Risk Analysis: myths, confusions and real sense

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What is Risk analysis?

- **Risk** means the possibility of dangerous or unwanted event to occur;
- People analyze risk **for ages and every day** to be protected against unwanted events;
- Purpose is to understand chain:

Reason	→	Event	→	Consequence
Defect of tablet press punch, for example		Break of punch		for product Metal parts in the tablet

GMP EU and ICH Q9 promise

- **2005: ICH Q9** "Quality Risk Management";
- **2008**: **ICH Q9 became Annex 20** GMP EU;
- **2010**: it became **Part III** of GMP EU

Introduction to GMP EU says:

"The aim of Part III is to **clarify regulatory expectations** and it should be viewed as a source of information on ***best current practices***".

Is it true?

GMP EU and ICH Q9 promises

- ***General methods*** include Flow charts, Check sheets, Fishbone diagram & others.

  General methods are ***trivial*** and ***no special guide is needed***

- ***Other methods*** include FMEA, FMECA, HACCP and so on abbreviations.

  Let's look how they work on example of **FMEA** *(Failure Mode Effect Analysis)* method that is propagated widely.

FMEA method: "***Quantity estimation of risk***"

1st Step. Setting ***evaluation criteria*** of risks :

- ***Severity****/Impact (I)*;
- ***Occurrence*** *or probability of event (O)*;
- ***Detectability*** *(D).*

2nd Step: Each criteria has ***numerical value***

For example, numbers from ***1 to 5***,

- ***1*** means the ***lowest risk*** and

  5 means the ***highest*** risk.

FMEA method

3d Step

- ***Risk Priority Number (RPN)*** is calculated by multiplying ***evaluation criteria:***

  RPN = **I × O × D;**

- ***RPN*** grows from ***1*** to ***125*** with risk increasing

4th Step

- ***Acceptance level*** of ***RPN*** shall be specified in advance;
- It can be any number within ***RPN*** range (1 -125), say, 27; 51 or 109.

FMEA method

- If ***RPN < Acceptance level***, then risk is low;

- ***No*** further action needs to be implemented;

- **In contrary** if ***RPN > Acceptance level***, correction actions are needed.

FMEA has **three fundamental mistakes**:

1st mistake:

Acceptance levels (and RPN) are assigned by human ***arbitrary*** or ***subjectively***, by his own mind.

2nd mistake

- Values with ***different sense*** **(I; O; D)** are multiplied, that ***is not allowed*** by science!

- To ***compare incomparable*** is a huge and obvious ***methodical*** mistake.

3d mistake

- ***Mathematical play*** with ***RPN*** gives ***image*** of Quantity analysis only;

- This ***arbitrary*** estimation serves further as a basis for ***responsible decision;***

- This play has ***nothing common*** with science!

It is a very dangerous approach!

FMEA Example: Two events for **airplane**

Event	Evaluation criteria			RPN
	Severity	Occurrence	Detectability	
Delay of plane arrival	1	5	5	**25**
Crash of plane	5	1	5	**25**

- Delay and Crash are ***equivalent*** by FMEA

- Is it better than discussions of medieval monks from ***Thomas Aquinas*** times: ***"How many devils can be accommodated on the tip of the needle"?***

FMEA - Example for pharmaceuticals – Ac. Level=27

Process step or equipment	Possible failure/risk	Consequence of failure	Occurrence	Severity	Detection	RPN	Further action
			1–5	1–5	1–5		Yes/No
Machine preparation	Cleaning not sufficient	Cross contamination/ microbiological contamination	1	5	2	10	No
Machine preparation	Recalibration interval violated	No GMP conformity	1	4	2	8	No
Machine preparation	Punches installed not correctly	Tablets contaminated (metal) machine defect, loss of production	1	3	1	3	No
Loading	Not enough loading goods	No delivery of granules for the compression process	2	2	1	4	No
Automatic loading	Wrong granules	**Patient dead**	1	5	2	**10**	No
Machine adjustment	Wrong Adjustment	Tablet content too high, patient harm	1	5	1	5	No
IPC	Balance wrong	Wrong weight, **Patient harm**	1	5	3	**15**	No
Etc							

ICH Q9 (Part III of EU GMP) says that it helps ***manufacture*** and ***inspector***

How it helps manufacture?

- Does it help ***to construct*** process flow charts, to find critical points, to draw HVAC, WFI and other schemes? – No!

- They all shall be ***in the design***!

- To arrange ***routine testing/control*** and to write documents? ***But is already in GMP!***

Risk analysis helps inspector? *How?*

One of **inspectors** writes:

- Inspector has ***not enough time*** and papers on risk analysis ***prepared by manufacturer*** make his task easier to estimate the plant.

So Inspector observes:

- not **primary documents** (records, etc.),
- but **secondary ones**,
- that reflect primary sources ***only partly;***
- *And* prepared by ***persons to be inspected***.

A fundamental danger is hidden in this approach!

Inspections and Delayed-action Mine

It is a very important opinion:

- Inspector observes not **primary documents** (WFI schemes, records, etc.);

- but **secondary ones**, i.e. papers that reflect primary sources ***only partly;***

- prepared by ***persons to be inspected***.

A fundamental danger is hidden in this approach!

Inspections and Delayed-action Mine

It would be interesting to look:

- How ***financial/tax*** inspector will check the company on ***interpretations*** of financial documents made by people under inspection, not on the very documents;
- How ***road police*** will judge guilty drivers on driver's *own interpretation* of accident;
- and so on.

Inspections and Delayed-action Mine

- Customer buys ***medicinal product*** that shall comply ***with primary documents*** not with exercises;

- It cannot be allowed to evaluate manufacturer by ***extracts from documents*** or comments, especially made by ***persons under control***.

This is a Delayed-action Mine!

Risk analysis – Danger of formal approach

Why are we so anxious?

- ***Time and human resources*** in real manufacturing life are always ***limited***;
- Plays with formal methods can distract attention from ***care on quality;***
- Methods can serve as ***excuse for risk***

It breaks the main condition:

No risk for medicines is permitted!

Can Risk analysis can *be positive?*

- Yes, if it ***professional, clear and useful***.

Example of Company *Nutricia*

- In 1993 the batch of product contained ***residues of disinfectants*** was recalled from the market;
- This accident pressed company to implement ***Risk analysis system***.

Real sense of risk analysis **is to show how facility is protected** against (design)**:**

- ***Cross contamination*** (layouts; airflows; pressure differences; materials, personal flows etc.);
- ***Mixing*** of materials and products;
- ***Mixing*** of sterile and non-sterile products;
- ***Non-sterility*** in aseptic processes;
- ***Contamination*** (particles, viables…);
- Surfaces contamination;
- ……

Experience of *Nutricia*

Soon ***problematic places*** were revealed:

- personnel;
- contamination;
- raw materials defects;
- out-of-standards deviations.

It is very close to problems of pharmaceutical factories.

Conclusion

1. Method has ***no right*** to exist in two cases:

- if it is ***wrong and misleading*** for users;

- if it gives ***trivial result*** (result that can be got by simpler way or is obvious).

ICH Q9 methods fall under these two cases and are ***not suitable for use***.

Conclusion

2. Special danger of methods enforced is that they ***allow unacceptable events***.

These methods, moving from the office to manufacture can be used by somebody to ***justify wrong work***.

3. Science says that we belong to creatures named ***"Homo sapience"*** or ***"Wise man".***
If so, why do we accept exercises like FMEA method?

Conclusion

4. Everybody speaks about manufactures, inspectors and consultants.

- What about ***customers,*** who the main party?
- ***What can be their reaction on ICH Q9 and similar methods?***

5. It is necessary to arrange wide discussion on Risk analysis methods with all ***pro and contra*** to form public opinion