

# Compliance to Good Laboratory Practice; OOS results

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## **“Getting prepared for FDA or PIC inspections”**

APV/IKEV Seminar on Good Manufacturing Practice: Compliance and Inspection, Istanbul, June 10/11, 2004

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# Laboratory GMP: Regulatory Guidelines

## EEC Guide to Good Manufacturing Practice for medicinal products

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  - 6.5 – 6.6 Good Quality Control Laboratory Practice
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## 21 CFR 210/211 (cGMP for finished pharmaceuticals)

- **Subpart I Laboratory Controls**
  - § 211.165 Testing and release for distribution
  - § 211.166 Stability testing
  - § 211.167 Special testing requirements
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# EEC GMP Guide

## Chapter 6: “Quality control”

- General (6.2)
- Good quality control laboratory practice (6.5, 6.6)
- Documentation (6.7 – 6.10)
- Sampling (6.11 – 6.13)
- Testing (6.15 – 6.22)

## Also see:

- Chapter 2, Personnel
- Chapter 3, Premises and equipment (quality control areas)
- Chapter 4, Documentation  
“sampling” and “testing”  
} are not mentioned in other chapters

## Personnel (chapter 2)

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- General
  - adequate number
  - necessary qualification
  - practical experience
  - organisation chart
  - job descriptions
- Key personnel (besides “head of production”)
  - head of quality control
- Training
- Personnel hygiene

# Premises and equipment (chapter 3)

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- 3.26 – 3.29 Quality control areas
  - 3.26 Quality control laboratories should be separated from production areas
  - 3.27 Mix-ups and cross-contamination are to be avoided (also see chapters 5.18 – 5.20 and 5.44)
  - 3.28 Sensitive instruments are to be protected from vibration, electrical interference, humidity, etc.
  - 3.29 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples

# Documentation (chapters 4 and 6)

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- Chapter 4
  - **Specifications**
  - Manufacturing formulae
  - Processing and packaging instructions
  - **Procedures**
  - **Records**
  - **Sampling**
  - **Testing**
- Chapter 6
  - **Specifications**
  - **Sampling**
  - **Records**
  - Certificate of analysis
  - Monitoring data (reports)
  - Validation records (testing methods)
  - **Procedures**
  - **Testing**

## Testing (chapter 6)

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Chapters 6.15 – 6.22 deal with the testing and documentation of quality control results

### Points to consider:

- In-process-control (IPC; 6.18): The EEC GMP Guide leaves the responsibility for IPC open:
  - production or
  - quality control personnel ?

It is only mentioned that the IPC procedure has to be approved by QC.

**In general it is agreed that – if the procedure(s) for IPC does/do not bear a risk for the manufactured drugs – the IPC may be performed by production personnel.**



# Conclusions

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In several sections of Chapter 6 of the EEC GMP Guide reference is made to earlier chapters.

It can therefore be concluded that testing of pharmaceuticals is to be performed with the same level of safety as in production; e.g. EEC GMP Guide Annex 1.3 and Chapter 2.6.1, test for sterility, in the European Pharmacopoeia:

- Annex 1.3. requires a “class A” production area in a “class B” environment for aseptically manufactured drugs.
- the European Pharmacopoeia requires that a “test for sterility” be performed in a “class A” LAF that is located in a “class B” environment (or use of an isolator).

# OOS Results

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A result is considered OOS when – if generated according to the valid testing procedure – it does not comply with the requirements given in the specification(s).

# Definitions

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1. Re-testing: Retesting of a portion of the original sample.
2. Re-analysing: A new mixture from the original sample is prepared.
3. Re-sampling: While re-testing refers to analysis of the original sample, re-sampling involves analysing a specimen from the collection of a new sample from the batch.
4. Reference sample: Sample from a batch which is known to deliver unobjectionable results.

## “Failure investigations I and II”

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- Failure investigation I: refers to the test/laboratory environment
- Failure investigation II: refers to sampling/production/processing

# Draft FDA Guideline (1998): OOS Results

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Failure investigation I, laboratory environment:

1. Re-testing the original sample
2. Re-analysing the original sample. The re-analysis must be described in the relevant SOP.

## Evaluation of laboratory faults (1/3): Responsibility of the analyst

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- The analyst is responsible for:
  - only using calibrated equipment
  - only using equipment which meets the requirements of the “system suitability test”
  - informing the supervisor as soon as an OOS result has been generated which cannot be blamed directly on a laboratory error, before further tests are carried out

## Evaluation of laboratory faults (2/3): Responsibility of the supervisor

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The supervisor must check and evaluate the available data within the scope of “failure investigation I” before further tests are carried out. As a rule, the evaluation includes the following steps (besides systematic testing of the analytical procedure, including inspection of the test run and sample preparation):

1. equipment calibration
2. review of equipment parameters
3. “system suitability test”
4. review of laboratory reagents
5. review of standards used
6. sample preparation
7. calculations

## Evaluation of laboratory faults (3/3): Responsibility of the supervisor (cont'd)

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Depending on the results of “failure investigation I” and of a possible subsequent test, it is incumbent on the supervisor to decide whether:

1. a laboratory error has occurred
2. a laboratory error can generally be ruled out or
3. if the problem lies outside the laboratory environment (-> failure investigation II)



## Procedure in the event of an apparent laboratory error

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When the OOS result can be attributed to an apparent laboratory error, re-testing takes place.

Keep in mind: OOS results should not always be blamed on (a) laboratory/staff error(s)

## Procedure in the event of a non-apparent laboratory error

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If the OOS result cannot be attributed to an apparent laboratory error, a subsequent re-analysis is carried out before “failure investigation II” is started.

## Failure investigation II

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During “failure investigation II”, sampling and the entire manufacturing process is systematically checked. This also includes inspection of the quality of the raw materials and excipients utilized.

The results of “failure investigation II” are to be documented

– in addition to the results of “failure investigation I”.

## CFR 211.165 (Re-testing)

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1. The FDA permits the release of a batch with an OOS result without query if the subsequent result of the re-test was o.k., but not necessarily if only the subsequent results of the re-analysis were o.k. This is important to know for microbiological tests, as the original sample often is no longer available due to the long period of time between sample handling and the final results.
2. If the OOS result is based on a clear-cut laboratory error, it can be dealt with by performing a single subsequent test. However, if the (laboratory) error cannot be clearly defined, ...*extensive re-testing for inconclusive failure investigation ...* \* is expected.

\*United States versus BARR laboratories, 2/93

# Averaging

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If the Standard Operating Procedure (SOP) doesn't explicitly say that the average and not the single value(s) (is)are to be considered, all generated results are indicated and evaluated individually.

Creating an average value is recommended if variability and standard deviations are important to consider, e.g. validation of the LAL test: if the labelled lysate sensitivity must be confirmed in quadruplicate, the standard deviation must not exceed a certain value.

## Parallel tests

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Several parallel preparations of the same sample are particularly suitable for tests that show a high level of variability in the results, e.g. microbial count determinations, due to the system inherent variability.

If the standard operating procedure, SOP, requires parallel tests of a preparation, only the average value received and not the single values are documented as result.

Keep in mind: If the single and not the average value(s) is/are required when reporting the result, one is not permitted to “improve” the results by generating an average value if an OOS result was obtained!

## “Test for outliers”

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The test for outliers is used when a result from a data pool with mainly homogenous results differs so greatly from the others that it is rather unlikely that the obtained result relies on “real data”.

The “outlier” may result from a laboratory or production error that was not identified and is thus not representative.

Keep in mind: In the relevant USP chapter, “Outliers” are only accepted as such if they can be proved statistically (e.g.  $>$  triple standard deviation) and only for biological and not for chemical tests!

## CFR 211.167 “special testing requirements” (for microbiological tests)

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- 211.167(a) Sterile products: Written test procedures for sterility and ..... testing....
- Interpretation: When drawing up a OOS SOP there should be 2 SOPs: one for sterile and one for non-sterile products.  
Rationale: The procedure for sterile products in the case of OOS results is completely different from that for non-sterile-products.



## CFR 211.167 “special testing requirements” (for microbiological tests)

1. 211.167(a) Sterile products (interpretations\*)
  1. It is difficult to justify invalidation of an initial positive sterility test result.
  2. Presence of the same micro-organism in test sample and lab environment does not automatically rule out product contamination.
  3. A “high threshold” of justification is needed to invalidate a positive sterility test result.
  4. A positive sterility test result rate above 0.5% requires investigation (-> both false and correct positive; trending over a 12-month period is required).

\* FDA Human drug GMP notes, 6/99