of system (Usage)	Select where the System is implemented	A: One site B: Within a region C: Throughout the global organization
Criticality of business system	Can the business continue to operate if the system fails	A: There is no alternative system or manual procedure
		B: YES, with a backup system or an alternative system
		C: YES, with manual processes - a major resource impact
		D: YES, with manual processes - a minimum resource impact

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Risks on Comp. systems & comp. controlled equipment
Business risk 3/3

Category	Questions	Choices
Criticality of records contained in the system	Is the system the sole source of data for the business process?	A: Yes B: No
Cross organizational boundaries	Does this system supply critical data from this business process to other business processes (outside of this one)?	A: Yes B: No

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ICH Q9 QUALITY RISK MANAGEMENT

EXAMPLE

II.4: QRM for facilities, equipment and utilities

- Risks on Comp. systems & comp. controlled equipment
Infrastructure risk

Category	Questions	Choices
Complexity	On which geographical infrastructure the system will operate?	A: Local - Proprietary B: Local C: Regionally D: Globally
	What is our experience with the infrastructure?	A: New technology B: Mature technology but new to us C: Mature technology previously used by us D: Technology approaching obsolescence
Security	Does the system rely on the "public internet" in the operation of the system?	A: Yes B: No

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II. 5 Quality risk management as part of...

Materials Management



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.5: QRM as part of materials management

- Assessment and evaluation of suppliers and contract manufacturers
 - > To provide a comprehensive evaluation
 - > Auditing
 - > Supplier quality agreements
- Starting material
 - > To assess differences and possible quality risks associated with variability in starting materials
 - > Age
 - > Route of synthesis

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II.5: QRM as part of materials management

- Use of materials
 - > Appropriate use material **under quarantine**
 - > for further internal processing
 - > Appropriateness of **Reprocessing, reworking, use of returned goods**

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II.5: QRM as part of materials management

- Storage, logistics and distribution conditions
 - > Adequacy of arrangements to ensure **maintenance of appropriate storage and transport conditions**
 - > Temperature
 - > Humidity
 - > Container design
 - > Determine the effect on product quality of discrepancies in storage or transport conditions
 - > Cold chain management (see other ICH guidelines)

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II.5: QRM as part of materials management

- Storage, logistics and distribution conditions
 - > Maintain **infrastructure**
 - > Capacity to ensure proper shipping conditions
 - > Interim storage
 - > Handling of hazardous materials and controlled substances
 - > Customs clearance
 - > Provide information for ensuring the **availability** of pharmaceuticals
 - > Ranking risks to the supply chain (e.g. Anti-Counterfeit)

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II. 6 Quality risk management as part of...

Production

Industry

Competent Authorities

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ICH Q9 QUALITY RISK MANAGEMENT

II.6: QRM as part of production

- Validation
 - > To identify the **scope and extent** of verification, qualification and validation activities
 - > Analytical methods
 - > Processes
 - > Equipment
 - > Cleaning methods
 - > To determine the extent for **follow-up** activities
 - > Sampling
 - > Monitoring
 - > Re-validation
 - > To distinguish between critical and non-critical process steps to facilitate design of a validation study

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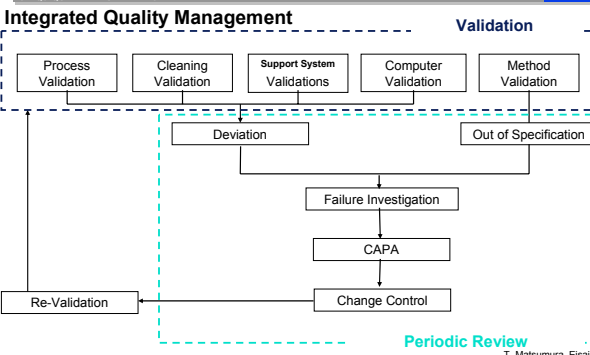
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II.6: QRM as part of production

- In-process sampling & testing
 - > Evaluate the frequency and extent of in-process control testing
 - Justify reduced testing under conditions of proven control
 - > Evaluate and justify the use of Process Analytical Technologies (PAT) in conjunction with parametric and real time release
- Production planning
 - > To determine appropriate production planning
 - Dedicated
 - Campaign or concurrent production process sequences

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II. 7 Quality risk management as part of...

Laboratory control and stability testing

Industry

Competent
Authorities

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ICH Q9 QUALITY RISK MANAGEMENT

II.7: QRM as part of laboratory control and stability testing

- Out of specification results
 - > To identify potential root causes and corrective actions during the investigation
- Retest / expiration date setting
 - > To evaluate adequacy of storage and testing of intermediates, excipients and starting materials
 - Challenge results of use tests
 - Stress tests

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II. 8 Quality risk management as part of...

Packaging and labelling

Industry

Competent
Authorities

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QRM as part of packaging and labelling

- Design of packages
 - > Design the secondary package for the protection of primary packaged product
 - Ensure product authenticity
 - Label legibility
- Selection of container closure system
 - > Determine the critical parameters of the container closure system

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ICH Q9 QUALITY RISK MANAGEMENT

QRM as part of packaging and labelling

- Label controls
 - > Design label control procedures based on the potential for mix-ups
 - Involving different product labels
 - Including different versions of the same label

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Quality risk management as part of...

Conclusion

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ICH Q9 QUALITY RISK MANAGEMENT

Using ICH Q9 will...

- **Facilitate**
 - > Communication and transparency
 - > More informed, scientifically based decision making
 - > Patient focused actions on quality risks
 - > Realistic and appropriate solutions
 - > Use of existing solutions (Share best practice/prior knowledge)
- **Manage critical to quality aspects**
 - > Through systems, organisations, processes & products
 - > Maintain responsibility & accountability for QRM
- **Focus activity towards patient protection**

It should never be used as a "hobby horse" / preconceived idea

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ICH Q9 QUALITY RISK MANAGEMENT

Opportunity for the Industry & Competent Authorities

- Using **the same guideline** apply QRM to industry (Development & Manufacture) and regulators (Reviewer & Inspectorate)
- Provides for establishing a defined program for **what we already do** every day in our jobs
- **Supports science-based** decision making
- Optimisation of **resources**
- Prevention from **overly** restrictive and unnecessary **requirements**
- Facilitates **communication** and **transparency**

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

Challenges for Industry & Competent Authorities

- **Interpreting and adopting the concepts** of quality risk management into specific areas
 - > Embed this **behavior** into quality aspects of business, technology and regulation
 - > Adopt in existing **structures, organizations and Quality System**
 - > Balance the documented use of "**informal**" and "**formal**" quality risk management

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Integration of QRM
into existing systems
and regulatory processes
will require a
development of trust over time

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