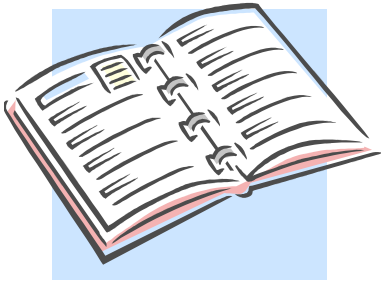
PHARMACEUTICAL
CONSULTANCY
SERVICES

RISK MANAGEMENT

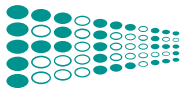
Jaap Koster

AGENDA

- Introduction to Risk Management
- Basic Principles of Risk Management
- FMEA-technique
- Risk Ranking Technique
- Preliminary Risk Analysis



INTRODUCTION TO RISK MANAGEMENT



DANGER / RISK

- What is the difference between danger and risk?
- What is danger?
- What is risk?

DANGER / RISK

Danger:

A real or potential situation that can lead to damage to people or organizations either directly or in the long-term. This includes the loss off or damage to a system, equipment, property or other valuable items.

Danger depends on:

- Exposure
- Effect

DANGER / RISK

Risk:

Risk is the probability of an event occuring, multiplied by the effects of the event and the chance that a certain scenario containing the event will happen. This is in contrast to insecurity, where chances are unknown.

The event can either be positive or negative, on most occasions the word ‘risk’ is used in a negative context.

Risk can also be calculated as the exposure multiplied by the effects and probability. This ‘calculation’ is especially useful for long processes, the first definition can mostly be applied to sudden processes.

RISK MANAGEMENT

DANGER / RISK

Risk

=

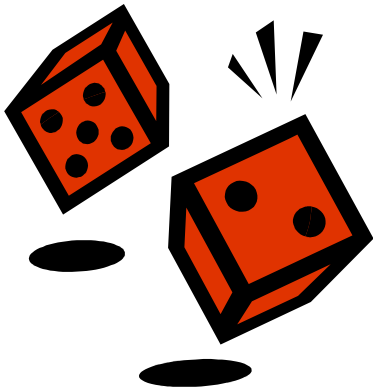
Chance

x

Gravity (Seriousness)

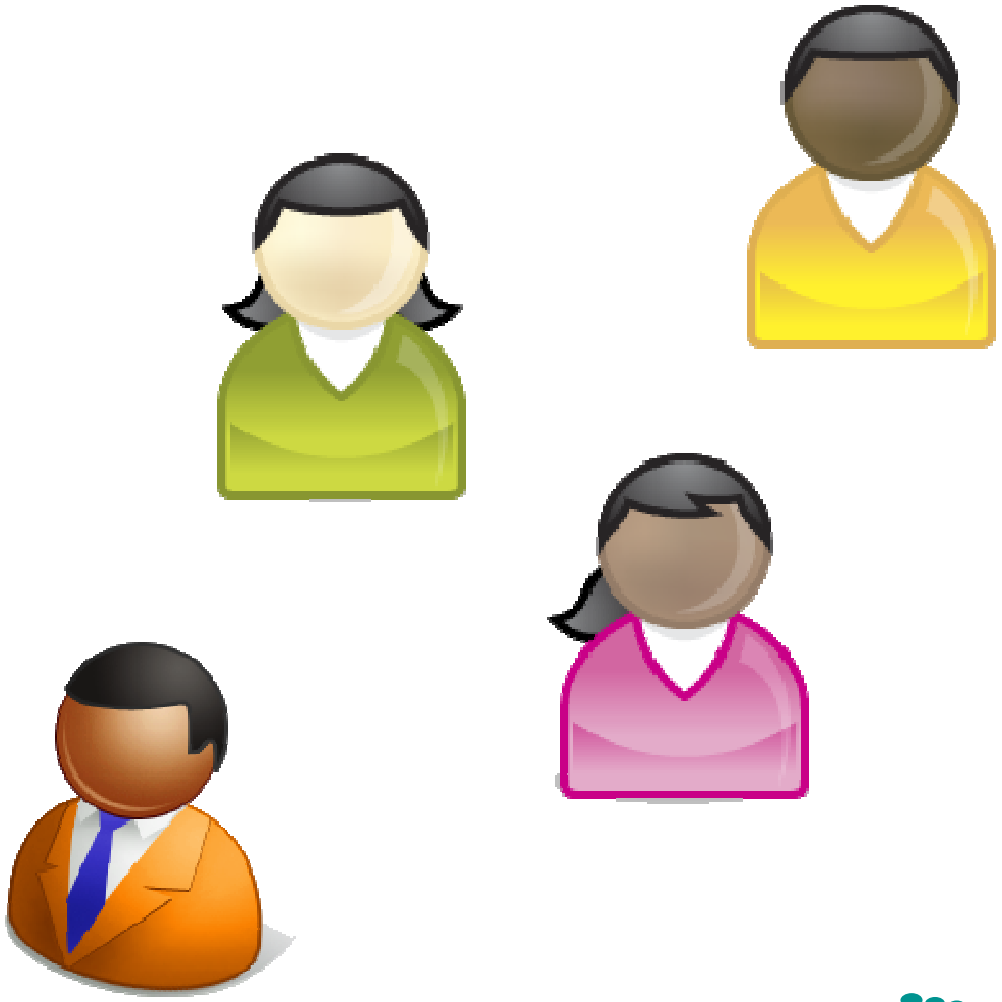
x

Possibility of Detection



ASPECTS OF RISK

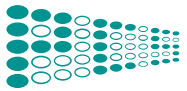
- Insecurity
- Subjectivity
- Persons Involved



TYPES OF RISK

- Acceptable Risk
- Remaining Risk
- Unacceptable Risk
- Unidentified Risk
- Unknown Risk

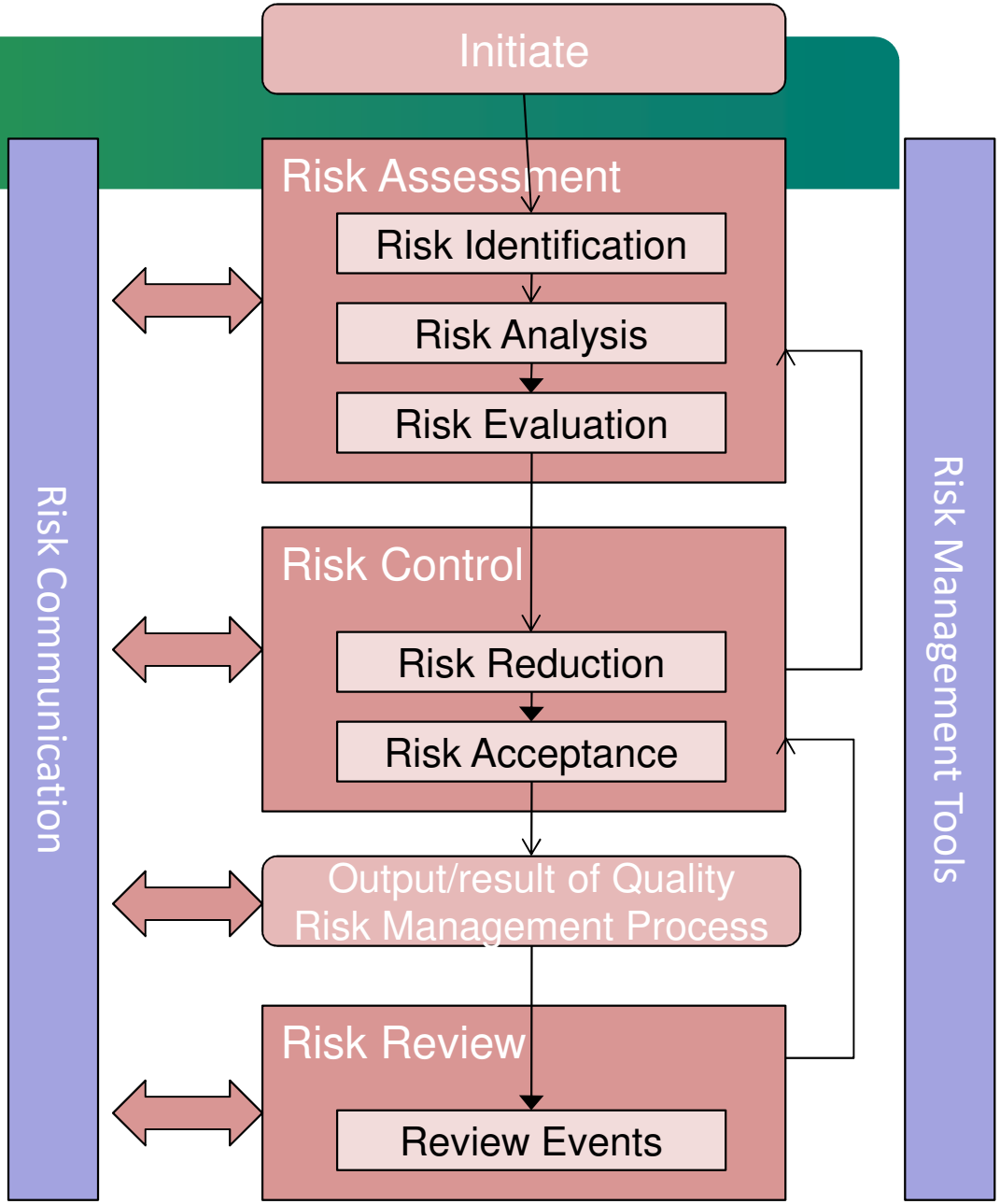
BASIC PRINCIPLES OF RISK MANAGEMENT



REGULATIONS

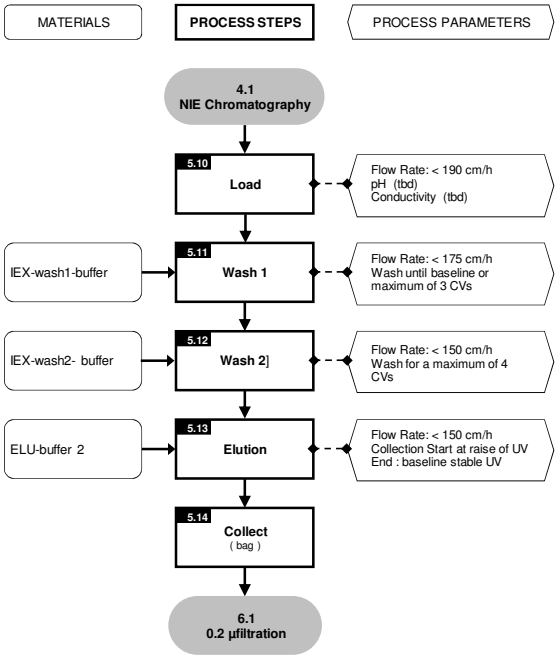
- ICH Q9 - Quality Risk Management (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002873.pdf)
- MHRA (UK) – Quality Risk Management Frequently Asked Questions (June 2010, http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/FAQ/QualityRiskManagement/index.htm)
- WHO – Quality Risk Management (Draft QAS/10.376) (August 2010, http://www.who.int/medicines/services/expertcommittees/pharmprep/QualityRiskManagement-QAS10-376_18082010.pdf)

ICH Q9



INITIATE RISK MANAGEMENT PROCESS

- Clearly define the problem/question
  - **System to Investigate (“the case”)**
  - Risk question
  - Scope
    - What part/process (logistical, production, purchasing, …)
    - “nature” of the analysis (microbiological, parameters, attributes ?)
    - Analysis only ?
    - Performing risk reducing actions
  - Define the goal



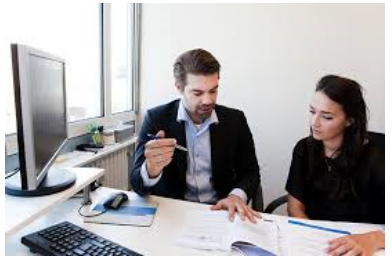
INITIATE RISK MANAGEMENT PROCESS

- Compile **a team**
  - Facilitator
  - Experts (SME – Subject Matter Expert)
  - Knowledge / training
  - Interdisciplinary
  - Team size

INITIATE RISK MANAGEMENT PROCESS

- Ensure you have a **SPONSOR** !
  - Time = man hours
  - FMEA's can be time consuming and long-lasting (selecting a scope)

- Ensure you have a well-defined goal
- Select an appropriate **risk analysis technique**
  - Define the criteria
- Clearly define the method
- Compile information / documentation
- Define (intermediate) reporting with the sponsor



RISICO ANALYSIS / RISK ASSESSMENT

- Identify possible dangers/risks
- Identify how critical the risks are
  - Qualitative
  - Semi-Qualitative
  - Quantitative
- Perform **Risk Evaluation:**
  - Compare Result to the Criteria
- If needed, perform a “Sanity Check”
  - Do the reality and perception match up?

RISK CHECKING

Determine:

- If a risk is acceptable
- If the risk(s) need(s) to be reduced

- Prioritize the risks to be reduced

RISK CHECKING

- **Identify** possible risk prevention measures
- (Preventative measures)
  - Reduce the possible amount of occurances
  - Reduce the severity of the events
  - Increase the identification possibility

- **Re-evaluate** the measures
  - Have no new risks arisen?
  - Am I reaching the right goal?

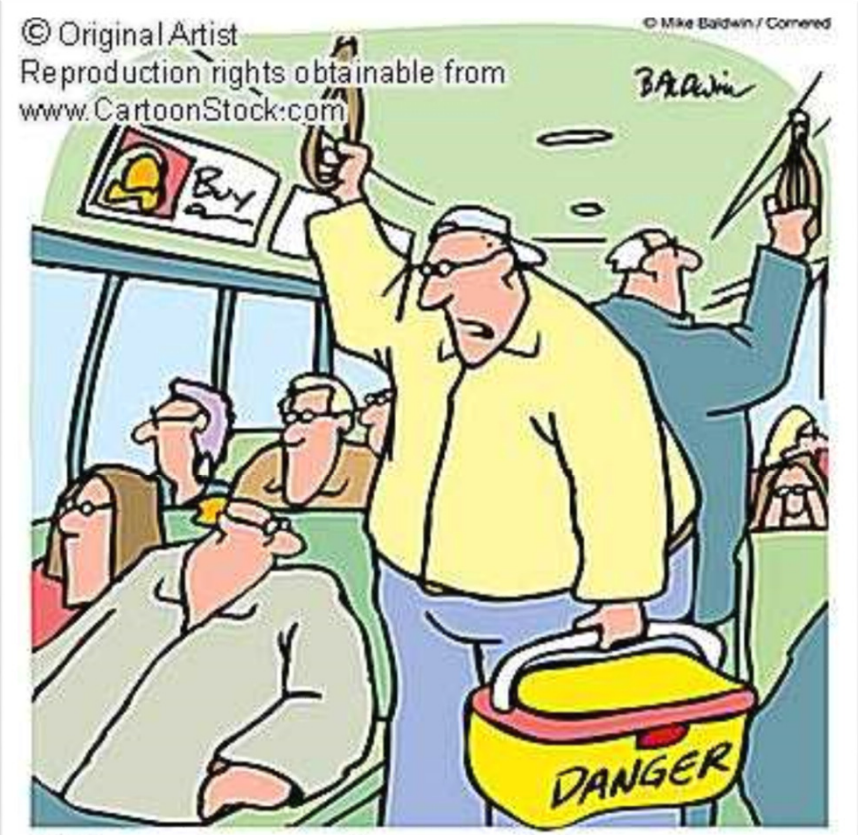
- **Implement** the risk prevention measures

RISK COMMUNICATION

- Reporting:
  - A Report records the situation at a certain moment in time (short shelf life)
  - How to revise / when to revise?
  - In what system does a report need to be recorded?
  - What is the standard lay-out?
  - According to the assignment

- Communication
  - Report to sponsor / principal
  - Inform concerned parties

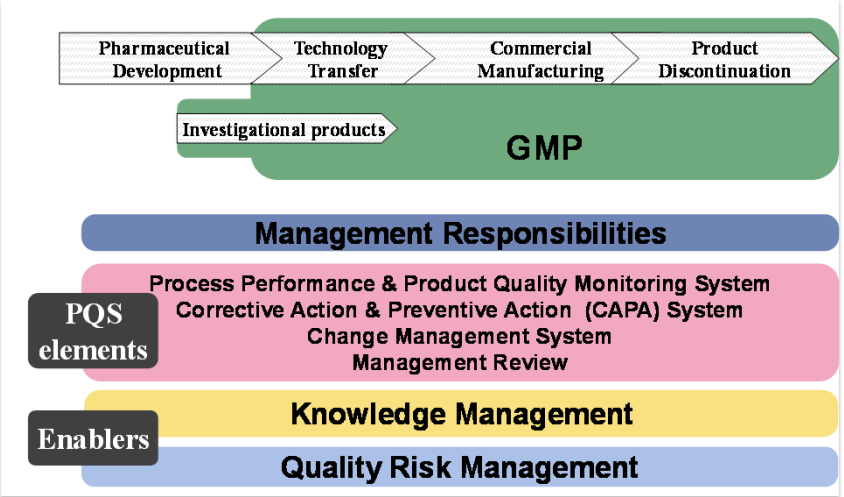
RISK COMMUNICATION



"They always give us minimum-wage, part-time guys the riskiest jobs."

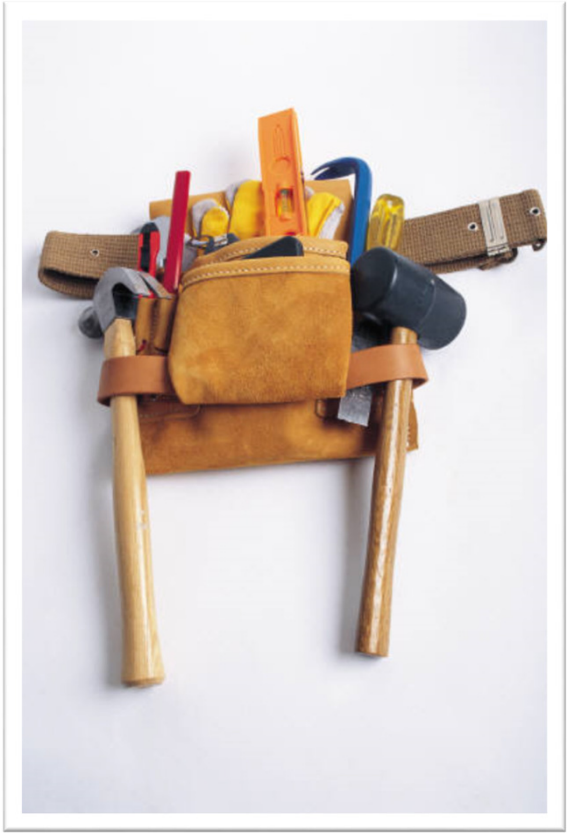
RISK MANAGEMENT REVIEW

- Risk management is a non-interchangeable component of the QMS (Quality Management System)



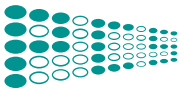
- Implement Risk Management in Existing Systems:
  - Annual Product Review
  - Deviation management
  - Change control
  - Monitoring System for water, HVAC, EM
  - ……..

RISK ANALYSIS TECHNIQUES



- Failure Mode Effect (Criticality) Analysis **(FME(C)A)**
- Fault Tree Analysis **(FTA)**
- Hazard Analysis and Critical Control Points **(HACCP)**
- Hazard Operability Analysis **(HAZOP)**
- Preliminary Risk Analysis **(PRA)**
- Preliminary Hazard Analysis **(PHA)**
- Risk Ranking & Filtering Method
- Intuitive (i.e. SME's)

FMEA TECHNIQUE

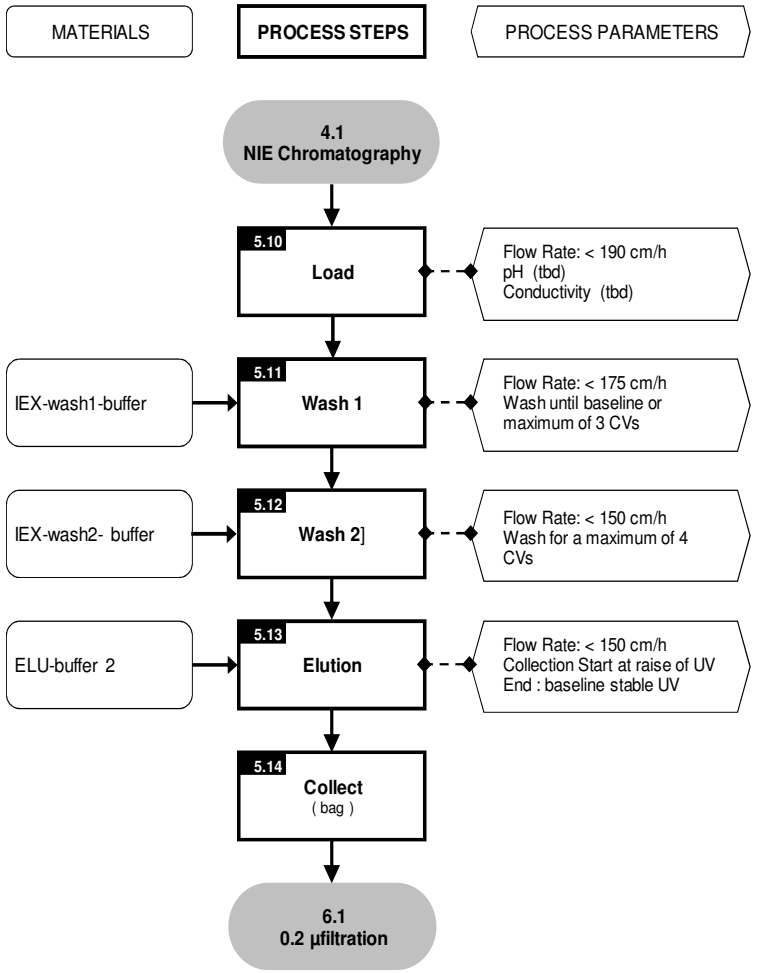


FMEA

- **Basic Principle:**
  - **RPN (Risk Priority Number)**
    = C (chance) x S (severity) x D (detectability)
- **(Others: LxFxD)**
- **Ask:**
  - **What can go wrong?**

FMEA (PROCESS)

- Gather as much detailed process information as possible concerning “the case”.
- Check if the information is correct
- Is all information that is related to the scope (i.e. Microbiological view) present?
- It all comes down to detail(s).



FMEA

1. Consecutively: divide –if not done already- the process/system into steps (pay attention to the numbering)

Process-step	Fault/ failure	Cause failure	Existing Measures	P	S	D	RPN	Explanation
1.Materials are received								
2. Compare to order								
3. Creating labels (identity)								

FMEA

2. Assess the pit-falls and why are they existing?

Process-step	Fault/ failure	Cause failure	Existing Measures	P	S	D	RPN	Explanation
3. Creating labels	3.1 Wrong label	Faulty data input						
	3.2 Wrong label	Wrong label in machine						
	3.3 Wrong label	Old data still in the labelprinter						

FMEA

3. Welke maatregelen zijn al aanwezig

Process-step	Fault/ failure	Cause failure	Existing Measures	P	S	D	RPN	Explanation
3. Creating labels	3.1 Wrong label	Faulty data input	N/A					
	3.2 Wrong label	Wrong label in machine	Machine Output: Error					
	3.3 Wrong label	Old data still in the labelprinter	N/A					

FMEA

4. Determine the chance that the situation occurs

Numerical (real numbers)

Semi-quantitative (1,3,5 of 1 to 10). Never Use 1,2,3!!

Qualitative (L, M, H)

1	It's unlikely this fault will occur
3	The fault can occur but only on few occasions
5	It is highly likely the fault will occur

FMEA

4. Determine the chance of occurance:

Process-step	Fault/ failure	Cause failure	Existing Measures	P	S	D	RPN	Explanation
3. Creating labels	3.1 Wrong label	Faulty data input	N/A	5				
	3.2 Wrong label	Wrong label in machine	Machine Output: Error	1				
	3.3 Wrong label	Old data still in the labelprinter	N/A	3				

FMEA

5. Determine the severity of the event:

Numerical (real numbers)

Semi-quantitative (1,3,5 of 1 to 10). Never Use 1,2,3!!

Qualitative (L, M, H)

1	This fault can have a possible, minor influence on the process
3	This fault can have a mild influence on the process
5	This fault will have major consequences for product quality and will negatively influence the quality

FMEA

Process-step	Fault/ failure	Cause failure	Existing Measures	P	S	D	RPN	Explanation
3. Creating labels	3.1 Wrong label	Faulty data input	N/A	5	5			
	3.2 Wrong label	Wrong label in machine	Machine Output: Error	1	5			
	3.3 Wrong label	Old data still in the labelprinter	N/A	3	5			

FMEA

6. Determine the detection possibility

   Numerical (real numbers)

   Semi-quantitative (1,3,5 of 1 to 10). Never Use 1,2,3!!

   Qualitative (L, M, H)

1	The fault can be detected in advance 100% and the process can be adjusted in time
3	There is a possibility the fault can be detected and that the process can be adjusted in time
5	The fault will most likely not be detected / is detected too late or cannot be influenced

FMEA

Process-step	Fault/ failure	Cause failure	Existing Measures	P	S	D	RPN	Explanation
3. Creating labels	3.1 Wrong label	Faulty data input	N/A	5	5	3		
	3.2 Wrong label	Wrong label in machine	Machine Output: Error	1	5	3		
	3.3 Wrong label	Old data still in the labelprinter	N/A	3	5	3		

FMEA

7. Calculate the RPN
8. Explain why the score has been made

Process-step	Fault/ failure	Cause failure	Existing Measures	P	S	D	RPN	Explanation
3. Creating labels	3.1 Wrong label	Faulty data input	N/A	5	5	3	75	...
	3.2 Wrong label	Wrong label in machine	Machine Output: Error	1	5	3	15	...
	3.3 Wrong label	Old data still in the labelprinter	N/A	3	5	3	45	...

FMEA

RPN, Risk Priority Number

JK2

Risk Value	Risk of contamination of the product	Preventative measures
≥75	Very High. There is a large chance that the quality of the product is endangered with this approach	Direct action needs to be taken production needs to be halted
26-74	Medium. There is a chance that the product quality cannot remain/be ensured.	Preventative measures have to be taken
6-25	Low, the risk of adverse effects on the quality of the product is low.	Where possible, preventative actions need to be taken to reduce the possibility
1-5	Very low, the risk to the quality of the product is very low	No actions needed, acceptable risk
0	None; there is no risk to the product	

Diapositive 37

JK2 Kan niet vertalen?
Julian Koster; 20/05/2015

FMEA

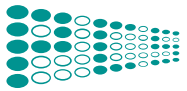
9. Propose possible preventative measures, examine their effectiveness.

Process -step	Fault/ failure	Cause failure	Existing Measures	P	S	D	Measure	P'	S'	R'	RPN'
3. Creating labels	3.1 Wrong label	Faulty data input	N/A	5	5	3	Operator 2 Check	5	5	1	25
	3.2 Wrong label	Wrong label in machine	Machine Output: Error	1	5	3	N/A	1	5	3	15
	3.3 Wrong label	Old data still in the label printer	N/A	3	5	3	Adjustment of System	1	5	3	15

FMEA (MODULE)

If not a process, but a machine or utility:

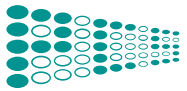
- Define the individual components
- Number those
- Continue with the same approach as discussed above, but not process-step wise, but component wise.



FMEA

- **Advantages**
  - Structured
  - Qualitative and (semi)-quantitative
  - Provides a good tool for evaluating possible preventative measures
  - Widely adopted, well known
  - Highly applicable to a large number of situations/cases/etc.

- **Disadvantages**
  - Less suitable for creating interactions
  - Can lead to excessively large analyses, that will be hard to read/understand and maintain in the long run
  - Longevity (many man-hours)



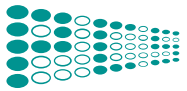
FMEA

Usage:

Wide range of suitable situations:

- Equipment
- Computerized Systems
- Production processes

RISK RANKING



RISK RANKING METHOD

- Ask:
  - What should and should not be done?
  - What has the highest priority?

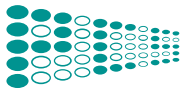
RISK RANKING METHOD

1. Determine critical factors (qualifiers) related to the question

Question: What are the critical raw-materials?

JK1

- Originating from an animal (TSE sensitive yes/no?)
- Use of raw-material in the production process
- Quality of the raw-material



JK1 Vertalen?
Julian Koster; 20/05/2015

RISK RANKING METHOD

2. Determine criticallity per qualifier

- can also be done qualitatively (yes/no, L/M/H)

RISK RANKING METHOD

Qualifier	L	M	H
Animal Origin	No	Yes, non-cow	Cow
Used in the process	Is purified		Used in final product
Quality of Raw-material	USP/ EP	Other pharmacopoeia	No pharmacopoeia

RISK RANKING METHOD

Qualifier	L	M	H
Animal Origin	1 No	3 Yes, non cow	5 Cow
Used in the process	1 Is purified		7 Used in final product
Quality of Raw-material	1 USP/ EP	3 Other pharmacopoeia	5 No pharmacopoeia

RISK RANKING METHODE

3. Determine the calculation method for the Total Value
   - Sum up or r JK3 tiplying
   - Use weighted factors
4. Determine criteria of the Total Value

Total value	**Criticality of RAW material**	**Preventative Measures**
1-4	Not Critical	No measure needed
5	Barely Critical	Risk is acceptable, measures can be taken, however this is not necessary
6-7	Critical	Raw materials need to be fully analyzed
>8	Very Critical	Raw materials need to be fully analyzed and the supplier needs to be audited

JK4

Diapositive 48

JK3 Geen directe vertaling
Julian Koster; 20/05/2015

JK4 Kan niet vertalen, is afbeelding, bron?
Julian Koster; 20/05/2015

RISK RANKING METHODE

5. Make a list of subjects that will be ranked

   Make sure this list is complete!

Raw-Material	Animal Origin?	Usage in Production -Process	Quality of Raw Material	Total Value	Ranking
Fetal serum					
Mannitol					
$CaCl_2$					

RISK RANKING METHOD

6. Determine the score per quality-parameter

Raw-Material	Animal Origin?	Usage in Production -Process	Quality of Raw Material	Total Value	Ranking
Fetal serum	5	1	3		
Mannitol	1	7	1		
$CaCl_2$	1	1	3		

RISK RANKING METHOD

Determine acceptable criteria of the Total Value (i.o.w. How will you process the total value?).

This can be numerical as well:

Total value	Criticality of RAW material	Preventative Measures
1-4	Not Critical	No measure needed
5	Barely Critical	Risk is acceptable, measures can be taken, however this is not necessary
6-7	Critical	Raw materials need to be fully analyzed
>8	Very Critical	Raw materials need to be fully analyzed and the supplier needs to be audited

Diapositive 51

JK5 Idem

Julian Koster; 20/05/2015

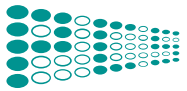
RISK RANKING METHOD

7. Calculate the Total Value

Calculation: origin x usage x quality

Raw-Material	Animal Origin?	Usage in Production -Process	Quality of Raw Material	Total Value	Ranking
Fetal serum	5	1	3	15	Very critical
Mannitol	1	7	1	7	critical
$CaCl_2$	1	1	3	3	Not critical

PRELIMINARY RISK ANALYSIS



PRELIMINARY RISK ANALYSIS

- Properties:
  - No formalized structure
  - Multidisciplinary
  - Intuitive

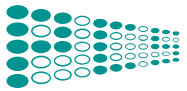
- Advantages:
  - Can be used to identify risks quickly and soon
  - Can be used as a pre-selection for FMEA studies
  - Easy to adjust
- Disadvantages:
  - No formalized structure

PRELIMINARY RISK ANALYSIS

- Usage:
  - At the beginning of a new process / equipment
  - Basic risk analysis (rough selection, process / equipment for example)
  - Less significant consideration such as;

    - Deviation wrap-up
    - Change examination

ALTERNATIVE RISK ANALYSIS



ALTERNATIVE RISK ANALYSIS (NOT PROMOTED)

As an example: RA on a process

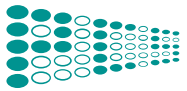
- Do mapping of process in One Unit Operations.
- Assess with a team of SME's (Subject Matter Experts), as follows:
  - What is the possible risk of each step (comparible with FMEA question)
  - DO RPN (basically the same as with FMEA)
  - Rank en discuss
  - Propose mitigations.

IN CONCLUSION (1)

- Always determine “the case” first: the underlying process/component.
  - What component of the entire operation are we studying

- Convince yourself/others that sufficient details have been gathered concerning:
  - The underlying process/component
  - The question

- Carefully select the appropriate analysis techniques
  - 1 overall-study can include multiple



IN CONCLUSION (2)

You are not allowed to “risk assess” non-GMP’s into your system.

Examples:

1. Annex 8 (EU), clearly states that it is not allowed (some softer wording is used) to skip test (not testing every container) of Raw Material for sterile products (all containers to be tested)

   A company was defending that they didn’t need to test each container for Excipients since an RA was showing of low risk. This was not accepted and the company got a formal observation on this.

2. Every 6 months is the frequency of Media Simulations

   A company RA-ed this into 9 months, and same story as above

THANK YOU FOR YOUR ATTENTION

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