

Deviation and Out of Specification Handling

APV Training Course
GMP Requirements
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Failure Investigations, Inspector's Expectations

Topics to be Covered

- **Legal background**
- **Expected Content of Deviation Report**
- **Where Companies Have Difficulty**
- **Example Citations**
- **Summary**
- **References**

Governing Authority, EU

- **Commission Directive 2003/94EC
(replaces 91/356/EEC)**
 - *“...All process deviations and product defects shall be documented and thoroughly investigated...”*
(Article 10, Production)

Governing Authority, EU

- **EC Guide to Good Manufacturing Practice, Chapter 5 (5.15)**
 - *“Any deviations from instructions or procedures should be **avoided** as far as possible. If a deviation occurs, it should be **approved in writing** by a competent person...”*

Governing Authority, US

- **21 CFR 211.192 and Multiple Other Provisions within 211**
 - *“Any unexplained **discrepancy**...shall be thoroughly **investigated**...The investigation shall extend to **other batches** ...that can have been associated with the specific failure or discrepancy. A **written record** of the investigation shall be made and shall include the conclusions and **follow-up**.”*

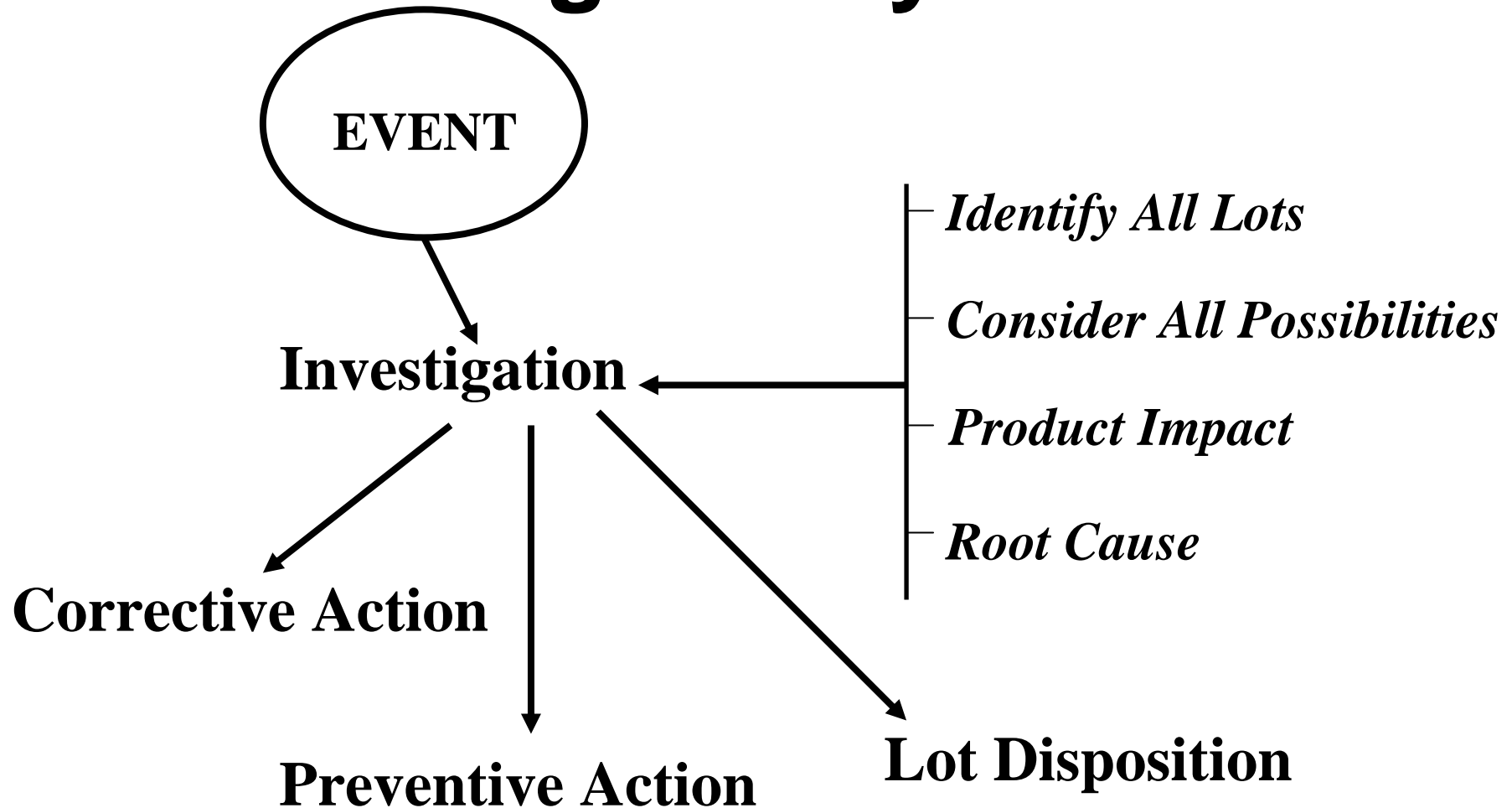
Governing Authority

- **ICHQ7A, GMPs for Active Pharmaceutical Ingredients**
 - *“Any deviation from established procedures should be **documented and explained**. Critical deviations should be **investigated**, and the investigation and its **conclusions** should be **documented**.”*
 - *“All deviation, investigation and OOS reports should be reviewed as **part of the batch record review** before the batch is released.”*

U.S. Legal Opinion

- **United States v Barr Laboratories, Inc. 1993 Described Requirements for Investigations**
 - *Specifies Content of Failure Report;*
 - *Requires Listing and Evaluation of Lots Potentially Affected;*
 - *Elements of “Thoroughness” Vary Depending on Nature and Impact of the Event;*
 - *Defines “Promptly” as 30 days from Event*

Linkage of Systems



Scope and Definition

- **Definition of Deviation**
 - *Departure from Written Instructions,*
 - *Unexpected Event,*
 - *Departure from cGMP;*
 - *Identify Exempted Incidents, Generally Documentation*
- **Multiple Systems Can be Problematic**
 - *Create Confusion and Difficult to Track*
- **Minimize “Notes” or “Comments”**
 - *Many Should be Deviations with Abbreviated Investigations*

Scope and Definition

- **Purpose of Investigations**
 - *Identify*
 - *Correct*
 - *Evaluate Product Impact / Disposition*
 - *Prevent Similar Events from Happening in the Future;*
- **The Deviation Event is the Initiating Feature of the CAPA Program**

Content of Investigation Report

- **Reason for the Investigation**
 - *What Event or Finding Prompted Investigation*
 - *How and When Identified*
 - *Remember to Consider Tracking / Trending Evaluation*
 - *Consider Related Activities, Think Global*
- **Describe What Happened**
 - *When*
 - *Where*
 - *What Immediate Actions Were Taken*

Content of Investigation Report

- **Identify Other Batches Potentially Affected**
 - *Justify Selection*
 - *Remember Distributed Lots*
- **Identify Root Cause, Where Possible**
 - *Why, Why, ... Why*
 - *Document Factors Considered*
 - *Ensure Data Support Conclusions*
 - *Avoid Conjecture*
 - *Often a Multi-Disciplinary Exercise*

Content of Investigation Report

- **Identify Corrective Actions**

- *Resist: Operator Error Corrected with Retraining*
- *May Include Additional Monitoring / Assessment*
- *Implementation Must be Timely*

- **Identify Preventive Actions**

- *Success Depends on Adequate Identification of Root Cause*
- *Interim Solution May Include Additional Monitoring*

Content of Investigation Report

- **Evaluate Product Impact / Disposition**
 - *Additional Testing / Results*
 - *Justify Accept / Reject Criteria*
 - *Justify if Differences in Lot Disposition*
 - *Remember to Consider Tox Evaluation*
- **Provide Follow-up to Assure Effectiveness**
 - *Does Preventive Action Provide a Durable Fix*
 - *What are Criteria for Durable Fix*

Where are the Deficiencies?

- **Lack of Documented Investigation**
- **Incomplete Investigation**
 - *Factors Not Considered / Documented*
 - *Associated Lots Not Identified / Evaluated*
 - *Root Cause Not Established or Justified*
 - *Conclusions Not Supported by Data*
- **Timelines Not Followed, Not Extended**
- **Corrective / Preventive Actions Not Implemented, Tracked or Completed**
 - *Effectiveness Not Verified*

“Operator Error” is Not Specific

- **Operator Action**

- *Inattention to Detail*
- *Verbal or Written Communication Problem*
- *Operator Monitoring Multiple Processes*

- **Operator Training:**

- *Not Trained on Procedure*
- *Not Trained on Current Version of Procedure*
- *Insufficient Practice or Experience*
- *Inadequate Content in Training*

“Operator Error”

- **Management System**

- *Inadequate Administrative Control*
- *Work Organization / Planning Deficiency*
- *Inadequate Supervision*
- *Improper Resource Allocation*
- *Information Not Adequately Defined, Disseminated or Enforced*

Equipment

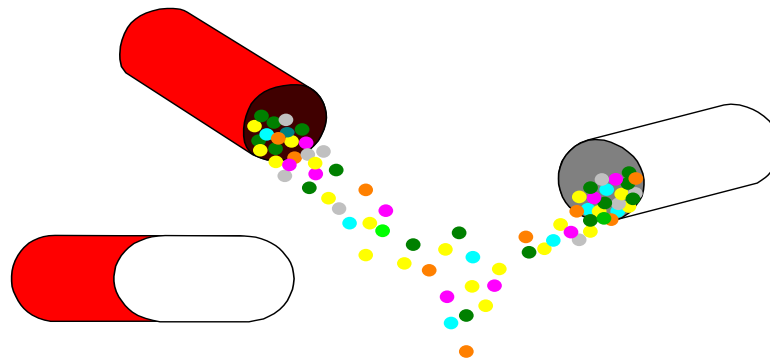
- **Equipment Failure**
 - *Calibration Not Current*
 - *Multiple Work Order(s) Addressing Same Issue Didn't Correct Problem*
 - *Preventive Maintenance Not Current*
 - *Out of Tolerance*
 - *Equipment Not Operated According to Validated Procedure*
 - *Defective Part*
 - *Improper Part*
 - *No IQ/OQ or Inadequate IQ/OQ*
 - *Electrical Power Failure or Surge*

Summary of Inspector Expectations

- **Implement and Follow an Adequate Procedure**
- **Perform and Document Thorough Investigations and Testing Commensurate with Event and Potential Impact**
- **Adhere to Time Limits**
- **Identify Other *Possibly* Affected Lots**
- **Evaluate Impact on Product**
- **Implement and Evaluate Corrective / Preventive Actions**
- **Quality Unit to Review and Approve Report and Disposition Product**

OOS-Results

Expectations of Monitoring Authorities



OOS-Results

Definition of OOS-Results

Importance of OOS-Results and drug legislation

Expectations of the monitoring authority

Content of an OOS SOP

Frequently asked questions

Surveillance of the release decision

Summary

OOS-Results Definition

Definition of “OOS-Result”

Test results, laying outside of the specifications, are OOS-Results.

Specifications cover a tolerance area with limits, in which the result to be determined should be.

These limits may be numerical without dimensions as well as numerical with dimensions.

Also terms like “complies”, “not more than”, “more or less colored than” or other terms from official test procedures are allowed limits.

OOS-Results

Specifications may be fixed in or may be diverted from:

- official **pharmacopoeia** (Ph. Eur., DAB, - any other national pharmacopoeia of an EC member state or those from third countries, e.g. USP)
- **registration files**
- old **registration documentation**
- **standard marketing authorization documentation**
- any other **product- or sample specific documentation**

OOS-Results: Scope 1

Scope 1

Investigations of "OOS-results" have to be done in cases of batch release testing and testing of excipients .

API, excipients



in-process control



?



final product



Is an investigation of IPC – OOS results really necessary?
Will those IPC data be transferred to batch release certificates?

If yes, IPC-testing has to be covered by OOS procedures.

OOS-Results: Scope 2

Scope 2

Are there other domains that require an investigation in case of OOS results?

- Stability studies on marketed batches of finished products and or active pharmaceutical ingredients, **ongoing / follow up stability** (no stress tests)
- Previous released batch used as reference sample in an OOS investigation showing OOS or suspect results
- Batches for clinical trails

OOS-investigation is necessary

Recall of the potentially defective product may be indicated

Example

Example: Reference sample with suspect results

Assay: 93,5 % Mixed sample of batch No. 015 (beginning, middle and of production)
 93,7 % first retest

OOS-investigation: no obvious laboratory failure
 no failure in sampling, sample transport and storage
 no conspicuous remarks in the batch protocol

2. Retest of batch No. 15, using **batch No. 14** as a reference sample with known content (**batch No. 014**, assay of batch release testing: **96,8 %**):

Results of the 2. retest:

batch 015:	97,4 %	→ in spec	
batch 014:	101,2 %	→ in spec	????

Obvious laboratory failure?

Batch release of batch No. 15? Further investigation necessary!

OOS-Results:Written procedures

What is expected by the inspectorate?

A QA-system with written procedures for e.g.:



Equipment: maintenance, calibration, documentation



Reference materials: CRS, in-house standards, ...



Sampling



Testing:

sample preparation
acceptance criteria

sample sequence

calculations



Trends



Release decision



...



OOS-Results

OOS-Results: SOP on Sampling



SOP on sampling

The amount of the sample taken should be sufficient for

- ⇒ the initial test sequence
- ⇒ investigation
- ⇒ confirmation of the OOS-results
- ⇒ retain sample

A lack of sample material is not a suitable reason for resampling during an OOS investigation

OOS-Results: Testing



Testing:

Sample preparation

one or more sample preparations per sample sequence

Sample sequence

number of standard preparations and injections

number of sample preparations and injections

quality control samples

Calculation of the result

definition of result, formula, average

Acceptance criteria for the sample sequence

OOS-Results:OOS-SOP 1

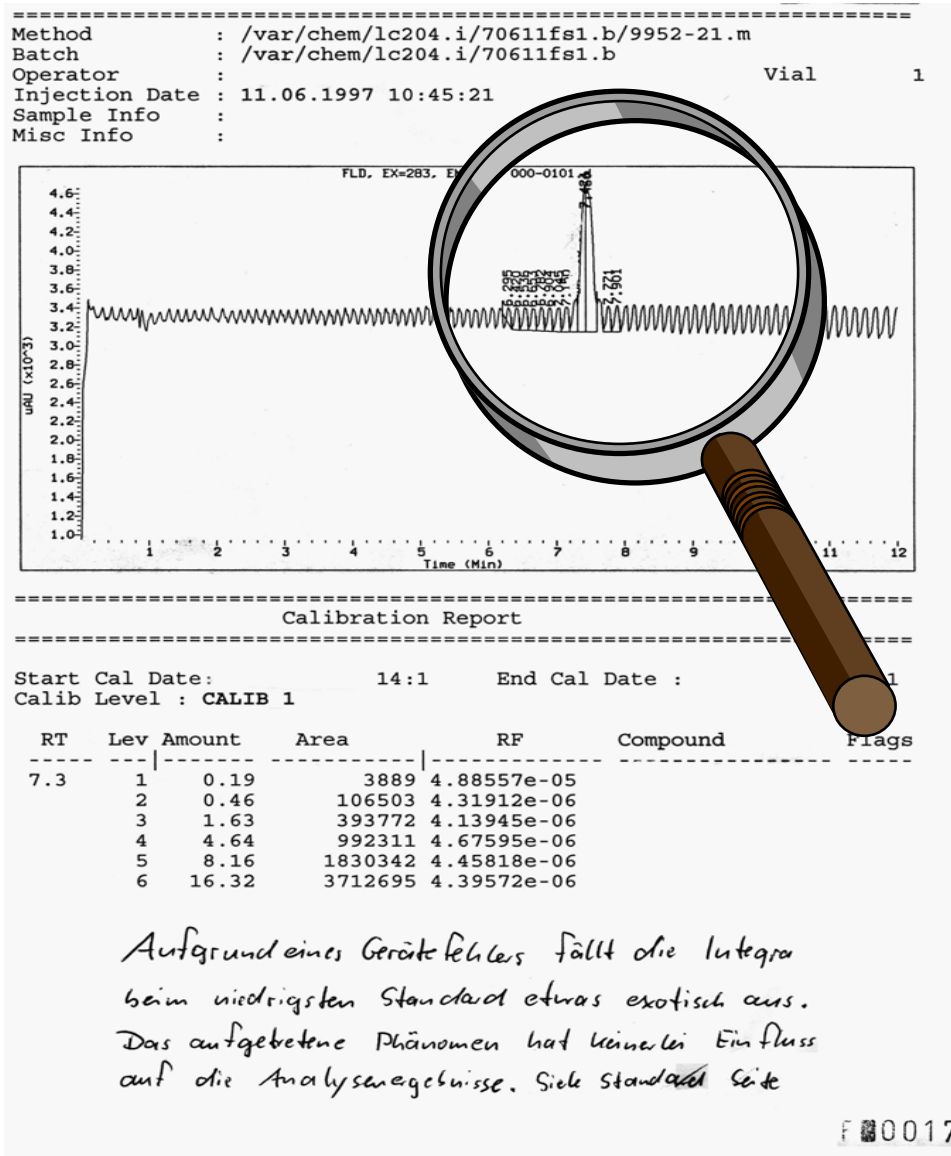
Content and possible structure of an OOS SOP

- ☰ Definitions

- ☰ Competent persons to identify an OOS result

- ☰ Investigation of reasons and conformation of OOS-results:
 - Laboratory level
 - ☞ Technician/analyst: checklist, obvious laboratory failure?
 - ☞ Head of laboratory: checklist, non obvious laboratory failure?

Raw data check



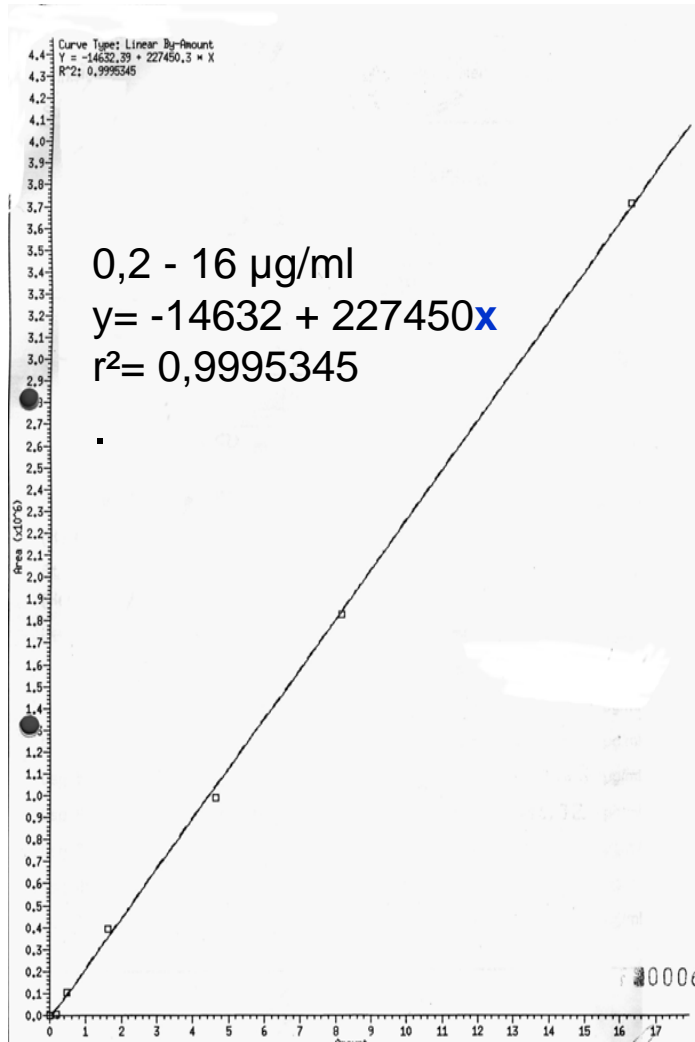
Written comment of the head of the laboratory:

“Due to an instrument error the integration with the lowest standard is a little bit exotic. The observed phenomena has no impact on the analytical results.”



OOS-Results: example

Raw data check



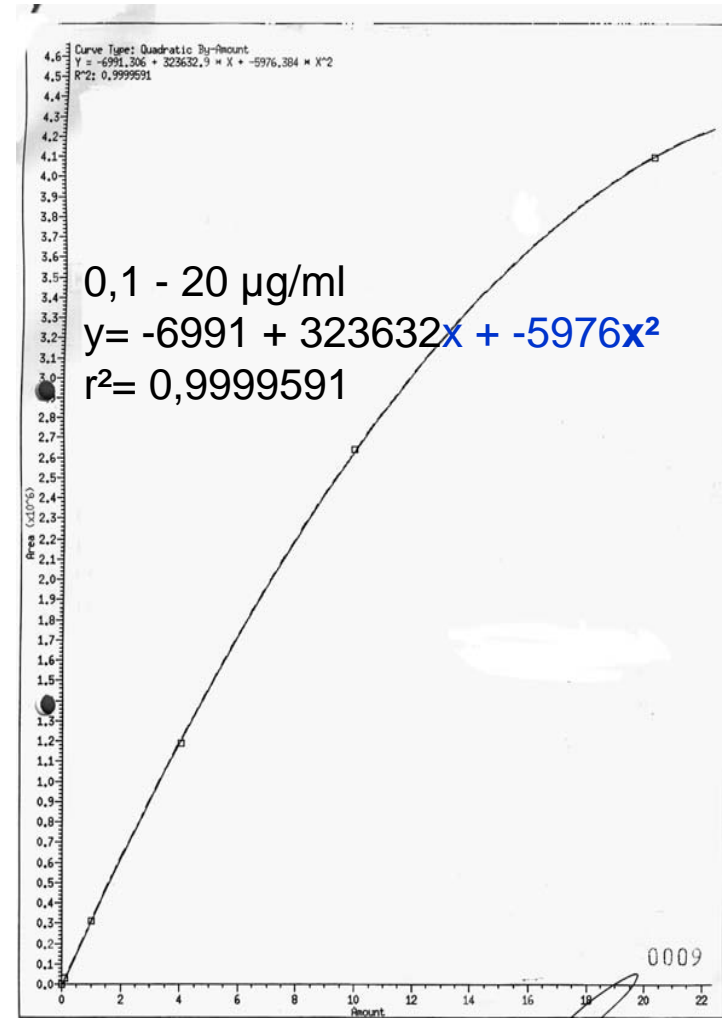
HPLC/DAD
calibration curves

day to day

identical standard
material and method

same concentration

no comments



OOS-Results: OOS-SOP 2



General proceedings for OOS investigations:

- ☞ Number of reanalysis (same sample preparation)
- ☞ Number of retests (new sample preparations)
- ☞ Prolonged sample sequence
- ☞ Inclusion of a reference sample?
- ☞ Statistic; average, out layers?

OOS-Results: OOS-SOP 3

- ☰ Level of failure investigation:
 - ☞ Laboratory internally
 - ☞ Sampling, sample transport and storage
 - ☞ Batch record review, production
 - ☞ Production process

- ☰ regulations for cooperation between all involved departments

OOS-Results: OOS-SOP 4

- ☰ Documentation of all OOS investigations and their reports
 - ☞ Evaluation of all OOS-results and investigations
 - ☞ Accumulation of OOS-results for some methods?
 - ☞ Accumulation of OOS-results for some products?
 - ☞ Accumulation of OOS-results for employees?

OOS-Results: OOS-SOP 5



Timetable for the investigation

☞ inside the laboratory

☞ sampling

☞ production

☞ report / decision

0 - 7

2 - 10

2 - 21

- 30 days

OOS-Results: OOS-SOP 6

- ☰ Report after the investigation with establishment for release, non release or other decision (e.g. reworking)
- ☰ Follow up?
- ☰ Change Control?
- ☰ “Flow chart / decision tree” with unequivocal decisions: release or quarantining

OOS-Results

Expectation of the monitoring authority

Quality control unit / qualified person of firm
“Mustermann”:

A sample for which an **OOS-result is confirmed**, will be complaint
and the corresponding batch of the

API,

excipient or

finished product

is **quarantined**.

OOS-Results:FAQ

Frequently asked questions

Are there specifications of a first and second level?

- Specifications of new registered products / older registrations
- Specifications of products with chemical APIs / herbal medicines
- Determination of physical parameter (pH, hardness) / HPLC-assay
- Safety relevant specifications / process-technical specifications

OOS-Results:FAQ

3AQ11a “Specifications and Control Tests on the Finished Product” 1

"The **aim of the application dossier** for a marketing authorization **is to set the quality level** of the medicinal product as intended for marketing. **It establishes specifications**, i.e. qualitative and quantitative characteristics, with **test procedures and acceptance limits**, with which the **medicinal product must comply** during its intended shelf life."

OOS-Results:FAQ

3AQ11a “Specifications and Control Tests on the Finished Product” 2

1.4.1

In the marketing authorization dossier, it must be shown that the manufacturing process used in compliance with GMP is capable of producing the **finished product consistently in compliance with the specifications chosen**;

1.4.2 Routine tests and periodic tests

Different types of tests may exist:

a) tests to be carried out **batch by batch** on the finished product ... or bulk

OOS-Results:FAQ

3AQ11a “Specifications and Control Tests on the Finished Product” 3

- b) tests ... on **intermediate products or in-process controls** will contribute a greater guarantee of finished product compliance than their performance on the finished product or on the bulk product;
- c) **periodic tests** ... (e.g. microbiological quality);
- d) tests whose performance on the finished product or possibly on the bulk product at manufacture can be **replaced by the verification of another highly dependent specification** (for example replacement of the **test for uniformity of mass with the test for uniformity of content**);

OOS-Results:FAQ

3AQ11a “Specifications and Control Tests on the Finished Product” 4

- e) tests which are **not carried out routinely** once the guarantees of compliance are furnished by the manufacturer; these specific cases are exceptional (e.g. identification of colorants);

- f) tests corresponding to **critical points** in the manufacturing process to be monitored particularly during the first “n” production batches and temporarily in the course of any substantial modification (for example changing the manufacturing site, materials, etc.). Subsequently, as a function of acquired experience and especially validation of the production process, their batch by batch performance can be omitted (e.g. residual solvents).

OOS-Results:FAQ

CPMP/QWP/155/96 – Note for Guidance on Development Pharmaceutics

"Properly conducted development studies should ensure that relevant release and shelf life specifications are applied in order that the desired characteristics of the product can consistently be met at release, and throughout shelf life."

OOS-Results:FAQ

Does the competent person has the liberty to interpret the given specifications?

Development ⇒ ⇒ ⇒ ⇒ **marketing** ⇒ ⇒ ⇒ ⇒ **in life phase**
authorization

OOS-Results: Release decision 1

Monitoring of the release decision

Regulation on pharmaceutical entrepreneurs (PharmBetrV), based on the German drug law

- § 6 (2) PharmBetrV: Testing ... has to be done in compliance with the specifications and limits established in the in the marketing authorization dossier.
- § 7 (2) PharmBetrV: Finished goods and excipients, not full filling the requirements have to be
 - labeled,
 - quarantined,
 - destroyed,
 - resend or
 - reworked

OOS-Results: Release decision 2

- During routine GMP-inspections the competent authority has to ensure, that the all legal requirement during production and release of a batch are met.
- Release of a batch, not full filling all specification, has to be complaint by the competent authority.
- "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval. (ICH-Topic Q 6 A Specifications) "
- It is not a task of the monitoring authority to evaluate the deviation from the approved specifications like a second-class licensing authority.

OOS-Results: Release decision 3

- The evaluation of the health risk is done in cooperation between monitoring and regulatory authority. Based on that evaluation the proper and indicated corrective action will be enforced by the monitoring authority.
 - OOS-result ... batch released medicinal product with **significantly reduced quality?** (§§ 8, 96 AMG, 1 year imprisonment).
 - OOS-result ... batch released **serious** medicinal product with **potential risk for the consumer health?** (§§ 5, 95 AMG, 3 Jahre)

OOS-Results:Summary

- Every OOS-result in case of release relevant specifications requires an investigation.
- The investigation has to follow a pre established investigation plan.
- The investigation has to be summarized in a report .
- The report is the basis for a release decision.
- All reports have to be documented and evaluated.
- If necessary and possible preventative/corrective action has to be taken.