Preparation and Escort of FDA Inspections

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Summary

Inspections by authorities are performed on a regular basis at pharmaceutical manufacturers to assess the GMP and regulatory compliance. Such inspections are not only performed by the local authority but also by authorities from foreign countries. Especially inspections by the US Food and Drug Administration (FDA) are of utmost importance for the companies concerned and will lead to a huge number of additional activities. But FDA inspections can be passed successfully, provided that they are prepared thoroughly. Besides the different types of inspections and their potential consequences, this article describes especially the preparation of inspections. Furthermore, the dos-and-don'ts during such inspections are explained and all employees should be trained in this. The advice given for the preparation as well as for the behaviour during the inspection is not only applicable for FDA inspections but for inspections by any authority.

Key words FDA · Inspections

1. Introduction

Every pharmaceutical manufacturer will be inspected regularly by the competent authority. It is their task to check if the drug products are manufactured according to the current regulations. The legal basis for such inspections is laid down in national laws. Usually the local authority is responsible to perform the inspections. But also the import of drug products from a foreign country might require an inspection by the authority of the importing country in the country of origin of the drug product.

When an inspection is announced, the enthusiasm of the pharmaceutical manufacturer usually is limited, as significant consequences might result from a negative outcome of the inspection. In case critical deficiencies become public, a loss of image as well as financial losses might result. Therefore, every company would prefer that no inspections are performed. However, the situation should also be looked at from a different point of view. Of course, every employee of a pharmaceutical company is deeply convinced of the quality of the products manufactured by "his" company. But at the same time he might become a patient who is dependent on a drug product produced by another company. But as he does not know anything about the quality of these prod-

ucts he might not trust in their quality. Fortunately, the manufacturer of these products is also subject to authority inspections to guarantee the quality of these products. Therefore, inspections in the "own" company should be accepted as well.

2. Aims of inspections

The most important aim of all authority inspections is the protection of the consumer. In general, two aspects are checked:

- **GMP conformity**

  The compliance with the GMP regulations is one focus of authority inspections. It depends on the authority, which regulations will serve as the basis for the inspection. Inspectors from the EU will check the compliance with the EU GMP guidelines (including the annexes) in the EU as well as in the non-EU countries.

  FDA investigators will follow the requirements of 21 CFR Part 210/211, 600, 808, 812 and 820. Other authorities will base their inspections on the GMP guidelines of the WHO or local regulations. Sometimes it can be important according to which regulations an inspection is performed, e.g. with respect to the different clean room class definitions and requirements in the US and in the EU.

- **Regulatory conformity**

  In this case it will be checked if the manufacture and testing of drug products is really performed as described in the approved regulatory documentation. Sometimes it might be a challenge for the manufacturer to guarantee this compliance. It might happen that procedures are changed for "optimization purposes" without information of the regulatory agency. Especially in multi-national companies clear procedures and responsibilities are required to ensure that changes will be communicated to the authorities. During the inspection it will turn out if appropriate procedures are really in place.

3. The authorities

In Germany the surveillance of drug products is the task of the local authorities. Inspections are an essential part of this task and they are described in § 64 of the German Drug Law (Arzneimittelgesetz, AMG).

Due to the increasing globalization of the pharmaceutical industry, the manufacturers are no longer only inspected by their local authority but also by authorities from foreign countries. An inspection performed by the US Food and Drug Administration (FDA) is a prerequisite for the approval and marketing of drug products in the US. The legal basis for such inspections is laid down in chapter 704 of the Food, Drug and Cosmetic Act. With regard to the size and the economic importance of the US market it is understandable that the announcement of an FDA inspection will create some nervousness in the affected company.

However, it should be pointed out clearly that "the FDA" does not exist. The statement "The FDA has required that ..." on the occasion of an inspection is not correct. It is only permissible to say that a certain investigator in a certain situation had this requirement. That does not necessarily mean that this is a general requirement of "the FDA". Investigators are human beings with per-

FDA Risk-based Approach for Validation

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Summary

The paper describes the classic risk assessment in the scope of the validation of computer systems with the different assessment methods and the use of the results to focus validation activities. This is the basis for the presentation of a new risk-based validation approach in line with the FDA initiative for the cGMP regulations for the 21st century.

Key words Computer system validation · Risk analysis · Validation

1. Introduction

Risk analysis is a proven tool to focus validation effort on the critical areas.

Criticial areas of high risk need to be identified and appropriate risk mitigation measures are to be taken. The regulatory authorities defined for example through Good Manufacturing Practices mitigation actions for certain key areas. Within your company you need to analyze your processes considering your products and their specifics and define corresponding mitigating measures.

Within this document we will focus on mitigating measures in the context of computer systems validation.

Risk analysis can be applied on multiple levels. As part of a new system implementation a risk analysis can be used to drive the necessary level of validation effort, as proposed by GAMP4, but also in general a risk analysis of the existing system landscape or even better of the overall process model including supporting system can yield valuable information for the management of the IT landscape and also the IT budget.

2. Classic risk analysis

2.1. Basics

2.1.1. Areas of risk

Depending on the purpose of the company and the corresponding focus area there are different areas to be reviewed during a risk analysis:

- Production safety
  - Process security
  - Protection against explosions

- Environment
  - Protection from air and water pollution
- Security
  - Physical access control
  - Logical access control within a system
  - Data security
- Quality
  - Product safety
  - Reproducibility
  - Traceability
- Risk for the patient
  - Efficacy and prevention of side effects
  - Labelling errors
- Compliance with legal requirements
  - Compliance with guidelines and regulations
- Business critical functions
  - Customer invoicing
  - Payments to vendors
  - Other requirements of internal audit

The last two can also be used to handle Sarbanes-Oxley (SOX) compliance requirements. The same approach described in this article for GMP compliance is also suitable for the control points analysis for SOX regulation 404.

These are just examples for the development of company specific criterias. To clarify all these risks are related to the operation of the system and not to the implementation project.

2.1.2. Areas of application

A risk analysis is required when a new process, product or system is implemented to analyse the risk resulting from this change and the corresponding mitigating actions. But a risk analysis should also be part of the change control process for existing processes, products and systems.

2.1.3. Risk assessment

There are two basic approaches for risk assessments:

1. Qualitative assessment: In this approach the risk is assessed to be either high, medium, or low using a qualitative argumentation only.
2. Quantitative methods: In this method the determination if high, medium or low risk is the same but done at the lowest level based on different criteria and risks. The consolidation of the results at the lowest level of the various risk areas is done through a mathematical calculation formula. The assessment at lowest level is transformed into a numeric value which is first multiplied with a factor and then added up. Using the multiplication factor certain focus areas can be set. For the overall total ranges are defined which result in the overall risk assessment of the analysed object.

   Setting the ranges is critical. Executing a few trail assessments is recommended to verify the relevance of the results and fine tune the model. The multiplication factor is set to one normally. Setting it to two increases the weight of the risk criteria within the risk assessment calculation.

Handling Out-of-Specification (OOS) Results in the Laboratory

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Summary

In October 2006, the FDA issued the final Guidance for Industry "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production". This paper presents a workflow for the investigation to be initiated in the laboratory following an OOS test result. The presented approach follows FDA's expectations, not to conduct a retesting regimen automatically after determining no laboratory errors occurred, but to start a full scale investigation of potential deviations outside the lab prior to any retesting. Initial OOS test results may be invalidated not only based on apparent laboratory errors, but also based on plausible evidence ("assignable cause") indicating a laboratory error. The OOS procedure in the laboratory has to be closely linked with the elements "CAPA" and "Deviation Management" of a companies' Quality System.

Key words Barr decision · CAPA · Deviation management · FDA · Laboratory investigation · Out of Specification (OOS) results · Quality Systems

1. Introduction

Since the often cited Barr-ruling (Wolin Judgement) of February 1993 pharmaceutical companies all around the world have implemented procedures and strategies on how to deal with results that do not comply with their predetermined specifications. Although more than 10 years have passed since that judgement, the investigation of OOS results is still a hot topic in FDA inspections. The incorrect handling and investigation of OOS results continues to be a frequent source of 483 citations and Warning Letters.

The Barr decision of 1993 [1], the FDA "Guide to the Inspection of Quality Control Laboratories" [2] published shortly thereafter, the Draft FDA Guidance for Industry "Investigating Out-of-Specification Test Results" [3] issued in 1998 and the final Guidance [4] of October 2006 described the following possible causes for the occurrence of OOS results:

- Laboratory errors (apparent laboratory error – non-apparent laboratory error)
- Non-compliant product due to non process related or operator error (single deviation)
- Non-compliant product due to process related or manufacturing process error

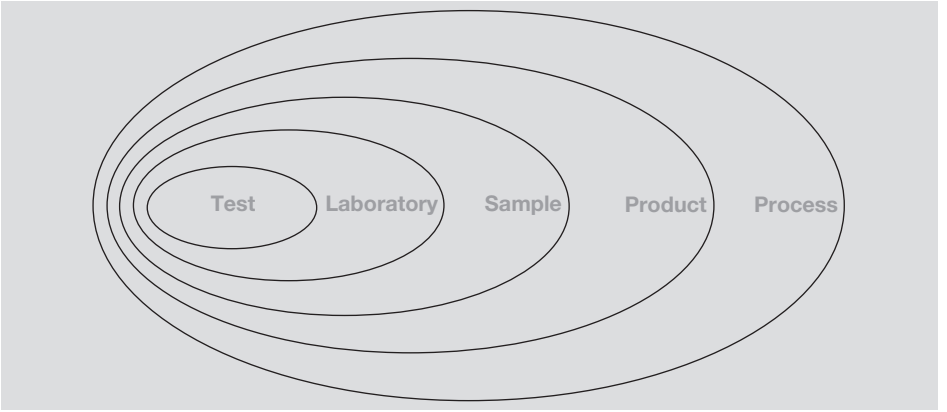

Fig. 1: Model of OOS investigation according to Häussler et al. [8].

This is a logical categorization, but it does not describe the order of the steps of an OOS investigation (failure investigation). The FDA draft Guidance did not provide a clear answer to this question, and the reviews on the topic [5, 6] also avoided any clear statement about the chronological order of the investigations in the laboratory and in production to be initiated.

Two German articles [7, 8] have aligned the steps of the investigation following this categorization. In a form of "containment", the investigation first focuses to the procedure and the testing laboratory to determine whether a laboratory error can clearly be identified, allowing invalidating the original OOS result. If this is not the case, one single retest is conducted. If this one retest does not confirm the initial OOS result, this is considered the proof of a non-apparent laboratory error and is therefore directly followed by an extended retest regime with an increased number of samples (usually six-fold). Only if this extended retesting regime fails should the investigation be taken out of the laboratory and extended to a full scale investigation covering sampling and the production process (Fig. 1).

"483"-letters issued during FDA inspections clearly showed that this sequence is not accepted by the agency, as documented by the following "483"-citation dating to 2003 [9].

> *"The Quality Control laboratory initiated retesting of XXX lot# 08P5402H, after experiencing an initial laboratory failure and determining no laboratory errors occurred. Retesting was conducted in accordance with OOS SOP BC1004, which fails to instruct to investigate manufacturing deviations before beginning retest analyses".*

Surprisingly, in contrast to the well-known position of the FDA, the PDA Science Advisory Board (SAB) OOS Committee's first draft of a planned technical report ["Out-of-Specification (OOS) Results: Clarification and Recommendations"] issued in September 2005 [10] again proposed a retesting regime to be started directly after the lab investigation did not identify a root cause for the OOS result in the lab – without starting a full scale investigation to clarify whether there is a root cause for the OOS result in manufacturing. This point has been criticized especially by the FDA in its comments to this draft:

> *"A firm relies on this assumption that their established and defined procedures are sufficient when passing results are obtained.* ***It is not consistent to assert, however, that this same set of pre-defined procedures is insufficient or somehow less reliable when it delivers an OOS result."***