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# PRACTICAL DEVELOPMENT ASPECTS OF RISK MANAGEMANT IN PHARMACEUTICAL INDUSTRY

*Risk management is a very old concept, but until recently it hadn't been given a full development in terms of pharmaceutical quality. As often happens with self-evident concepts, a quality risk management approach has to deal with many more implementation problems that it could be imagined beforehand. These practical risk management introduction problems are here reviewed and commented.*

*Key words:* risk analysis; risk assessment; validation

## FORMULATION OF A QUESTION

Over the past three years, in the pharmaceutical industry there have been significant developments in terms of risk management. As an implementation measure related to the ICH Q9 guideline on quality risk management, the European Commission has reviewed the existing GMP provisions. With the revision of GMP quality risk management becomes an integral part of a manufacturer's quality assurance system. This concept will also be considered in a future revision of GMP It is well known that the Annex 20 is intended to create new philosophy and expectations for pharmaceutical industry, providing an inventory of internationally acknowledged risk management methods and tools together with a list of potential applications at the discretion of manufacturers. However, practical implementation of this new approach raises a lot of outstanding questions and opened issues.

## REVIEW OF PUBLICATIONS

GMPs regulate the pharmaceutical production since the 1960s, but they didn't consider assessing risk from the beginning. Thus, although in 1998 in the text of European GMPs the word «risk» appeared quite often (more then 70 times in 143 pages), it was just used in the sense of «the possibility of something bad happening», such as in the expression «risk of contamination». This edition contained 9 chapters of basic requirements and 14 annexes. As far as the US CFR 21 is concerned their parts 210 and 211 didn't include the term «risk» [1].

In 2001 a new annex on «Qualification and Validation» was added to the European GMPs [2]. Through its 11 pages the word «risk» appeared several times adding a new dimension, once as «risk assessment» and twice as «risk analysis». As one might suppose, in an annex devoted to validation risk was only considered in the following context:

(a) «A risk assessment approach should be used to determine the scope and extent of validation».
(b) Risk analysis was defined as a «Method to assess and characterise the critical parameters in the functionality of an equipment or process».

This was an important step forward. The pharmaceutical industry followed the example set by other industries and turned an empiric term used in everyday life into a new tool to ensure quality. Unfortunately, the importance of «risk assessment» was overshadowed by validation, as it appeared linked to it.

In 2005 the ICH approved a guideline devoted to «quality risk management» [3]. Risk was finally in the limelight as a «stand-alone» GMP element. This document became annex 20 to the European GMP in 2008. A further evolution was reached in the 2008 ICH document concerning a «pharmaceutical quality system» [4]. In this document «quality risk management» was recognized as an «enabler» (a tool or process which provides the means to achieve an objective), besides «knowledge management».

It is not by accident that «risk management» and «knowledge management» are the two enablers mentioned in guideline ICH Q10. As required by FDA in its initiative of GMPs for the 21st century, decisions should be based on sound scientific knowledge [5]. Thus, risk assessment is a way to deal with scientific knowledge and come to decisions supported by science.

## IDENTIFICATION OF PREVIOUSLY NOT ADDRESSED QUESTIONS

The introduction of validation in the pharmaceutical production was the result of a natural evolution. Whereas GMPs provided general orientation, the message of validation was «study, challenge and understand your process». The objective of validation was to make certain that processes were kept under control or, as it was put, «to ensure that they produce the expected results and keep operating in a valid manner».

Usually process validation is based on experimental studies. Yet it was clearly established that two essential questions remained opened. The first one was: «which tests had to be performed». The second one was: «how much testing were enough.» The validation process must not get misinterpreted, since every validation study is unique. This is why Annex 15 to European GMP proposed an approach for risk assessment to determine the scope and extent of validation.

In routine practice, and as it is well known, validation studies became a great issue. The discussion went mainly about the assays and less about their significance. Most often discussion went around the «how's» instead of the «why's».

As costs linked to validation grew, while results stagnated or even diminished, its prestige was damaged. This didn't help risk analysis much, which was seen as a part of the same lot.

## THE PURPOSE OF THE ARTICLE

Quality risk management approach arrived very late to the pharmaceutical industry and it confronts a lot of misunderstandings and inappropriate use of risk assessment tools in terms of validation. The main purpose of the article is to share practical experience and knowledge on quality risk management for validation studies.

## RESULTS OF RESEARCH AND DISCUSSION

Only when risk management was recognised as an enabler for quality systems it was liberated from its dependence of validation. Now, it came to be seen as a global tool to study any pharmaceutical activity from the point of view of quality.

The practical introduction of risk management was, however, hindered by an question: «if we focus on our products to be only of perfect quality without any further discussion, where should the risk be placed in our work?»

To clarify this let us refer to two related examples.

Firstly, our own lives have an absolute value for us, but in practice we take decisions regarding them in measurable terms. Although we fight for an unlimited value, we are bound to a world of materially limited solutions.

Secondly, pharmaceutical product sterility has an absolute signification too (absence of microorganisms), but in practical terms we are obliged to establish a measurable value (probability of presence of viable microorganisms lower than 10–6) to work with it.

### Validation downgrade

The acknowledgement of risk management as an essential tool for ensuring quality coincides with a loss of significance of validation. As a consequence of the prevailing theories about quality assurance in the 20th century it was considered that, if we could find a way to work efficiently by yielding a good product, the best system for ensuring its quality would be to work always exactly in the same way. In a simplified way, we could say that validation is the tool to show that a good way of working has been reached and then revalidation would be a tool for ensuring that process variations didn't affect its quality.

But new approaches, such as quality by design and real time release, can ensure quality batch by batch, without need for validation. The new paradigm is that validation significance is downgraded, because each batch is fully controlled in real time.

### Success can be tricky

Too much success can be dangerous. Curious as it may seem, in a moment of success, risk management might inherit many of the problems faced by validation, e. g. concentration more on means than on objectives, increasing costs for decreasing results, too much paper work, etc.

### The role of tools in risk assessment

Guideline ICH Q9, transferred as Annex 20 to European GMP, in addition to developing quality risk management describes method and tools for risk evaluation and analysis.

At the ICH website potential applications of risk management are also available for review. Sometimes it would seem that the key point in risk assessment is to decide which tool has to be chosen. Although some tools are better adapted for certain uses than others, what really matters and has to be kept in mind is that results are much more related to the level and quality of the information at disposal than to the tool used.

Tools for risk management are usually classified in two groups: (a) non specific or non formal and (b) specific or formal.

Any form of information on a process or subject (histograms, diagrams, charts, check-lists, etc.) can be used for risk assessment and in this sense

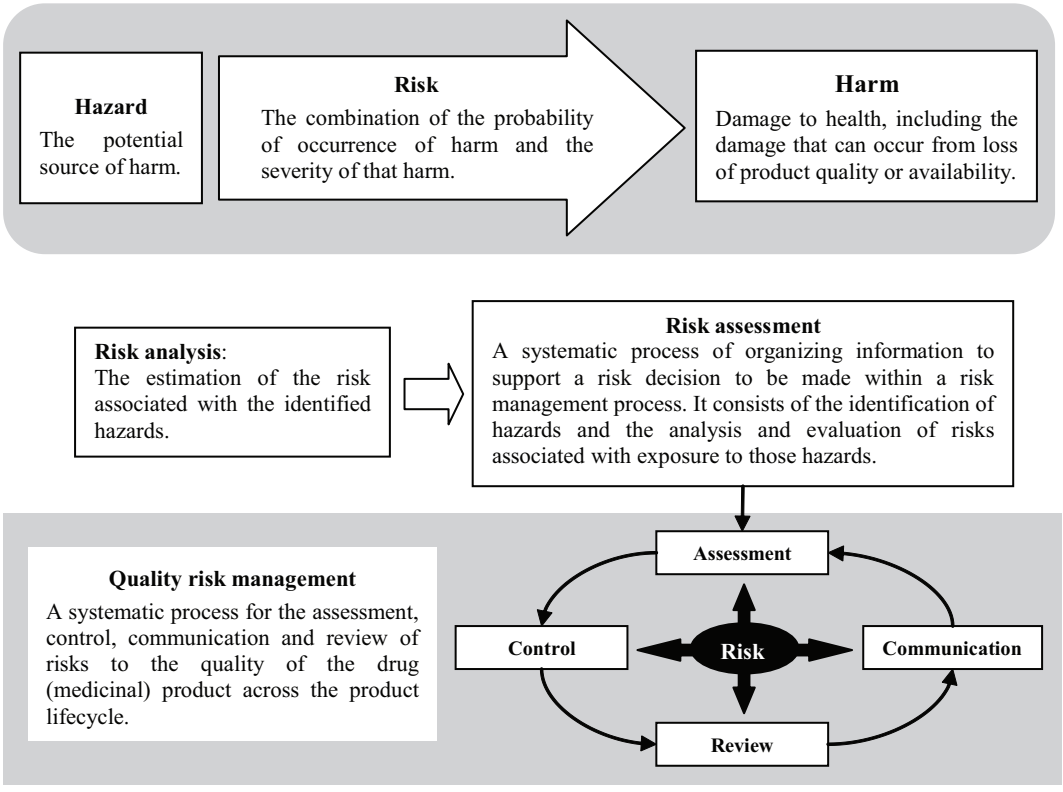



**Figure 1.** *Quality risk management concepts (Guideline ICH Q9)*

it is a tool, but it is non specific, because it wasn't devised for risk assessment and it lacks formality. If we want to use it for this purpose, we have to rework and reorder the information it contains.

Formal or specific risk assessment tools, on their side, are specifically devised to order and process information on the subject being studied and in this sense they may be considered complementary of the non formal or non specific tools.

Formal tools offer a whole palette of approaches to assess risk, in terms of:

- Outlook: Information can be organized and evaluated by means of tables, as it is the case in most methods. But there are also other ones, such as FTA, which uses a pictogram.
- Method of analysis: HAZOP provides us with «guidewords» to analyze the different possibilities of failure, while other methods rely on different forms of brainstorming.
- Process of analysis: Deductive methods, such as FMEA/FMECA, start by identifying failure modes and then its causes and effects, whereas inductive methods, e. g. FTA, try to determine the causes which have led to an event.
- Capacity to combine multiple causes: Most methods can only analyse the effects produced by a single cause, whereas a method like FTA can be used to understand how multiple factors can affect a question.
- Capacity of comparison: If we have to compare different items (units, processes, sites, etc.) with varied risks, then RRF is the right method. It is applied to reduce all items to a common denominator in order to compare them and establish priorities.

As any tool has its pros and cons and our objective is gaining knowledge to identify and estimate risk, all tools can be used and combined freely.

One might tend to think that the better, the more «sophisticated» a tool is, the more accurate the assessment results. This is the same kind of blunder that was made in the past when performing a validation and it was thought that just a sheer increase in the number of tests would lead to a better validation. Exactly as only testing related to the critical stages of the process increased the value of its validation, the value of a risk assessment depends on the amount of knowledge of the risk subject. Reduced or inaccurate knowledge cannot be compensated with any tool.

**Evaluation of the factors creating risk**

The decision on how to evaluate the factors involved in risk has often led to long discussions. This is just the consequence of attaching a great importance (value) to it. But this is also not 100 percent clear. Here also the appropriateness of the system is linked to the degree of knowledge. If you have

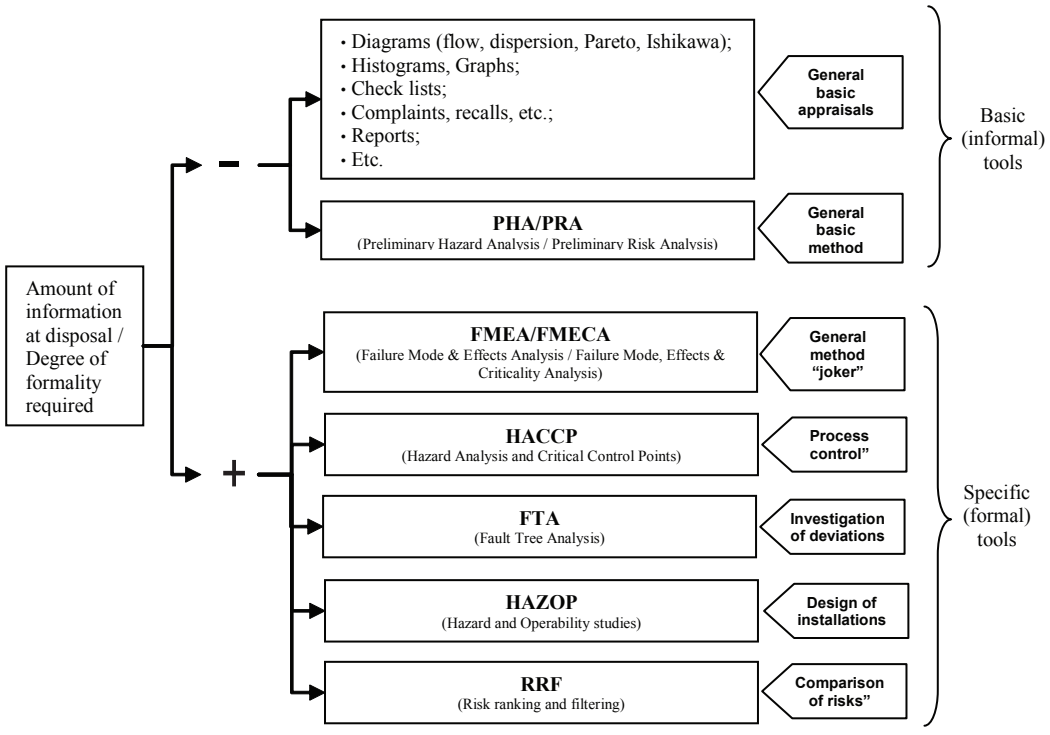



**Figure 2.** *Risk analysis tools*

a very limited amount of experience on the probability of a fact, no system will improve it. Therefore it can't be said that quantitative tools are better than qualitative. It is true that when we, for instance, estimate a risk in terms of probability and severity, the result might be different. And this usually depends on the competence of the risk analysis team. If we use a quantitative appraisal (1, 2, 3), the risk could be, say, 3 x 2 = 6, whereas if we use a qualitative assessment (low, medium, high), it would be high x medium = high or medium. A definite value, like 6, seems to cause a better response than a quite indefinite value, like high or medium, which might cause doubts. But it should be also considered that in the first case we might get a result showing a wrong degree of knowledge and accuracy, whereas the second case reflects the reality, with a limited amount of information and accuracy.

Any risk assessment should include information on the system of evaluation chosen, describing whether it is qualitative or quantitative and explaining the meaning of the different levels in use.

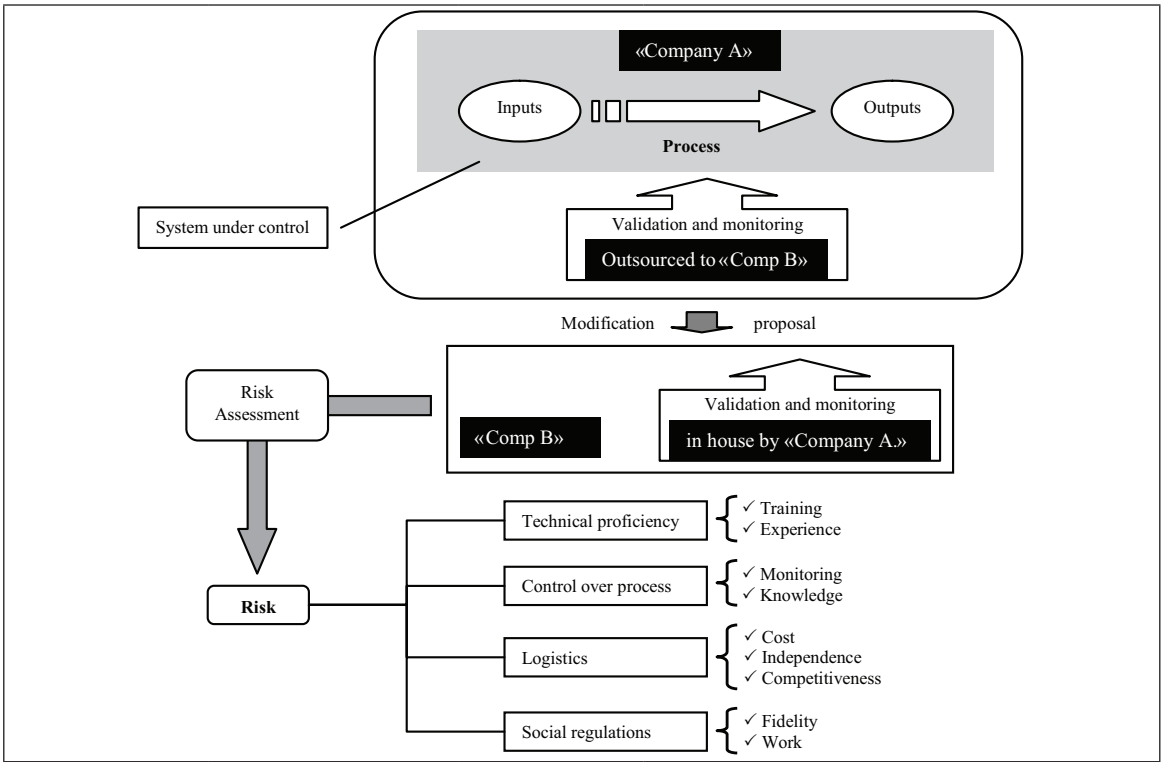
**What is really risk assessment?**

One might be tempted to answer this question by saying that it is the application of one of the methods described in the literature (e. g. in Guideline ICH Q9) to a given pharmaceutical process. But this would be a rather imprecise response, because it would refer to «how we did it» but not «what we did». A much better response could be something like «a profound study of a process in order to deeply understand how it works, what the synergy with other processes is and which its weaknesses are».

If processes are not well known, relevant and reliable information is not gathered and there is no communication among the different parts involved in the process, then risk assessment has a strong probability of becoming a hollow paper.

The managers must compare the existing and accepted level of risk with the new one appearing as a result of the modified situation. This might be performed by means of RRF [6]. In this method it is necessary to identify the components of risk. These components are the result of different factors. By evaluating the factors it is possible to get a global ranking of the risk in a given situation and compare it with other situations to establish priorities.

The factors can be evaluated in different ways. The outsourced validation activities were evaluated as example. In this case, taking into account the level of information at disposal, each one is classified in three levels in relation to its contribution to the global risk, from low to high. A column with comments is added to further clarify the rationale for the appraisal of the level of risk.




| Option A: Outsourced control | | | |
|---|---|---|---|
| **Components** | **Factors** | **Risk level (1=low/ 2=medium/ 3=high)** | **Comments** |
| Technical proficiency | Training | 1 | professional knowledge was well known |
| | Experience | 1 | Already cooperated with Company A since its foundation |
| Control over process | Monitoring | 1 | There hadn't been problems |
| | Knowledge | 3 | The true knowledge remained exclusively |
| Logistics | Cost | 1 | Costs are very reasonable |
| | Independence | 3 | Company kept the ultimate control |
| | Competitiveness | 1 | Company B was well known with excellent services |
| Social regulations | Fidelity | 1 | full fidelity required |
| | Work | 1 | work planed and conducted according timetable |
| | | 13 | |

| Option B: In-house control | | | |
|---|---|---|---|
| **Components** | **Factors** | **Risk level (1=low/ 2=medium/ 3=high)** | **Comments** |
| Technical proficiency | Training | 3 | Professional knowledge is very limited |
| | Experience | 3 | There hadn't been any practical experience |
| Control over process | Monitoring | 2 | There was limited experience of monitoring |
| | Knowledge | 1 | Process very well known |
| Logistics | Cost | 3 | Needs to invest in equipment |
| | Independence | 1 | acquire full independence |
| | Competitiveness | 1 | Very low competitiveness |
| Social regulations | Fidelity | 3 | New tasks may arise misunderstanding |
| | Work | 3 | Need more internal resources to work |
| | | 20 | |

**Figure 3.** *The RRF chart*

## CONCLUSIONS

Risk evaluation has been introduced only recently into the pharmaceutical sector. And although this experience is not yet extensive, some concerns might already be raised:

1. What really counts in risk assessment is not how you perform it but what you obtain. And this should be a complete oversight of the process and of the level of criticality of its steps.
2. The quality of a risk analysis depends much more on the amount of knowledge and information about the process which is studied than on the tool used. Risk management tools are just an aid to better study the facts that you already know.
3. In the article has been shown that you can always combine different tools, which might organize your data in different ways, to get a better overview.
4. The discussions about the evaluation of the risk factors (probability, severity and detection) have, often, little relevance, because the final quality will depend on the quality of the knowledge of the process as well.
5. A risk analysis is only useful if it allows managing a process better. If this is not the case it will probably be just more paper.
6. Risk assessment is just the first step to get to the complete and timely control of a process and in a controlled process each batch is concurrently validated. Then, a traditional prospective validation is losing its importance.
7. The success of risk assessment relies on the mastering of knowledge and this requires a multidisciplinary competent team and an adequate management of knowledge within the company.

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**УДК**

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**ВНЕДРЕНИЕ ПРАКТИЧЕСКИХ АСПЕКТОВ УПРАВЛЕНИЯ РИСКОМ В ФАРМАЦЕВТИЧЕСКОМ ПРОИЗВОДСТВЕ**

Проанализирован процесс внедрения концепции управления риском качества в сферу фармацевтического производства. Несмотря на актуальность применения этой концепции, практическое использование ее в фармацевтической промышленности пока еще недостаточно распространено. Показана целесообразность использования как формализованных, так и неформализованных инструментов управления риском для планирования и проведения работ по валидации. Проведено практическое исследование применения оценки рисков при проведении валидационных работ привлеченной компанией или внутренними силами компании, которая имеет малый опыт проведения таких работ. Сделанная количественная оценка рисков однозначно свидетельствует о целесообразности привлечения аутсорсинговой компании в описанном случае.

Сделан вывод о том, что оценка рисков является первым этапом для достижения постоянного контроля над управляемым процессом, в котором каждая производимая серия продукции подвергается, фактически, непрекращающейся сопутствующей валидации. Впервые сделан вывод о том, что, с точки зрения данного подхода, традиционная перспективная валидация в значительной степени теряет своё значение.

**Ключевые слова**: анализ риска; оценка риска; валидация

**УДК**

**В. Краукліс, Дж. Ботет**

**ВПРОВАДЖЕННЯ ПРАКТИЧНИХ АСПЕКТІВ УПРАВЛІННЯ РИЗИКОМ У ФАРМАЦЕВТИЧНОМУ ВИРОБНИЦТВІ**

Проаналізовано процес впровадження концепції управління ризиком якості у сферу фармацевтичного виробництва. Незважаючи на актуальність застосування цієї концепції, її практичне використання в фармацевтичній промисловості досі є недостатньо розповсюдженим. Показано доцільність використання як формалізованих, так і неформалізованих інструментів управління ризиком при плануванні та проведенні робіт з валідації. Проведено практичне дослідження використання оцінки ризиків при виконанні валідаційних робіт залученою компанією або власними внутрішніми силами компанії, яка не має досвіду проведення таких робіт. Виконана кількісна оцінка ризиків однозначно свідчить про доцільність залучення аутсорсингової компанії в описаному випадку.

Зроблено висновок про те, що оцінка ризиків є першим етапом для досягнення постійного контролю над керованим процесом, в якому кожна вироблена серія продукції підлягає, фактично, безперервній супутній валідації. Вперше зроблено висновок про те, що, з точки зору даного підходу, традиційна перспективна валідація здебільшого втрачає своє значення.

**Ключові слова:** аналіз ризику; оцінка ризику; валідація

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