

Risk Analysis: myths, confusions and real sense

Dr. Alexander Fedotov,
Director of “Invar-project”
Company, Moscow, Russia
fedotov@invar-project.ru
www.invar-project.ru

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:



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**:

$$RPN = I \times O \times D;$$

- **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