Quality Risk Management ICH Q9

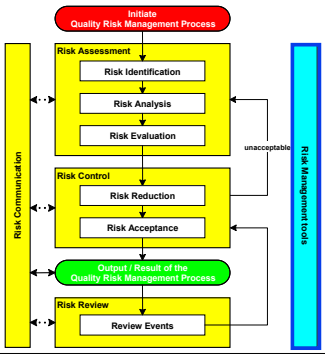
Annex I: Methods & Tools

Disclaimer: *This presentation includes the authors views on quality risk management theory and practice. The presentation does not represent official guidance or policy of authorities or industry.*

Purpose of this part

- 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

Chapter 5 & Annex I

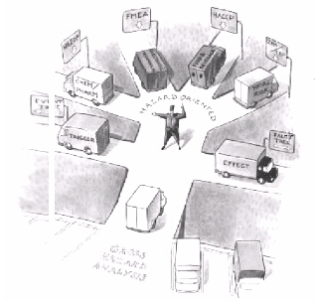


Introduction

- 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.

ICH Q9

5. Risk Management Tools



Use the appropriate tool(s)!

No one tool is "all inclusive"!

Contributing items to manage quality risks

- **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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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

Annex I: Methods & Tools

Annex I.1

Basic Risk Management Facilitation Methods

Annex I: Methods & Tools

I.1: Basic risk management facilitation methods

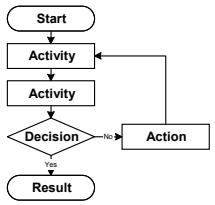
- **Flowchart**
- **Check Sheets**
- **Process mapping**
- **Cause and Effect Diagrams (Ishikawa / fish bone)**

They might be helpful to support risk identification

Annex I: Methods & Tools

I.1: Basic risk management facilitation methods

Flowcharts

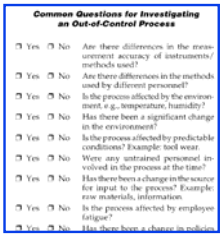


- **Pictorial representations of a process**
- **Breaking the process down into its constituent steps**

Annex I: Methods & Tools

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**

Annex I: Methods & Tools

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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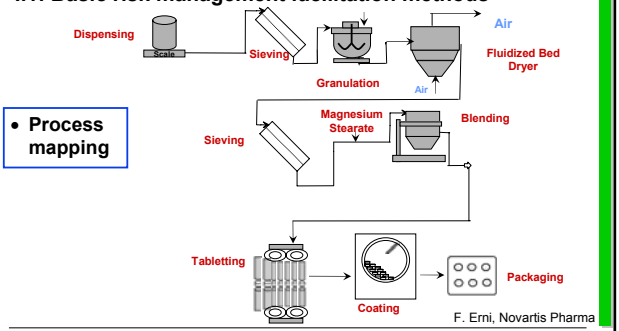
Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.1: Basic risk management facilitation methods



- Process mapping

F. Erni, Novartis Pharma

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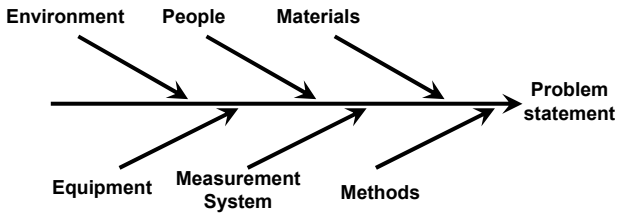
ICH Q9 QUALITY RISK MANAGEMENT

I.1: Basic risk management facilitation methods

Cause and Effect Diagrams (Ishikawa / fish bone)



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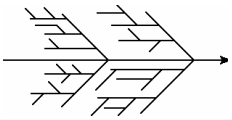
ICH Q9 QUALITY RISK MANAGEMENT

I.1: Basic risk management facilitation methods

Cause and Effect Diagrams (Ishikawa / fish bone)

- To associate multiple possible causes with a single effect
- Constructed to identify and organize possible causes for it

- Primary branch: represents the effect
- Major branch: corresponds to a major cause
- Minor branch: correspond to more detailed causal factors



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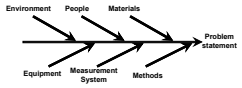
ICH Q9 QUALITY RISK MANAGEMENT

I.1: Basic risk management facilitation methods

Cause and Effect Diagrams (Ishikawa / fish bone)

How to perform?

- Define and agree a precise problem statement (put as "head" of fish bone) Think "What could be its causes?" for each node
- Add it to the "fish bone" diagram
- For each line pursue back to its root cause
- Consider splitting up overcrowded sections "bones"
- Consider which potential root causes and the need for further investigation on them



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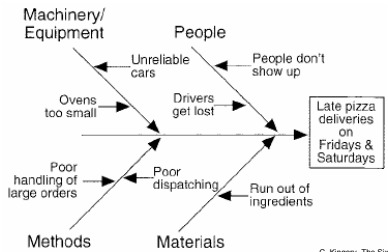
I.1: Basic risk management facilitation methods

Cause and Effect Diagrams (Ishikawa / fish bone)



C. Kingery, The Six Sigma Memory Jogger II

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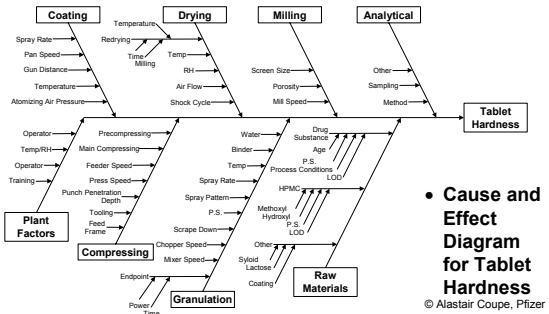
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.1: Basic risk management facilitation methods



- Cause and Effect Diagram for Tablet Hardness

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Annex I.2

Failure Mode Effects Analysis (FMEA)

I.2: Failure Mode Effects Analysis (FMEA)

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

Item or Process Step	Potential Failure Mode	Potential Effect(s) of Failure	Severity	Potential Cause(s)	Occurrence	Current Controls	Detection	RPN	Recommended Action	Responsibility and Target Date	"After" → Action Taken	Severity	Occurrence	Detection	RPN

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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I.2: Failure Mode Effects Analysis (FMEA)

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

I.2: Failure Mode Effects Analysis (FMEA)

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

   Multiplying different scales will differentiate the outcome

The aim is to come up with a method of prioritising

I.2: Failure Mode Effects Analysis (FMEA)

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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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT — 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 noncompliance with GMP regulations or product registrations. Failure possible to lead to recall. Financial: $500,000
7	High	Failure leads to customer percept ion 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

Dr. Gary Harbour, Pfizer

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ICH Q9 QUALITY RISK MANAGEMENT — 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 <1σ).
9		One occurrence every three to four days or a probability of three occurrences in 10 units (C_{pk} ~ 0.33 or ~1 σ).
8	High: Repeated failures	One occurrence per week or a probability of 5 occurrences in 100 units (Cpk ~ 0.67 or ~2 σ).
7		One occurrence every month or one occurrence in 100 units (Cpk ~ 0.83 ~2.5 σ).
6	Moderate: Occasional Failures	One occurrence every three months or three occurrences in 1,000 units (C_{pk} ~ 1.00 or ~ 3 σ).
5		One occurrence every six months to one year or one occurrence in 10,000 units (Cpk ~ 1.17 or ~ 3.5 σ).
4		One occurrence per year or six occurrences in 100,000 units (Cpk ~ 1.33 or ~ 4 σ).
3	Low: Relatively few Failures	One occurrence every one to three years or six occurrences in 10,000,000 units (Cpk ~ 1.67 or ~5 σ).
2		One occurrence every three to five years or 2 occurrences in 1,000,000,000 units (Cpk ~ 2.00 OR ~6 σ).
1	Remote: Failure is unlikely	One occurrence in greater than five years or less than two occurrences in 1,000,000,000 units (Cpk > 2.00 OR >6 σ).

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

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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT — 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 systemic 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 occur Seen once on a similar product. High volume production: Problem occurred once in 2 years	Confident systemic 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. Mendson, Menson & Associations, Inc
ICH EWG London, March 2004

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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT — 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	damage of inlet-air filter				
	degradation of product	damage of thermometer				
3. Maintain temperature	long drying time	unstable supply-air volume				
	high Loss On Drying (LOD)	damage of timer				
	low LOD	high dew-point				
	non-uniformity of LOD	uneven temperature distribution				

RPN: Risk Priority Number = S*P*D

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ICH Q9 QUALITY RISK MANAGEMENT — 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 due-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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ICH Q9 QUALITY RISK MANAGEMENT — 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
Take action when severity is over 5
Remaining critical parameters after taking action; further controls required

RPN: Risk Priority Number = S*P*D

Based on Takayoshi Matsumura, Esai Co.

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I.2: Failure Mode Effects Analysis (FMEA)

- **Analyse a granulation process step because only a few parameters are adjustable and many problems can occur by manual operations**

Severity (Consequences):	
3: high	Predicted to cause significant impact to quality (failure to meet specifications)
2: moderate	Predicted to cause minor impact to quality (failure to meet specifications)
1: minor	Predicted to could have minor impact on quality of the product (quality within specifications)
Probability	
4: regular failures	Expected to happen frequently
3: repeated failures	Could happen occasionally
2: occasional failures	Expected to happen infrequently
1: failure is unlikely	Unlikely to happen
Detectability	
3: probably not detected	May overlook a fault or failure possibly can not be detected (no technical solution up to now)
2: occasionaly not detected	Failture may be missed (manual control, routinely work with statistical control)
1: detectable	Failture can and will be detected (e.g. using statistical tools)

S. Rönninger, Roche

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Failure Mode Effects Analysis (FMEA)

Risk Assessment							Risk Reduction							
Sub-Step	Event (Failure mode)	Effect	Severity (S) [1<2<3]	Probability (P) [1<2<3<4]	Detectability (D) [1<2<3]	Risk factor (S*P*D)	Actions: Risk reduction strategy	Severity (S) [1<2<3]	Probability (P) [1<2<3<4]	Detectability (D) [1<2<3]	Risk factor (S*P*D)	Risk reduction	Comments
Wet saving Drying	Temperature	not meet specification of degradation	2	4	1	8	implement 2 temperature measures	1	1	1	1	7	automatically interruption by not meeting range; Temperatur monitoring in batch record
Granulation Drying	water content	not meet specification of degradation	2	3	1	6	introduce online NIR	2	1	1	2	4	indirect measurment
							introduce IPC analytic	2	2	1	4	2	direct measurement; time consuming
							humidity measurement in the exausting air	2	1	2	4	2	indirect measurment; unspecific
Granulation	kneeding time	not meet specification of dissolution	3	3	1	9	reduce personnel fluctuation	3	3	1	9	0	operator knowledge; depending on power consumption automatisation not possible at that time
Granulation	power consumption	not meet specification of dissolution	3	2	1	6	try to get to a minimum an optimum of kneeding time	3	2	1	6	0	depending on kneeding time depending on material properties
Pre-mixing	mixing time	not meet specification of content uniformity	3	2	3	18	IPC measure on content uniformity	3	2	1	6	12	influence on efficacy
Pre-mixing Granulation	speed of adding water	not meet specification of dissolution and disintegration	3	3	3	27	Analyse (kneeding of granulate sieve analysis); use of dosage pumps	3	2	1	6	21	to get fine appropriate granulate
Pre-mixing Granulation	manner of adding water	not meet specification of dissolution and disintegration	3	1	1	3	install spray nozzles	1	1	1	1	2	to get fine appropriate granulate
Granulation	Quality of Excipients	all parameters have to be re-evaluated	3	4	3	36	Adapt internal specification of physical parameters (e.g. density, metability sensibility)	1	2	2	4	32	contact supplier
Granulation	Quality of API	all parameters have to be re-evaluated	3	4	3	36	Adapt internal specification of physical parameters (e.g. density, metability sensibility)	1	2	2	4	32	contact supplier
Overview		Risk before control				Max 36 Average 17 Min 1	Risk after control				Max 32 Average 14 Min 0	32 13 0	

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ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.2 Failure Mode Effects Analysis (FMEA)

Risk Assessment						
Sub-Step	Event (Failure mode)	Effect	Severity (S) [1<2<3]	Probability (P) [1<2<3<4]	Detectability (D) [1<2<3]	Risk factor (S*P*D)
Granulation Drying	water content	not meet specification of degradation	2	3	1	6

Risk Reduction						
Actions: Risk reduction strategy	Severity (S) [1<2<3]	Probability (P) [1<2<3<4]	Detectability (D) [1<2<3]	Risk factor (S*P*D)	Risk reduction	Comments
introduce online NIR	2	1	1	2	4	indirect measurment
introduce IPC analytic	2	2	1	4	2	direct measurement; time consuming
humidity measurement in the exaust air	2	1	2	4	2	indirect measurment; unspecific

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ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

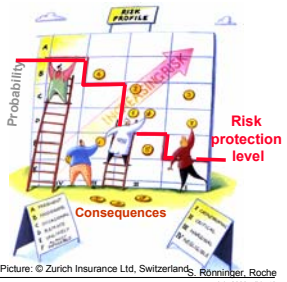
- **Prepare a risk profile**

Severity / Consequences

i	negligible
ii	marginal
iii	critical
iv	catastrophic

Probability

A	frequent
B	moderate
C	occasional
D	rare
E	unlikely
F	very unlikely



Picture: © Zurich Insurance Ltd, Switzerland

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ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

- **Prepare a risk profile: Probability**

Class	rating	Probability
A	frequent	once in a week or more
B	moderate	once in 1 month
C	occasional	once in 1 years
D	rare	once in 10 years (e.g. once in life cycle of the system)
E	unlikely	once in 100 years (e.g. once in life cycle of a site)
F	very unlikely	once in 1'000 years or less (e.g. once in life cycle of Roche or less)

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ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

- **Risk Evaluation**

> **Prepare a risk profile: Consequences**

class	rating	Consequences	
iv	catastrophic	Patient:	fatalities, non-reversible side effects
		Availability:	interruption: permanent stock-out
		GMP:	close down of site / drug shortage; withdrawal of product or loss of marketing authorisation etc.
		Business:	loss: > 20'000 k€
			image: severely damaged international scope
		Employees, neighbourhood:	fatalities, evacuation outside the site area
		Environment:	irreversible, long-term damage outside site area
iii	critical	Patient:	reversible side effects
		Availability:	interruption: < 12 weeks
		GMP:	recall, process interruption, unable to get new products approved etc.
		Business	loss: 1.000 - 20'000 k€
			image: damaged, national scope
		Employees, neighbourhood:	serious injuries, affected outside the site area
		Environment	reversible, short-term damage outside site area

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ICH Q9 QUALITY RISK MANAGEMENT — 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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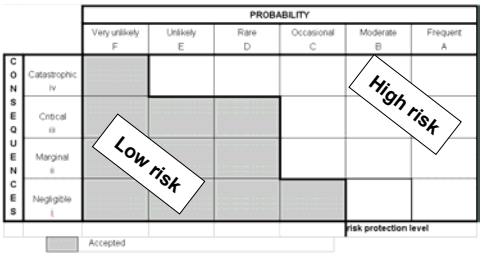
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)

- **Risk Evaluation: Risk Profile**



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

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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT — 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

Based on Takayoshi Matsumura, Esai Co

Annex I.3

Failure Mode, Effects and Criticality Analysis (FMECA)

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)

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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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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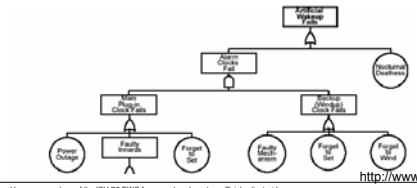

http://www.sverdrup.com/safety/fta.pdf

I.4: Fault Tree Analysis (FTA)

- Basic symbols: Basic Flow

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

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

AND
- 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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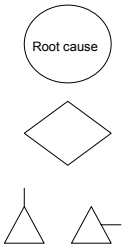
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.4: Fault Tree Analysis (FTA)

- Basic symbols: End Points & Connector



- Root cause (= basic fault)
  (e.g. part failure, software error, human error)
- Fault to be further analyzed
  with more time or information if needed
- Transfer-in and transfer-out events

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

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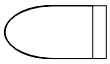
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

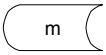
I.4: Fault Tree Analysis (FTA)

- Additional Symbols

- Exclusive OR Gate:
  Fault occurs
  if only one of the input faults occurs



- Priority AND Gate:
  Fault occurs
  if all inputs occur in a certain order



- Voting OR Gate:
  Fault occurs if "m" or more out of "n"
  input faults occurs

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

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ICH Q9 QUALITY RISK MANAGEMENT

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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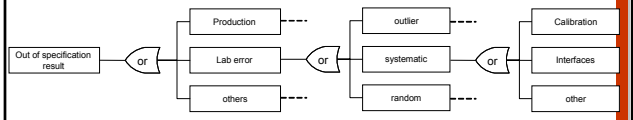
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.4: Fault Tree Analysis (FTA)

- Investigation of laboratory failures



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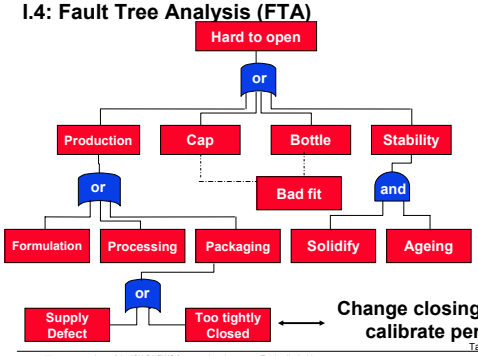
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.4: Fault Tree Analysis (FTA)



Change closing torque and calibrate periodically

Takayoshi Matsumura, Eisai Co

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ICH Q9 QUALITY RISK MANAGEMENT

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

EXAMPLE

I.2: Failure Mode Effects Analysis (FMEA)
I.4: Fault Tree Analysis (FTA)

FTA	FMEA
• Assumes failure of the functionality of a product	• Assumes component failure
• Identifies the root cause of functional failure	• Identifies functional failure as a result of component failure
• Top down	• Bottom up

Annex I.5

Hazard Analysis and Critical Control Points (HACCP)

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/qsm/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?

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

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See WHO

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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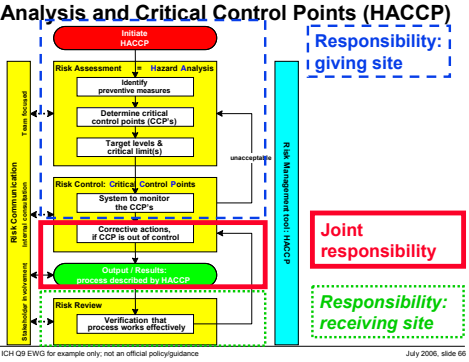
EXAMPLE

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

- Site change or Technical transfer



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ICH Q9 QUALITY RISK MANAGEMENT — 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 maschine 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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ICH Q9 QUALITY RISK MANAGEMENT — 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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ICH Q9 QUALITY RISK MANAGEMENT

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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ICH Q9 QUALITY RISK MANAGEMENT

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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ICH Q9 QUALITY RISK MANAGEMENT

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).*

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")**

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 LESS	Quantitative increase or Quantitative decrease	This applies to quantities & properties such as flow, temperature, and also for functions such as heating and reacting.
AS WELL AS PARTIALLY	Qualitative increase or Qualitative decrease	All desired functions & operations are achieved. Additionally, something else happens. Only a few functions are achieved, some not.
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.

Nail L. Maxson. (2004).

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).

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**

Annex I.7

Preliminary Hazard Analysis (PHA)

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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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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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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Annex I.8

Risk ranking and filtering

Annex I: Methods & Tools

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

Footing 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. Marrer, Roche

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ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

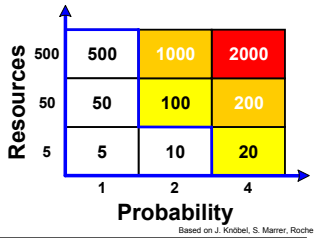
I.8: Risk ranking and filtering

Evaluation of products and processes with recurring quality relevant problems

Risk assessment: Risk 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. Marrer, 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

J. Knöbel, S. Marrer, 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 evaluation

Risk evaluation added to production problems

Site	Product name	Type of recurrent problem/defect	Proba-bility	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

J. Knöbel, S. Marrer, 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 Control

Risk control actions added to production problems

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

J. Knöbel, S. Marrer, 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

J. Knöbel, S. Marrer, 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 evaluation

Risk evaluation added to process problems

Process	Products concerned	Proba-bility	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

J. Knöbel, S. Marrer, 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 Control

Risk control actions added to process problems

Process	Products concerned	Corrective actions instituted to date	Proba-bility	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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ICH Q9 QUALITY RISK MANAGEMENT — 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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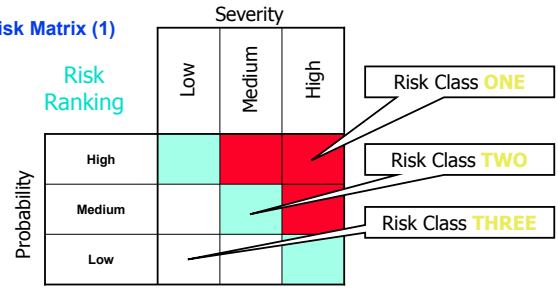
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.8: Risk ranking and filtering

Risk Matrix (1)



Takayoshi Matsumura, Eisai

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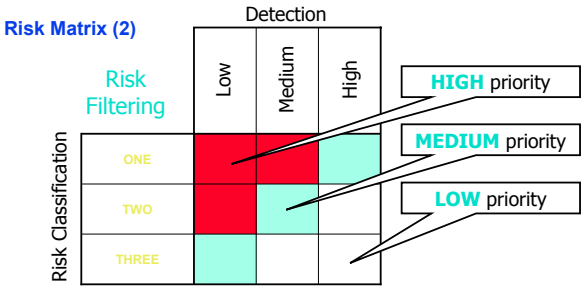
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

I.8: Risk ranking and filtering

Risk Matrix (2)



Takayoshi Matsumura, Eisai

Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT

Annex I.9

Supporting statistical tools

Annex I: Methods & Tools

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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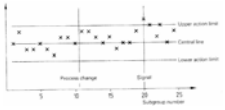
ICH Q9 QUALITY RISK MANAGEMENT

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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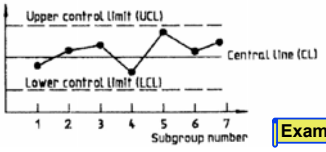
ICH Q9 QUALITY RISK MANAGEMENT

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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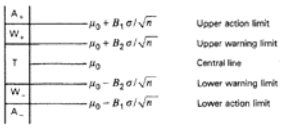
I.9: Supporting statistical tools

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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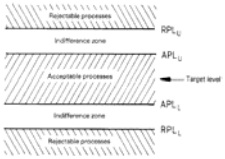
I.9: Supporting statistical tools

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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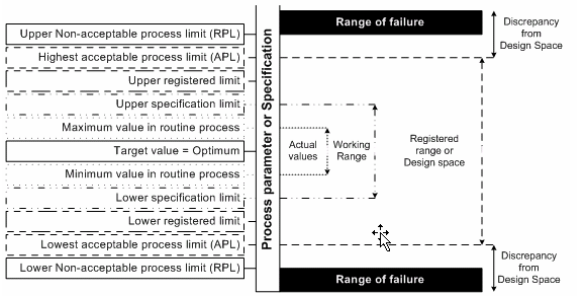
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Compilation of limits and ranges



S. Rönninger, Roche

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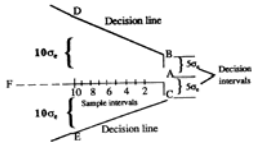
ICH Q9 QUALITY RISK MANAGEMENT

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

Annex I: Methods & Tools

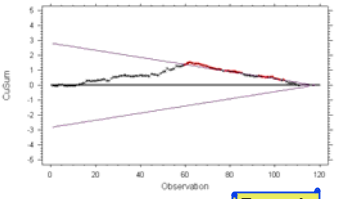
ICH Q9 QUALITY RISK MANAGEMENT

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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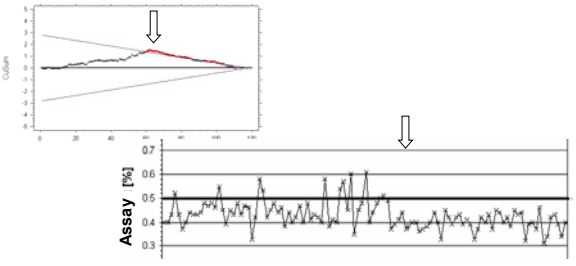
I.9: Supporting statistical tools

Control Charts: Cumulative Sum Charts (ISO 7871)



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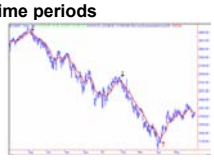
ICH Q9 QUALITY RISK MANAGEMENT

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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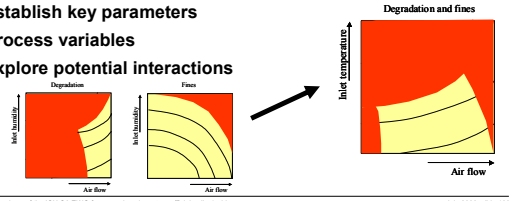
ICH Q9 QUALITY RISK MANAGEMENT

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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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

Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT 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

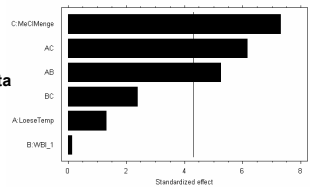
Annex I: Methods & Tools

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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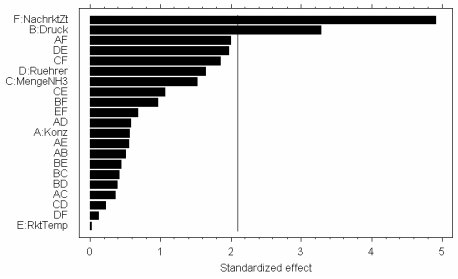
I.9: Supporting statistical tools

- **Pareto Chart**



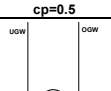
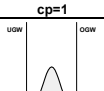
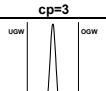
Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT

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 %	> 99,999999 %
Result:	process statistically out of control	**process statisticaly 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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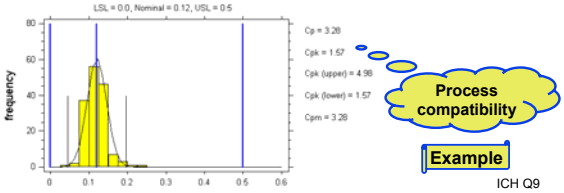
I.9: Supporting statistical tools

Histogram

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



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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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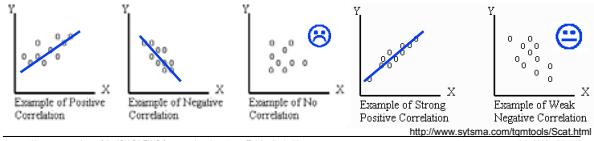


http://www.sytsma.com/tqmtools/Scat.html

Others

Combination of tools

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

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

Annex I: Methods & Tools

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

Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

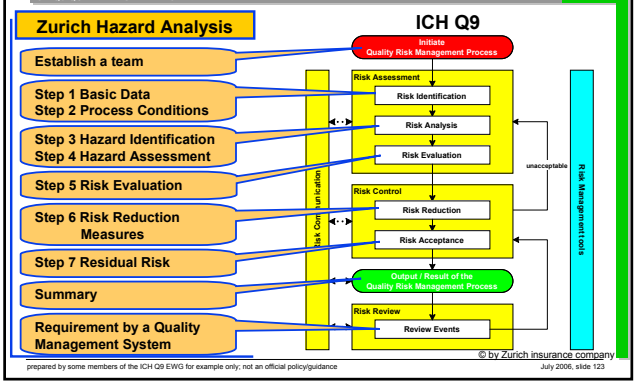
Examples of combination of tools

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

Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE



Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT — 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

Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT — 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

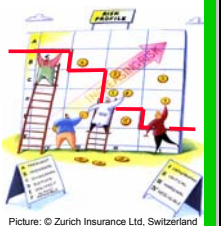
Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT — 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



Picture: © Zurich Insurance Ltd, Switzerland

- Step 6 Risk Reduction Measures
  - > Measures to be taken for every unacceptable risk to reduce the consequences and the probability or both
  - > Prioritise actions

Picture: © Zurich Insurance Ltd, Switzerland

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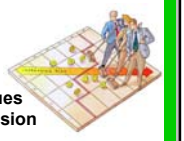
Examples of combination of tools

"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



Picture: © Zurich Insurance Ltd, Switzerland

Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT

Conclusion

Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT — 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

Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT

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

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

Annex I: Methods & Tools

ICH Q9 QUALITY RISK MANAGEMENT

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.

ICH Q9 Introduction to Annex I

Annex I: Methods & Tools

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

Annex II: Potential Applications

Quality Risk Management ICH Q9

Annex II: Potential Applications

Disclaimer: *This presentation includes the authors views on quality risk management theory and practice. The presentation does not represent official guidance or policy of authorities or industry.*

Annex II: Potential Applications

Purpose of this part

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

Annex II: Potential Applications

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.
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Annex II: Potential Applications

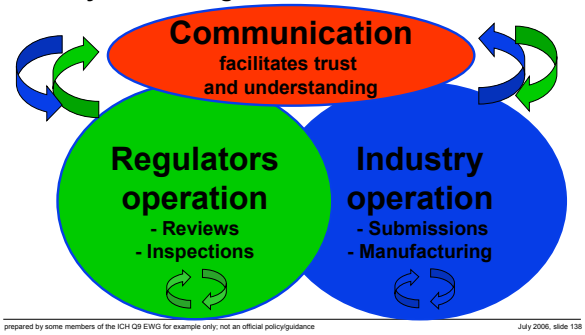
Potential Applications for Quality Risk Management

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

Annex II: Potential Applications

Quality risk management



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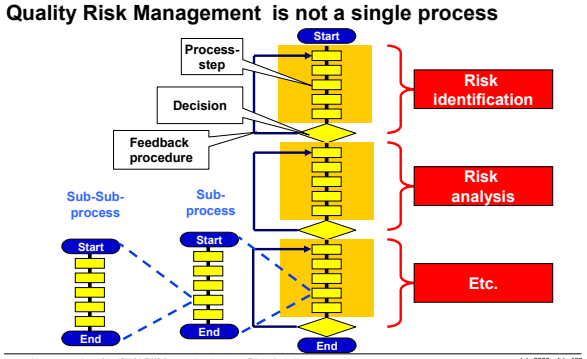
Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

Quality Risk Management is not a single process



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. Claycamb, FDA, Sept. 2005

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. Claycamb, FDA, Sept. 2005

Annex II: Potential Applications

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. Claycamb, FDA, Sept. 2005

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

Challenges for potential applications

Problem:
What is the risk of a rain shower now?

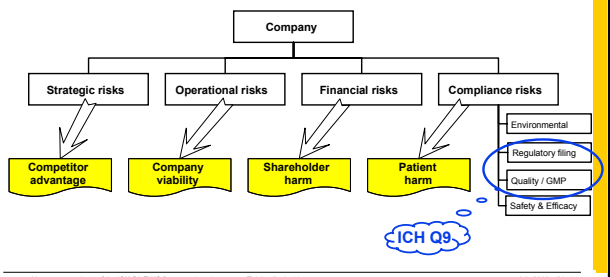
- **Answer 1:**
  - **> Set up a new department with 5 employees**
  - **> Develop a computer program for this risk ("weather forecast")**
  - **> 10 external meetings, 2 conferences, 5 publications,…**
  - **> Verify with experimental data**
  - **> Revisit your program on an annual basis**
  - **>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

S. Rönninger, Sept. 2005

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

Managing risks in a company



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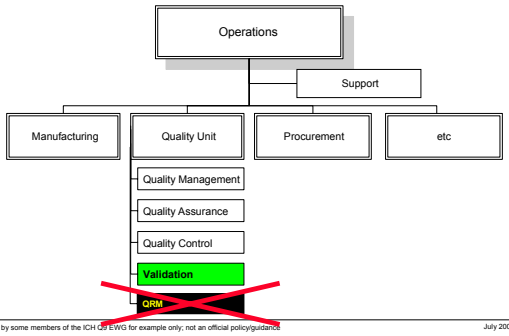
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Existing organisation



Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Risk Management Strategy for Excipients

Development	Manufacturing	Launch	Surveillance
Estimate risk vs hazard	Confirm acceptability	Implement protective measures	Implement surveillance measures
• Characterize materials	• Define specs/quality system practices	• Create literature/define surveillance criteria	• Monitor issues and assess root causes
• Conduct "hazard exposure assessment"	• Define process controls	• Monitor process controls	• Re-assess effectiveness of process controls
• Develop risk mitigation strategy	• Confirm risk mitigation strategy	• Implement risk mitigation strategy	• Re-assess effectiveness of Risk mitigation
• Define risk control measure (s)	• Select risk control measure (s)	• Implement risk control measure (s)	• Re-assess effectiveness of Risk control measure(s)

Evaluate results and make appropriate course corrections based on regulations, customer expectation, company policies and procedures, societal trends and needs

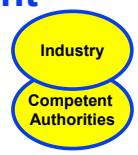
Patricia Rafidison, Dow Corning Life Sciences; IPEC Europe, June 2005

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II. 1 Quality risk management as part of…

Integrated Quality Management



Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

Quality risk management as part of…

II.1: Integrated quality management

> Documentation
> Training and education
> Quality defects
> Auditing / Inspection
> Periodic review
> Change management / change control
> Continual improvement

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.1: QRM as Part of integrated Quality Management

- **Documentation**

> To review current *interpretations* and application of regulatory expectations

> To determine the *desirability* of and/or *develop* the content for SOPs, guidelines, etc.

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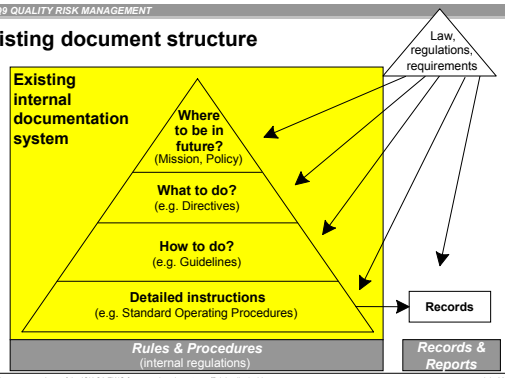
Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

Existing document structure



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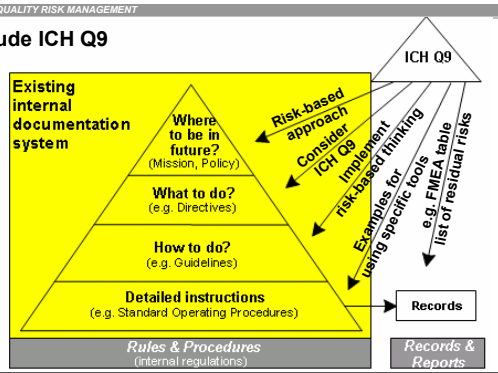
ICH Q9 QUALITY RISK MANAGEMENT

Include ICH Q9



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

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*

ICH Q9

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

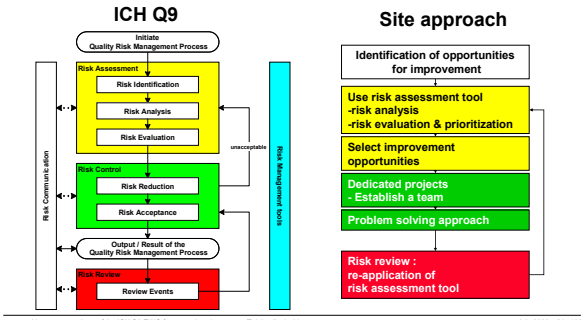
Assess the history of known quality defects

- 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

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

Assess the history of known quality defects



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — 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

Annex II: Potential Applications

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

Annex II: Potential Applications

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

Annex II: Potential Applications

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

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Deviation/ Investigation Report

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

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

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Deviation/ Investigation Report

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

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Deviation/ Investigation Report

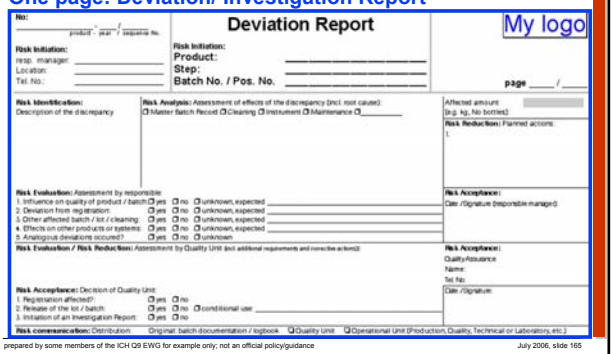
- **Risk Review**
  - > Follow up of action items
  - > Summary and evaluation

    e.g. Annual Product Review

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

One page: Deviation/ Investigation Report



Annex II: Potential Applications

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***

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Complaint/ Issue Management

- **Risk assessment: Risk analysis**
  - > **Assessment of effects of the discrepancy**
    Examples 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***

Annex II: Potential Applications

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***

Annex II: Potential Applications

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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Annex II: Potential Applications

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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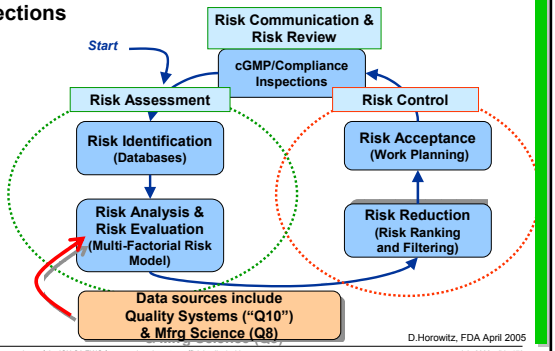
Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Inspections



D.Horowitz, FDA April 2005

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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)

S. Rönninger & EFPIA TG foreign inspections Feb.06

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — 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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — 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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Annex II: Potential Applications

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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Annex II: Potential Applications

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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Annex II: Potential Applications

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 / specified 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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Scheduling audits: A framework

- **History (Detectability)**

Factor	Impact	Example audit/inspections conducted according local and/or commune GMP standards (e.g. PIC/S, WHO or VFA, APIC)
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 by 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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — 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

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Annex II: Potential Applications

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
- > History: Detectability = 3 years ago (4) or more

This would result in 3 x 4 x 2 x 4 = 96

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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	St: Compliance status	St: Strategic interests	P: Complexity	H: Audit history
			[1,3,5,10]	[1,2,4,6]	[1,2,4,6]	[1,2,4,6]	[1,2,4,6]
WWX	hh	zzz	1440	5	6	8	6
MNO	ee	yy	320	10	4	2	4
STU	gg	yyx	240	5	6	8	1
GTH	nn	zxy	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
PQR	ff	xxy	60	10	6	1	1
ABC	aa	xx	60	5	2	1	6
GHI	cc	zz	48	3	1	4	4
JKL	dd	xy	24	1	6	4	1
WEER	pp	yxz	16	1	4	4	1
AABB	kk	yxz	12	3	2	1	2
EDF	oo	xzy	12	1	1	2	6
XXZ	ii	xzx	12	1	6	1	2

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

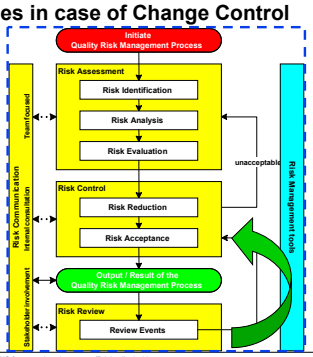
ICH Q9

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Responsibilities in case of Change Control

Industry



Regulators

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II.1: QRM as Part of integrated Quality Management

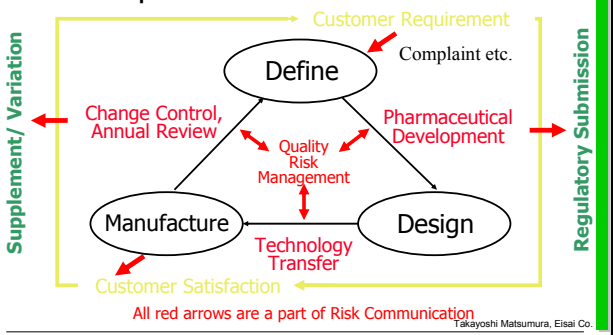
- Continual improvement
  - > To facilitate continual improvement in processes throughout the product lifecycle

ICH Q9

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

Continual Improvement

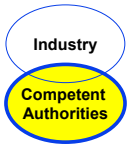


Takayoshi Matsumura, Eisai Co.

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II. 2 Quality risk management as part of…



Regulatory operations

Inspection and assessment activities

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

ICH Q9

Annex II: Potential Applications

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

Annex II: Potential Applications

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))

ICH Q9

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II. 3 Quality risk management as part of…

Development

Industry

Competent Authorities

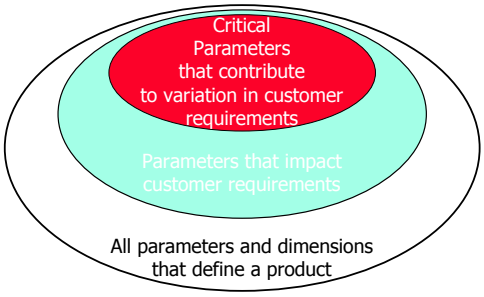
See also next chapters
using the intention to be applicable for development
- **II.4: Facilities, Equipment and Utilities**
- **II.5: Materials Management**
- **II.6: Production**
- **II.7: Laboratory Control and Stability Studies**
- **II.8: Packaging and Labelling**

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

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT CONSIDERATIONS

About development



T. Matsumura, Eisai Co.

Annex II: Potential Applications

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**

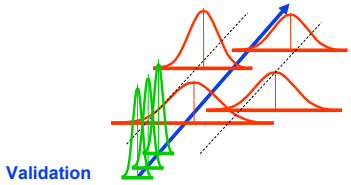
ICH Q9

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"**

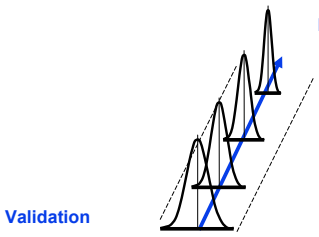
Result: Unstable process

Based on A. Hussain, FDA, September 2004

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

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



- **Reduce "Common Cause" Variability**
- **Consequence: On the continuous improvement path**

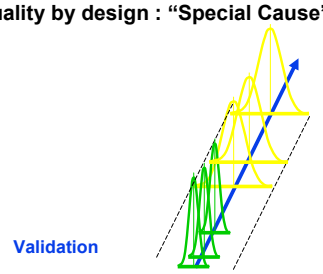
Result: Stable & Capable

A. Hussain, FDA, September 2004

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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Annex II: Potential Applications

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

ICH Q9

Annex II: Potential Applications

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)

ICH Q9

Annex II: Potential Applications

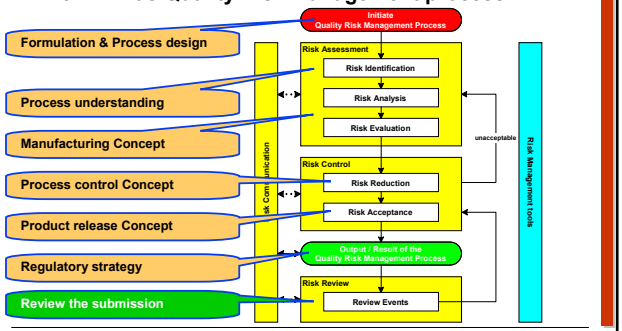
ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

P2 of CTD as part of a regulatory submission

Annex II: Potential Applications

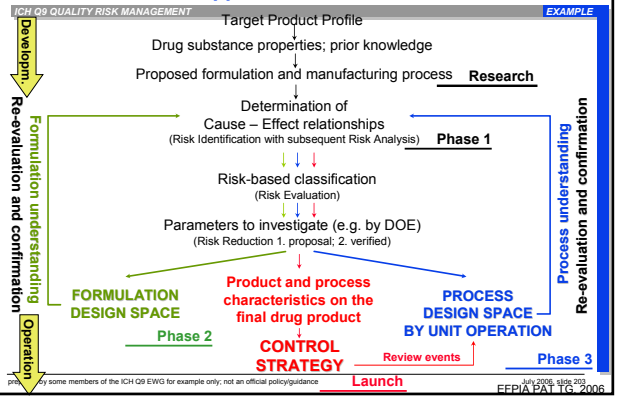
ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

P2 of CTD as Quality Risk Management process ?



Annex II: Potential Applications

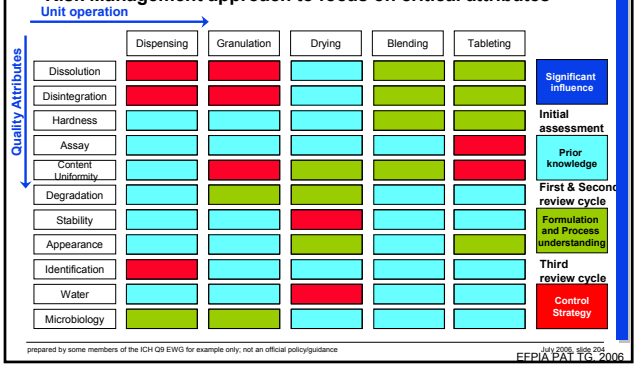
ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE



Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

Risk Management approach to focus on critical attributes



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Risk to patient

Unit operation →

low
Process understanding
Control Strategy

Quality Attributes ↓

Unit operations / Quality attributes	Dispensing (Raw Material Properties)	Granulation	Drying	Blending (Magnesium Stearate)	Tableting	Packaging
Dissolution	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	Not critical to quality	Not critical to quality	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	Not critical to quality	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	Prior knowledge	Control water content	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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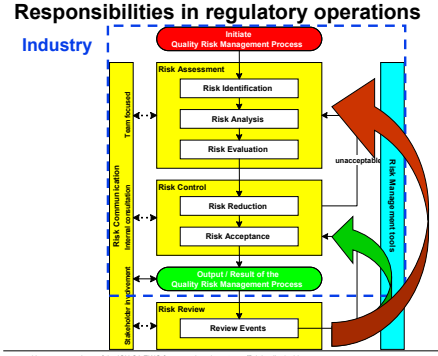
EFPIA PAT TG, 2006

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Responsibilities in regulatory operations



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

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

Past	Future
Parameters and range	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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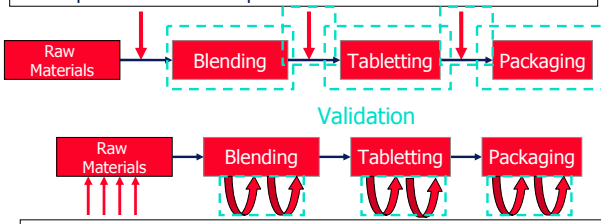
Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Development and Manufacturing

Conventional approach: Testing after each step to minimize the risk prior to the next step



Validation

PAT: Continuous or more frequent testing and control during each step to minimize/control the risk prior to the next step

PAT: Process Analytical Technology Takayoshi Matsumura, Eisai

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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II. 4 Quality risk management as part of…

Industry
Competent Authorities

Facilities & Equipment

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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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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 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 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,.)
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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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 1/2**

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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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 2/3**

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 HVAC/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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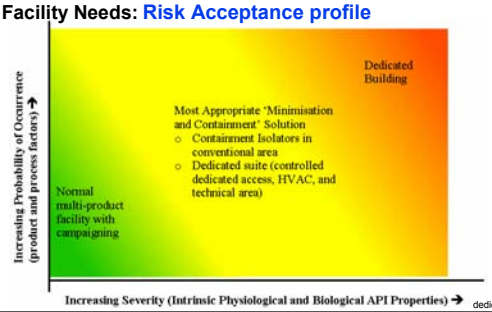
Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

II.4: QRM for facilities, equipment and utilities

Facility Needs: Risk Acceptance profile



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Annex II: Potential Applications

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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Annex II: Potential Applications

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**

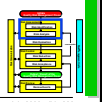
K.-H. Bender, F. Hoffmann-La Roche

Annex II: Potential Applications

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**



K.-H. Bender, F. Hoffmann-La Roche

Annex II: Potential Applications

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

K.-H. Bender, F. Hoffmann-La Roche

Annex II: Potential Applications

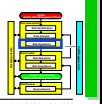
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Zone concept for API

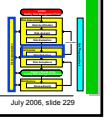
- Risk control

> 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

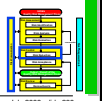
Zone concept for API

- 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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Annex II: Potential Applications

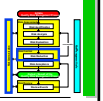
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

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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Annex II: Potential Applications

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

K.-H. Bender, F. Hoffmann-La Roche

Annex II: Potential Applications

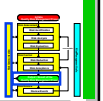
ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — EXAMPLE

Zone concept for API

- The review phase

> Audits / Inspections

> Regularly assessment of complaints/ deviations on (cross-) contamination topics

K.-H. Bender, F. Hoffmann-La Roche

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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Annex II: Potential Applications

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

B. Dreissig, F. Hoffmann-La Roche

Annex II: Potential Applications

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
Reduction in the number of documents:	52%

Document consolidation equals risk reduction via constancy, easy maintenance/training reduces non compliance risk to patient

B. Dreissig, F. Hoffmann-La Roche

Annex II: Potential Applications

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE

II.4: QRM for facilities, equipment and utilities

Cleaning validation

- 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

P. Gough, D. Begg Ass.

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

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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Annex II: Potential Applications

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

W. Schumacher, Roche

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT 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

W. Schumacher, Roche

Annex II: Potential Applications

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? OR Is the business process regulated by an agency?	A: Yes
		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

W. Schumacher, Roche

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT 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

W. Schumacher, Roche

Annex II: Potential Applications

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

W. Schumacher, Roche

Annex II: Potential Applications

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

W. Schumacher, Roche

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT — 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

W. Schumacher, Roche

Annex II: Potential Applications

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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Annex II: Potential Applications

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II. 5 Quality risk management as part of…

Materials Management

Industry

Competent Authorities

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

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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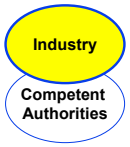
Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II. 6 Quality risk management as part of…

Production



Annex II: Potential Applications

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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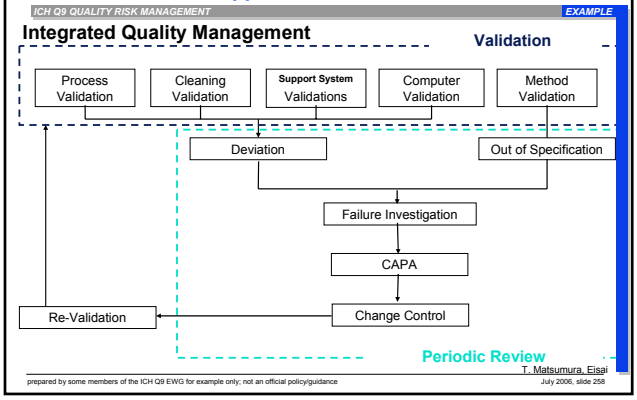
Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT EXAMPLE



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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II. 7 Quality risk management as part of…

Industry

Competent Authorities

Laboratory control and stability testing

Annex II: Potential Applications

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

II. 8 Quality risk management as part of…

Industry

Competent Authorities

Packaging and labeling

Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

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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Annex II: Potential Applications

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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Annex II: Potential Applications

ICH Q9 QUALITY RISK MANAGEMENT

Quality risk management as part of…

Conclusion

Annex II: Potential Applications

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

Annex II: Potential Applications

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

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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