Risk Management from the Point of View of a Competent Authority

Rudolf Völler

GMP Inspectorate,
Regierungspräsidium,
Darmstadt (Germany)

Summary

A working risk evaluation system is a key element of drug safety. This is valid for industry as well as for licensing and inspecting authorities.

Risk assessment is a legal obligation. The state of the art is discussed on international level and is laid down in GMP guidelines which have to be observed by all involved parties.

In German QA documents for competent authorities these principles were transferred into SOPs for inspectors.

Pharmacovigilance and pharmaceutical-technical procedures are subject to a risk assessment system. Indications and drug characteristics have an influence on potential risks of the particular measures. During the production process QA systems and periodic quality reviews ensure that each product and each process is assessed continuously.

Inspectorates are subjected to inspection planning and the conduction of inspections according to a risk assessment system. Failure evaluation and corrective actions are risk orientated.

Key words Failure evaluation · GMP conformity · Pharmacovigilance · Product characteristics · Risk factors · Validation

Risk is rated danger. With a functioning risk evaluation system in place, therefore, no dangerous medicines, but only safe medicines exist, for which the risk evaluation was accomplished competently.

Coherence

For the theme “risk” there are different views, which are all relevant, also for the responsible authority. As often in the GMP relevant area, the interests of industry and authorities focus on the same topics.

Indeed the different approach is interesting in risk evaluation: In the German drug law (AMG) the fundamental ideas are formulated, in the “Ordinance on manufacturing of medicinal products and active ingredients” (AMWHV) international criteria are made precise and obligatory for the pharmaceutical entre-

preneurs. In international and European committees the respective state of the science is negotiated and formulated. In the German QA documents for the competent authorities the principles are laid down and made obligatory for the inspections.

During production the Quality Assurance Systems of the manufacturer and the periodically conducted product quality review ensure that each product and each process are evaluated continuously. For medicines in general two elements are important: pharmacovigilance (unexpected reactions, side effects, efficacy etc.) and the pharmaceutical-technical aspects.

The first element is intensified in the drug law and by the activities of the licensing authorities, meanwhile also special “pharmacovigilance inspections” are conducted. The second element has several aspects: API characteristics, preparation and application forms, processes, persons etc. Finally the inspections, the evaluation of findings and measures have to function efficiently and effectively under the aspect of risk evaluation.

Legal norms

Rated and rejected risks during manufacturing of medicines are legal norm, analogous is mentioned within the German drug law: It is the purpose of the drug law to guarantee in the interest of a proper supply of drugs to humans and animals, security in respect of the trade in drugs, ensuring in particular the quality, efficacy and safety of drugs. ... In the drug law quality is addressed as the condition of a medicine, which is defined by its characteristics or by the manufacturing process.

Defined as a risk for the health of the patient or the public health connected with the application of a medicine is each risk in connection with quality, safety or efficacy of the medicine.

The state of the art has to be followed during production of medicinal products.

Principles

The discussion of risk evaluation in production is not a new topic. Even the basic principles of GMP include prospective planning of quality under consideration of the particularities of the medicines: One can not test quality into a product. The productions processes must be safe, valid test methods allow a reliable appraisal of the product.

Before start of the industrial production qualified persons are responsible for planning of all steps and measures on risk-based decisions, which has been called “validation” since the end of the past millennium.

Validation of the processes and methods means an evaluation of the implemented processes and methods on the basis of an appraisal of the risk analysis.

In the QA manual of the German Bundesländer (part of it is accessible on the homepage of the Zentralstelle der Länder für Gesundheitsschutz (ZLG), Bonn, *www.zlg.de*) is implemented the Aide Mémoire (AIM) 07121104 (Inspection of qualification and validation of pharmaceutical manufacturing and quality control).

In this document risk evaluation was demanded already in the first version of 1998 before starting validation. Details from the current version as examples:

4.2 Risk analysis (product, equipment, procedures)

Suitable methods are for example:

- *FMEA*
- *Fault Tree Analysis (FTA)*
- *Ishikawa method (Fishbone analysis)*
- *HACCP concept*

National and international activities

Of course the German activities were never a stand-alone activity in respect to risk evaluation.

The principles of GMP are defined in the European GMP guidelines.
Guidelines are agreed upon internationally and represent the current state of science. In these documents and the enclosed appendices demands are evaluated and formulated again and again after appraisals of systems and risks.

The German legislator has determined explicitly the obligation of application of the EC-GMP guideline and considers currently the name-giving process of the Ordinance on manufacturing of medicinal products (Betriebsverordnung für Pharmazeutische Unternehmer). This was renamed to "Ordinance on the application of the good manufacturing practice at the manufacture of medicines and active agents" and on the application of the good specialized practice at the manufacture of products of human origin (Arzneimittel- und Wirkstoffherstellungsverordnung, AMWHV). To utilize the state of science is therefore (now and again) legal duty.

Essential basis for the implementation of GMP quality the EC guideline and its appendices. In this context additional international activities are carried out with increasing normative meaning also by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Goals of the current ICH initiatives are especially: harmonization of change-management systems, the relief of continuous improvement processes, increase of the self-responsibility of the industry, saving costs for industry (economic balance), prevention instead of correction and, last but not least, harmonisation of regulatory activities of the legislation, licensing and inspections.

These worldwide ICH activities seize current topics and process them scientifically with experts from industry and authorities. International harmonization is extremely valuable. Wrong priorities cost as a rule much money, which will be missed in other risky areas.

The manufacturing and quality control reports are evaluated as part of the application procedures and underlie a risk evaluation. These documents and the compliance with them are also object of inspections and the appraisals of the findings.

Quotation from the ICH Q9 document vision: "A harmonized pharmaceutical quality system applicable across the life cycle of the product emphasing an integrated approach to risk management and science".

The ICH Q9 document supplies help for the documents I Q8 "Quality by design" and Q 10 "Quality management". Risk management is with it an essential internationally acknowledged controlling instrument for the manufacturing of drugs.

Risk Management Tools

Denis Nienhüser

RRR – Reduced Rest Risk, Belp (Switzerland)

Summary

The Q9 ICH Guideline demands a lot of in-house Risk Management. It presents different tools which help to fulfil these requirements. However none of the listed methods can be used universally. Therefore they must be adjusted in most cases. The following article helps to identify the advantages and disadvantages of the recommended methods.

Key words ICH-Q9 · Methods · Risk analysis · Risk assessment · Risk communication · Risk control · Risk management

1. Introduction

The Pharmaceutical Inspection Convention (PIC) as well as the medicine and/or medical laws require quality Risk Management for pharmaceutical and medicinal products. The general understanding of Risk Management is a system of risk analysis, risk assessment and risk reduction. The same requirements are made by various other management systems (ISO 9000 ff (QMS), ISO 14000 ff (EMS), working security, bio-safety etc.). The Q9 ICH Guideline Step 4 "Quality Risk Management" is the most detailed paper requiring the implementation of a Risk Management system [1].

The purpose of the ICH Q9 is to ensure that the responsible persons in a pharmaceutical or medical-technical business always work at improving the quality of products produced. Since with a final control of the products the use of inappropriate products often can not be sufficiently prevented, the ICH Q9 requires a risk-oriented examination of all quality-relevant processes of a business (annotation by author: and corresponds thus to the principle of voluntary QMS).

The ICH Q9 determines the components and process of a Risk Management system and offers a choice of tools. According to the information provided by the authorities however, the following complaints are frequently made:

- the tools are used in the wrong manner
- the wrong tools are used
- the organisation of Risk Management is incorrect.

The purpose of this overview is to demonstrate the advantages and disadvantages of some tools so that the right tools can be used in the correct manner.

2. List of tools

There are two categories of tools:

1) Fault tree methods

- FTA: Fault tree analysis
- ETA: Event tree analysis
- CEA: Cause-effect analysis
- CCA: Cause-consequence analysis
- CCFA: Common cause-failure analysis
- Markov analysis
- etc.

2) Fault matrix methods

- Risk map
- HACCP: Hazard analysis and critical control points
- FMEA: Failure mode and effect analysis
- FMECA: Failure mode, effects and criticality analysis
- HAZOP: Hazard and operability study
- PHA: Preliminary hazard analysis
- Kepner-Tregoe method
- DRBFM: Design review based on failure mode
- SHA: System hazard analysis
- HHA: Health hazard assessment
- ZHA: Zurich Hazard Analysis
- HIP-HOPS: Hierarchically performed hazard origin and propagation studies
- FHA: Functional hazard assessment
- etc.

Some methods are represented exemplarily in the appendix.

3. Requirements on Risk Management

A well-established manufacturing process constantly produces products of constant quality. Accordingly, these products have definitions with narrow ranges of specification. Primarily insufficiently developed or produced products can be recognised by the non-observance of these specification areas: in-process testing and analytical results.

Since the analytical results do not necessarily reflect the quality of a product, legislation demands more information on the manufacturing process.

Different laws require concept, system and process risk analysis:

- infrastructure (building, plants)
- manufacturing process (including raw materials, material and personnel flow)
- software
- changes in the manufacturing process (changes)
- deviations from the manufacturing process (deviations)
- analytical methods.

Hence, a tool for risk analysis must be capable of including all quality-relevant parameters of a product. This includes all of the relevant input parameters

(raw materials, solvents, water etc.), process parameters (physical and microbiological parameters, exact description of the technical equipment and premises used etc.) and output parameters (analytical procedures and results, sensor data etc.). The risk analysis must describe the risk, its causes and effects. This requirement is difficult to meet if there are complex interactions between several risk causes and risk effects. The description of the risk must be so detailed, comprehensible and understandable that the subsequent risk estimation and evaluation are also understandable. If non-acceptable risks are identified (e.g. regarding the effectiveness or quality of the product), they must be reduced or eliminated. In the case of non-acceptable risks, the documentation must contain planned measures for improvement, responsible persons, planned deadlines for the implementation of the measures and a re-evaluation (after implementation of the measures for improvement). Apart from the requirements, there may exist further, business internal requests that reduce the amount of possible tools:

- many different manufacturing steps
- many different products and/or development projects
- many changes in / optimisations of established manufacturing processes
- frequent deviations in the manufacture of products
- multi-purpose buildings and plants
- etc.

In general the following points should be taken into account:

- Why is Risk Management to be used?

In selecting the correct risk tools, it is important to decide whether the aim is a minimum solution that meets only the legal requirements or whether further possibilities in use are planned (e.g. for external sub-contractors, assistance in decision-making for internal project management, process knowledge to be recorded and improved etc.).

- Are there similar tools in the enterprise?

Some areas (e.g. safety at work, bio-safety, disaster service etc.) also work with risk analysis and risk evaluation. In these cases, it should be decided as to whether separate methods are to be used or whether it makes more sense to find a common tool.

4. Risk analysis

All of the methods referred to above have the principle of risk description in common: risks (also standing for mistakes or faults) are represented in connection with causes and effects. In order to understand the advantages and disadvantages of the tools, a simple general example is introduced:

The filling volume of a bulk product does not meet the requirements.

(Annotation: This example is used exemplarily in the text as well as in the appendix).

4.1 Fault tree methods

The fault tree methods (see: Annex 1 FTA and Annex 2 ETA) are used for the prospective (e.g. in the development of new manufacturing processes or for the purchase of equipment which needs to be replaced) as well as for the retrospective risk analyses. In simple manufacturing processes, the fault tree

Use of Risk Assessment Tables during Development Stage

Dr. Andrea Weiland-Waibel

Explicat Pharma GmbH, Hohenbrunn near Munich (Germany)

Summary

This paper addresses the importance of analysis of the critical pharmaceutical process parameters during development stage. Practical recommendations are given as to how to apply this approach to manage the pharmaceutical development process and utilize the data package. The approach is in line with the FDA initiative for the cGMP regulations for the 21st century as it is shown that in relation to PAT (Process Analytical Technology) justified process parameter ranges and specifications may be developed, that the development report may be made compliant for the CTD (Common Technical Document) and how further activities for the product/process can be assessed.

Key words cGMP for the 21st Century · Design space · Pharmaceutical development · Risk assessment tables

1. Introduction

As pharmaceutical manufacturing processes are highly complex, do consist of multiple process steps and are of significant variability, it is essential to identify the important parameters and critical process steps during the development of the process/product.

In order to support transfer activities, e.g. scale up from pharmaceutical development into pharmaceutical manufacturing (production batch size) and consecutive pharmaceutical process validation (respectively "conformance batches") or site change, such information should completely be communicated to the receiving organization to be able to establish a robust production process.

In this article a project is presented, where use of a risk analysis (assessment) method was made to systematically identify the critical process steps and parameters already during the course of the development of the product.

The "information package" obtained by applying this approach may be used for several purposes; for the establishment of the pharmaceutical development report (e.g. pharmaceutical development section in the CTD (Common Technical Document)) or it can be used as basis for process validation (respectively for the manufacture of conformance batches as outlined in the FDA process validation compliance Guide 7132c.08).

The project described in this article, respectively, the risk assessment approach taken and the subsequent activities could also be used in relation to the FDA initiative "Pharmaceutical cGMPs for the 21st Century". This initiative is more thoroughly described e.g. in the FDA White Paper "Innovation and Continuous Improvement in Pharmaceutical Manufacturing" and in the "Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Manufacturing, and Quality Assurance" (please refer to literature list).

Also to be taken into account in this context is ICH Q8 (Pharmaceutical Development). ICH Q8 outlines the relationship of Pharmaceutical Development, CTD, risk analysis approaches and PAT. Additionally the new ICH Q9 Risk Management Guideline is of interest.

The data obtained through the approach presented in this article could also potentially be used for a *"PAT (Process Analytical Technology) Regulatory Process"* as an aseptically produced lyophilisation process is a typical PAT example for reason explained further on in the text ("the goal of PAT is to understand and control the manufacturing process ... by design and development").

2. Risk analysis during pharmaceutical development – regulatory requirements

2.1 Europe

The "Note for Guidance on Development Pharmaceutics" and the "Note for Guidance on Process Validation" of the EMEA (European Medicines Evaluation Agency) do require to identify the critical process steps during pharmaceutical development, as these data should be used as basis for a systematically planned process validation.

In Annex 15 ("Qualification and Validation") of the EC GMP rules the execution of a risk assessment approach is required as preparation for validation activities (Fig. 1).

Note for Guidance on Development Pharmaceutics, July 1998

"Pharmaceutical development studies ... aim to identify those formulations and processing aspects that are ***crucial*** *for batch reproducibility ..."*

"... process development studies will lay down the ***basis*** *for the process optimisation and* ***validation requirements."***

Note for Guidance on Process Validation, September 2001

"... in terms of pharmaceutical process validation it is intended that the combination of the guidance provided in the Note for guidance on Development Pharmaceutics with this guidance should cover all the critical elements in a manufacturing process for a pharmaceutical product, from development of the process through to final validation at the production scale ... ***Information generated during the development stage should thus be used to identify and evaluate the critical pharmaceutical process parameters."***

Annex 15 "Qualification and Validation" GMP, September 2001

"A risk assessment approach should be used to determine the scope and extent of validation."

Fig. 1: Relationship between pharmaceutical development, process validation and risk analysis.

Principally the conduct and use of risk analysis, evaluation and assessment methods should be standard during pharmaceutical development as the ultimate goal is to systematically identify critical process parameters.

2.2 USA

One of the intentions of the FDA Initiative "cGMP for the 21st Century" is to change the current conception of process validation and pharmaceutical development. Currently within pharmaceutical industry process validation studies are usually performed by manufacture of three consecutive validation batches in production scale.

In 2004 the Compliance Policy Guide 7132c.08 (CPG) was revised and no longer requires a specific number of process validation runs. The validation is now seen as a life cycle approach where "conformance batches" are consistently produced.

In order to comply with this concept the data obtained during the pharmaceutical development should be significant in relation to critical process steps and parameters, and an improved process understanding is a prerequisite.

The FDA wants to support pharmaceutical innovation and process optimization activities.

In this context please refer to the FDA Guidance for Industry "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" of September 2004.

In this guidance new terms are defined, i.e. "Design Space", this means a range of process parameters, respectively, the specification limits, within which the product can be reproducibly be produced having the predefined quality.

The scientific justification of these ranges by relevant data can only be derived from systematically planned pharmaceutical development studies, i.e. by design of experiments (DoE) or risk analysis based approaches for studies (Fig. 2).

"PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" (September 2004)

"The scientific, risk-based framework outlined in this guidance, Process Analytical Technology or PAT, is intended to support innovation and efficiency in pharmaceutical development, manufacturing and quality assurance ... It is important to note that the term analytical *in PAT is viewed broadly to include* ***chemical, physical, microbiological, mathematical, and risk analysis*** *conducted in an integrated manner. The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system:* ***quality cannot be tested into products; it should be built-in or should be by design.*** *Consequently, the tools and principles described in this guidance should be used for gaining process understanding and* ***can also be used to meet the regulatory requirements for validating and controlling the manufacturing process."***

"Process is well understood, when:

- *all* ***critical*** *sources of variability are identified and explained,*
- *variability is* ***managed*** *by the process,*
- *product quality attributes can be accurately and reliably* ***predicted*** *over the* ***design space*** *established for materials used, process parameters, manufacturing, environmental, and other conditions,*
- *the ability to predict reflects a* ***high degree of process understanding."***

Fig. 2: FDA-PAT (Process Analytical Technology); risk analysis during pharmaceutical development.