Best Practice in the Quality Control Laboratory

What we can learn from Warning Letters and Audit Observations.

Content of this presentation

Best Practice – a huge commitment .....

Based on recently issued FDA Warning Letters as well as other audit findings current hot topics regarding GMP-compliance will be presented and discussed. Useful guidance will be provided in order to avoid similar situations in your company. The following topics

- OOS-Management / Deviation Management
- Method Validation / Method Verification
- Documentation
- Sampling and Sample Management
- Data Management (will be presented in a separate presentation) and
- Training (will be addressed in a work shop)

will be addressed in presentations and / or workshops.

Content of this presentation

It is a prerequisite, that you already have a basic understanding regarding those topics; therefore only some critical items will be addressed again. By doing this, the current thinking of the European Authorities and FDA regarding the GMP-Compliance will be elaborated.

Also, some „non-typical“ examples will be presented to show the full range of different GMP situations in different QC laboratories.

OOS-Management / Deviation Management

Since many years, observations regarding OOS-management and deviation management are very common in FDA WLs, 483s and audit reports. Why is this an issue in so many companies? Let‘s take a look into a recent example:

Critical Audit Finding; API Manufacturer; QC laboratory; documented during an vendor inspection.

„Several analytical sequences were executed for the same batch xyz (sample xyz) on HPLC 012. The analytical sequence 100 (run on 17 May 2016) was used for the product batch release. Two additional executed sequences 099 (run on 15 May 2016) and 098 (run on 12 May 2016) were found in the system Chromeleon related to the same batch and disregarded without any documented OOS investigation.“ Note: it was explained that the two disregarded sequences were due to a known possible product / column interference and SST issue which was fixed through additional conditioning.

What are the issues found in this observation?

1) An issue with a long time known problem with the injection system has not been addressed and solved.
2) The root cause of several SST-failures have not been adequately investigated and solved.
3) Possible „Testing into Compliance“
4) Missing QA involvement; therefore QA
    - Has no possibility to get an adequate Quality Oversight regarding failures or quality issues, which are looking minor at the first look.
    - Has no possibility to fulfill their main responsibilities, (e.g..: Evaluation of the deviation regarding its criticality)
    - Has no possibility to release a batch considering any event occurred during manufacturing and testing.

What are the main issues?

- The system to document OOS-results and deviations is unreliable (many companies a using a very broad definition of „deviation“ or „OOS“).

- Another very critical issue has not been further addressed during the audit. Do you recognize this problem?

The aborted tests have been executed on separate days before the test, which has been used for the determination of the batch result. The respective Batch Record has been issued by QA just once. Why have those aborted tests not been documented on the batch record in a timely manner?

What would have been the adequate way to manage those incidents?

1) Immediate QA information regarding the aborted tests. (injection issues or SST-failures should be reported to QA). In case those tests have not been used for evaluation of the result, those tests could be invalidated by QA and repeated after QA approval.
2) Documentation of the incident in the batch record (batch release!)
3) Since (hopefully) the method has been validated, the equipment qualified, respective SOPs have been available and the employee has been trained the injection issues and the SST failures should have been treated as a deviation.
4) Root Cause Investigation and CAPA
5) Training regarding Good Documentation Practice and eventually labor legislation related actions.
6) Review of previous lots

Execution of a RCI using check lists: Pros and Cons

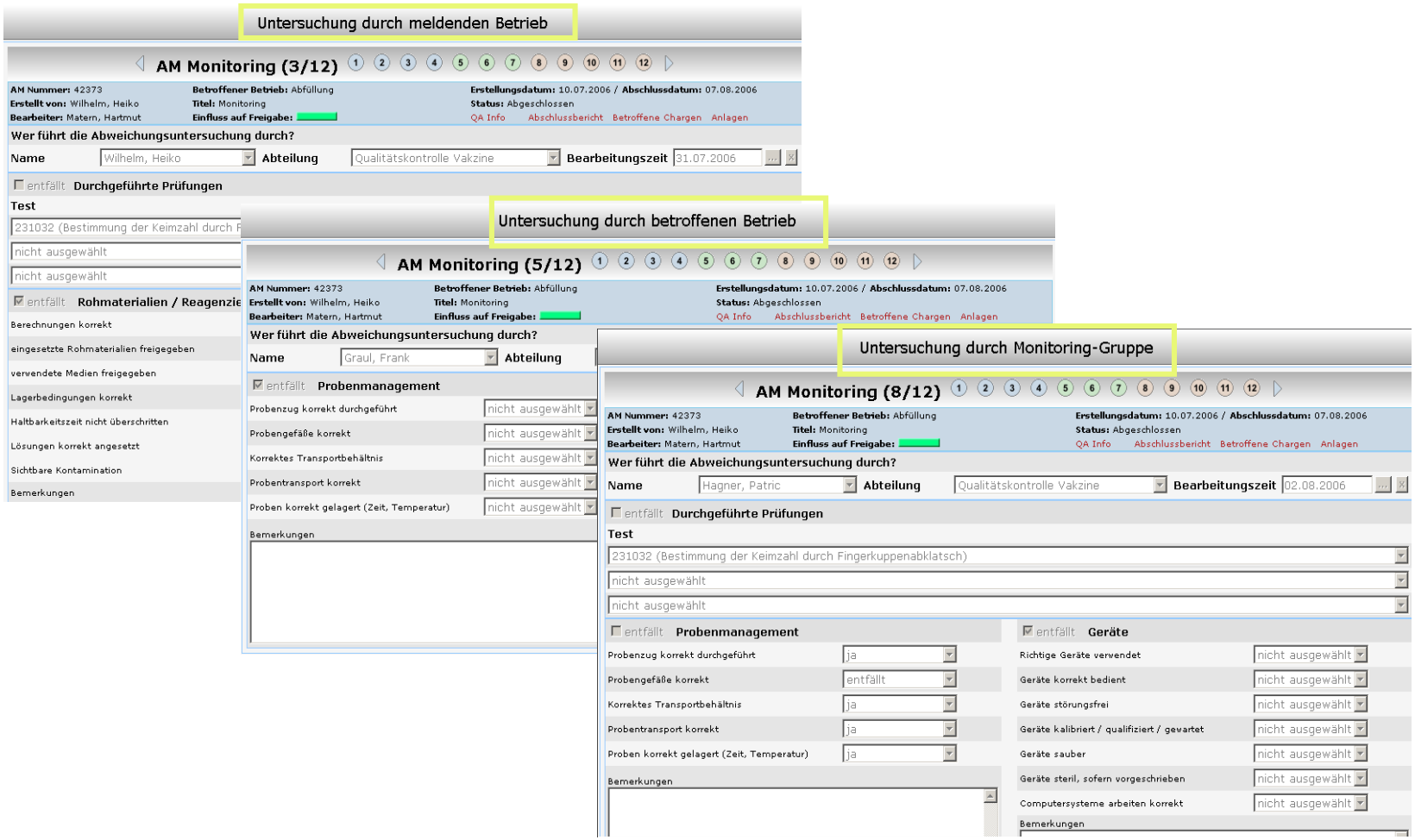
Advantages of using check lists:

- Systematic approach
- Complete
- Consistent
- Systematic improvement over the years

Disadvantages of using check lists:

- No more own thinking
- Big effort to implement check lists at the beginning

Execution of a RCI using electronic check lists: Example



Execution of a RCI using paper based check lists – Example:

Investigation of sampling:

No.:	Investigation:	Result:	
1	Sampling correctly executed?	Yes:	No:
2	Correct sample container used?	Yes:	No:
3	Correct transport container used?	Yes:	No:
4	Sample transport correctly done?	Yes:	No:
5	Correct sample storage (time / temperature)	Yes:	No:
6	Comments:		

Warning Letter; February 2017; pharmaceutical company

Failure to adequately investigate out-of-specification results.

Your firm did not initiate investigations into failing results as required by your standard operating procedure (SOP) ZL/SOP/ZK/00405. On October 5, 2015, when you encountered an OOS value for an unknown impurity peak through HPLC testing of (b)(4) API 12-month stability batch (b)(4), you prepared and tested new aliquots. You did not investigate the failing result.

What is the issue?

1) The OOS has been realized during a stability study. Since the product might be already on the market, a patient risk could not be excluded.
2) Critical disrespect of GMP regulations regarding the management of deviations and OOS results.

What would be the recommended action by the company?

1) Immediate documentation of the OOS including an involvement of QA and pharmacovigilance.
2) Eventually notification to the authorities, recall
3) etc

It is obvious, that this event has bee a very critical violation of current cGMP regulation's. How would you rate the following situation:

A monoclonal antibody currently used in a Phase III study has been tested during a parallel stability study. An unknown peak (about 1%) has been found. The specification for total degradation products has been defined as 5%. There was no specification for unknown products.

The Phase III study has been continued with this material without notification to authorities.

OOS-Management / Deviation Management

General recommended procedure to manage OOS results:

1) Immediate documentation of the OOS and QA notification within one working day
2) Laboratory investigation Phase I and Phase II in parallel; eventually hypothesis testing
3) Initial classification of the OOS by QA; further actions if necessary (recall)
4) Development of an investigation plan and starting a root cause analysis in parallel!!! In QC, production and sampling; further testing for the purpose of root cause investigation only (not for release!)
5) Evaluation of the result of the RCA by QA
6) Retesting in case no root cause could be found; initiation by QA
7) Final evaluation and lot disposition by QA

„Personnel Error“ – another issue related to the deviation management

Does it make sense to rate the result of a RCA as „Personnel Error“? Can you name an example?

In most cases the „human error“ is only the symptom of another, maybe more covered issue. High risk organizations< do not allow any human errors. The underlying reason of a „human error“ can be found / investigated by failure tree analysis (5-whys).

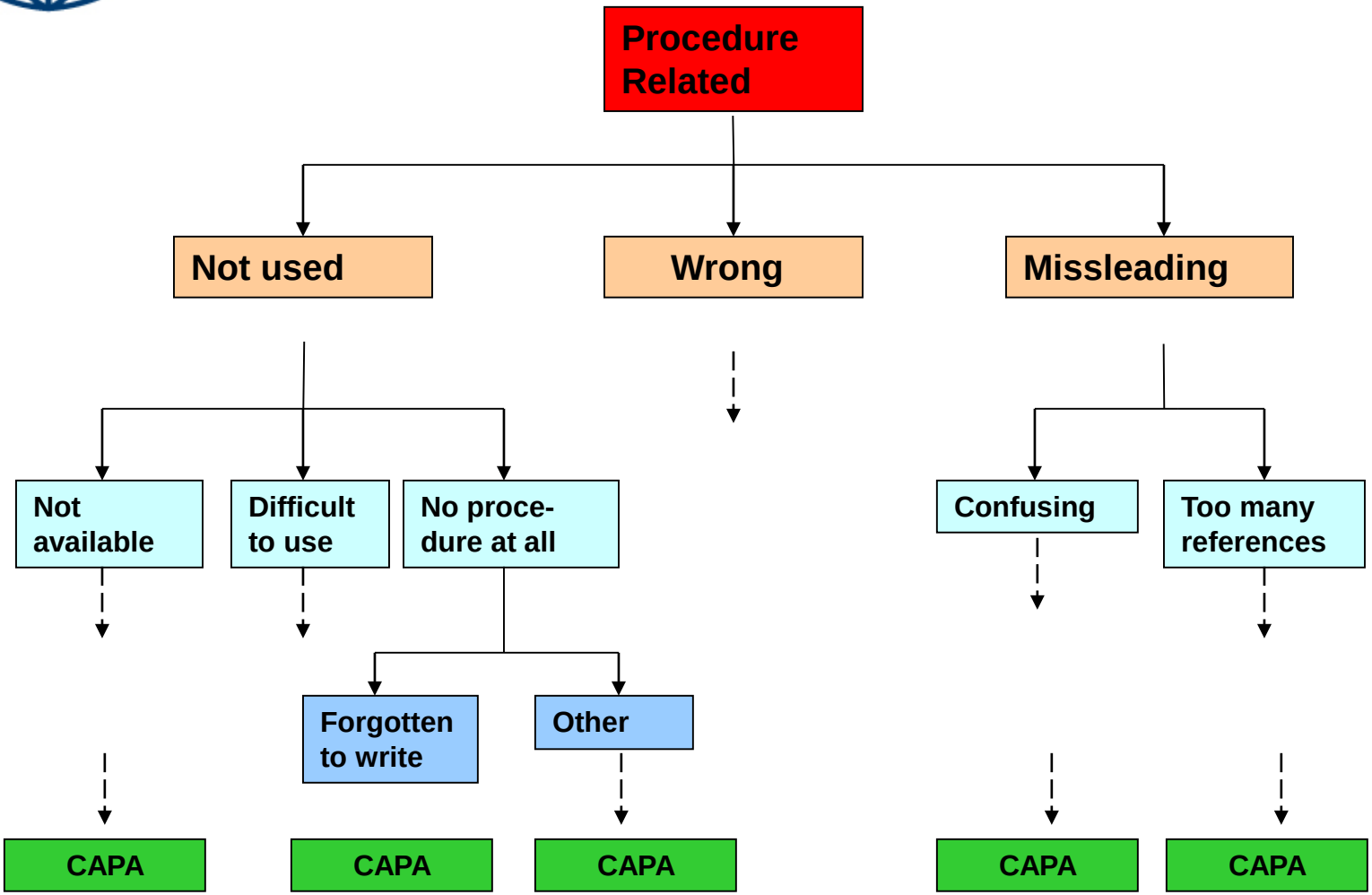
The Novartis company had initiated a few years ago an extensive program to abolish „personal errors“. The company has tried to predict “human errors“. The following human-related system failures have been identified:

The high-level system issue category can be further investigated by the 5-why-analysis before an issue will happen and respective CAPAs can be initiated. This leads to a significant time saving during the root cause investigation.

Human Error

- **1. Procedure related error**
- **2. Human factors engineering related error**
- **3. Training related error**
- **4. Supervision related error**
- **5. Communication related error**
- **6. Individual error/ Personnel performance**

OOS-Management / Deviation Management



And finally: The 5 myths related to deviation / OOS-management:

- Myth 1: There is exactly one root cause
- Myth 2: All deviations can be treated the same
- Myth 3: We have 30 days to manage the deviation
- Myth 4: KPIs, which encourage personal to reduce the number of deviations, make sense (for example # of deviations per department or site per year)
- Myth 5: Deviations can be investigated and solved from the writing desk

Warning Letter; MArch 2017; Drug manufacturer

Failure to verify the suitability of analytical methods.

You failed to ensure that the methods used by your contract testing laboratory, (b)(4), have been verified as suitable for their intended use. It is your responsibility to use a qualified contract testing laboratory that produces accurate and reliable results.

Your firm contracts with (b)(4) for release testing. Your quality assurance agreement with (b)(4) does not specify method validation responsibilities. During the inspection, our investigators requested the method verifications for the residual solvent, impurity, and microbiological tests performed by (b)(4). You stated that the requested documents were located at (b)(4) and that you would retrieve them within 15 days.

What would be the recommended action by the company?

1) When the method has been developed by the drug manufacturer, the methiod should have been formally transferred to the external laboratory
2) Formal qualification of the service provider including an audit ant the verification of the correct execution oif the test
3) Audit of test validation, approval of method validation protocoll and respective report
4) Quality Agreement which defines the correct testing method
5) Batch Record Review: At the beginning, the respective laboratory records should be reviewed by QA

Also Data Integrity aspects are questionable in this example: For example the access to any necessary data.

Warning Letter March 2017; API Manufacturer

Failure of your quality unit to prepare, review, and approve documents related to the manufacturing of API.

On August 16, 2016, our investigators found a large number of trash bags behind a building on your property. The trash bags contained torn original laboratory and production records, such as analytical test reports, (b)(4) water testing reports, and sample notebooks. The information on these discarded, torn documents did not match the official records. Your quality unit did not investigate these discrepancies. On August 18, 2016, when our investigators revisited the area where the trash bags had been, they found that the documents had been removed from the site. These findings indicate that your quality unit is not exercising its responsibilities.

Warning Letter February 2017 (Pharma) and May 2017 (API Manufacturer)

Failure to control the issuance, revision, superseding, and withdrawal of all documents by maintaining revision histories.

Your quality assurance unit provides analysts with blank controlled document forms that have already been approved and signed. Investigators observed torn, partially complete QA-signed calibration records in the trash and observed QA staff shredding documents without recording the identity or the reason for shredding the documents.

Failure to prepare adequate batch production records and record the activities at the time they are performed.

For example, our investigator found that your operator used process parameter values from previous batches of (b)(4) to complete new batch records when she was too tired to immediately record the data and had forgotten the values.

Documentation

What is the issue? What is the current situation in many companies?

It is obvious, that severe documentation (and data integrity) issues have been observed.

However, in many companies there are no clear advices regarding the following documentation aspects:

- Who finally approves documents for use
- What is the difference between acceptance / release / approval
- What exactly is included in the review of documents? (technical review vs. compliance review)

Observations regarding documentation are always related to data integrity.

Documentation – Some hints for inspections

In general, no GMP relevant documents are allowed to be destroyed. Only documents exceeding their pre-defined shelf live might be allowed to be discarded. Those documents have to be destroyed in a controlled manned (external service provider) according to a written procedure.

In order to avoid such kind of observations, it is recommended to clear all paper and electronical baskets up-front of an inspection. This might be helpful to avoid such kid of observations and related discussions.

Warning Letter April 2017 (Drug Manufacturer)

Failure to establish a sampling plan based on scientifically-sound sampling practices.

Our investigator documented deficiencies in your validation sampling plan for **(b)(4)** API. You did not conduct adequate monitoring and testing during process performance qualification stage to evaluate whether product quality was uniform throughout each batch. You only assessed water content at the drying step for homogeneity.

In your response, you acknowledged that a higher level of sampling during the revalidation of the manufacturing process revealed some inter-batch variability in residual solvents and particle size distribution of **(b)(4)**.

Your response is inadequate because it did not describe how your continued process verification program assures that quality attributes continue to be met batch-to-batch, as well as uniformly throughout each batch. Regarding uniformity, using only **(b)(4)** samples for attributes that may significantly vary within a batch is insufficient to ensure that your process remains in an ongoing state of control.

What are the GMP issues in that example?

- The number of samples taken during the process validation does not support the control of the quality of the process to assure adequate quality of the product.
- During the validation, strict control of the process is mandatory.
- The number of samples taken does not support the realization the deficiencies of the process. To realize those process deficiencies is necessary in order to define the respective worst case scenario and the frequency of sampling and sampling time for the process used during routine manufacturing.
- Missing risk evaluation regarding the already manufactured and planned lots; eventually immediate extension of the release testing. Definition how to handle fluctuations regarding the product quality.

What would have been adequate measures?

- Process related risk analysis
- Based on the results of the risk analysis mall-meshed sampling
- Take into consideration the range of the process parameters
- Eventually controlled reduction of the sampling during the routine production as further process knowledge is available
- Assessment of already available results and released lots

Any questions?
Thank you for your attention!