



# Lessons from Pharmaceutical Laboratory related FDA Warning Letters

The Agilent Critical Compliance Seminar 2016

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# Overview

**Q&AS**

- FDA Inspections and reports
- GMP compliance along the sample and data workflow
- Recent FDA warning letters & 483s and recommendations how to avoid FDA warning letters related to
  - Requirements for quality systems
  - Requirements for workflow steps
- Responding to Warning Letters and 483's
- Resources



# FDA Inspection Documentation

- 483 Form Inspection Observation
  - only deviations listed
  - written for inspection exit meeting
- Establishment Inspection Report (EIR)
  - very detailed (20-40 pages)
  - more like an inspection protocol
- Warning letter
  - With significant deviations
  - Reviewed by FDA centers

For examples, please check: **[www.fdawarningletter.com](http://www.fdawarningletter.com)**



# What about Europe

- EMA launched new version of the EudraGMDP website
- Includes statements of non-compliance with GMP and positive GMP certificates
- Information includes company name, location, issue date, nature of no-compliance and the action taken by issuing authority in order to protect public health
- Examples for actions taken
  - Withdrawal of current valid GMP certificate number
  - Batch recall

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2013/12/news\\_detail\\_001994.jsp&mid=WC0b01ac058004d5c1#press-release](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/12/news_detail_001994.jsp&mid=WC0b01ac058004d5c1#press-release)

# Example from EudraGMDP Website

GMP Non-Compliance Search Results - 8 items

Report Number	Site Name	City	Country	Postcode	DUNS Number	EudraGMDP Key	NCA Ref	MIA Number	Issue Date
UK GMP 31450 Insp GMP 31450/360311-0005 NCR	IND-SWIFT LIMITED	DISTRICT S.A.S. NAGAR (MOHALI)	India	IN-140507		8787	360311-IND-SWIFT LIMITED		2014-03-21
14MPP024	SOMET	MONACO	Monaco	98000		9170	A067 6822 597		2014-03-05
13MPP057	Smruthi Organics Limited	Taluka Mohol	India	413 255 Solapur, Maharashtra		15103	151031360840861198		2014-01-08
sukls186744/2013	VAKOS XT a.s.	Přibram VI/47	Czech Republic	261 01		3036	25656180_2	sukls53410/2013	2014-02-24
sukls186744/2013	VAKOS XT a.s.	Praha 8	Czech	186 00		3035	25656180_1	sukls53410/2013	2014-02-24

Issue Date  
March 21  
2014

Company and location

**Nature of non-compliance :** It was not possible to confirm the validity of stability testing data. Several falsified and inaccurate results had been reported in long term stability and batch testing. Discrepancies between electronic data and those results formally reported were identified.

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**Action taken/proposed by the NCA :**

Withdrawal, of current valid GMP certificate No. UK GMP 31450  
Withdraw UK GMP 31450 Insp GMP 31450/360311-0004

**Requested Variation of the marketing authorisation(s)**  
Marketing Authorisation Holders should be requested to remove the

**Recall of batches already released**  
The need for product recall is currently under assessment. The com



# Typical Warning Letter Statement

- Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to **correct violations**.
- Include an explanation of each step taken to prevent the **recurrence of violations** and copies of supporting documentation.

**Corrective and preventive action plan  
Within 15 days**

# Missing Roles and Responsibilities

## Response

- **Deviation**

Data security protocols are not established that describe the user's roles and responsibilities in terms of **privileges to access, change, modify, create, and delete projects and data** (242)

- **Root Cause** (assumed)

The company was not aware that user roles and privileges need to be defined

- **Corrective actions**

- Develop procedure to define access levels and user rights
- Upgrade the system with suitable software-
- Implement the procedure for the inspected system

- **Preventive actions**

Implement the procedure on all regulated computer systems

Reference: [www.fdawarningletter.com](http://www.fdawarningletter.com) (242)



# Poor Quality System

- It is apparent that you have not implemented a robust quality system at your firm.
- Be advised that corporate management is responsible for ensuring the quality, safety, and integrity of drugs
- FDA strongly recommends that your corporate management immediately undertake a comprehensive evaluation of global manufacturing operations to ensure compliance with CGMP regulations (W-287)

- ✓ Corporate initiates implementing a global quality system using ICH Q10 “Pharmaceutical Quality Systems” as a guidance.
- ✓ Make sure that the quality system is understood, implemented and maintained

**FDA  
Warning**

**FDA  
Advice**

**Other  
Advice**



# No on-going GMP Training

**FDA  
Warning**

- Our review of your firm's training program disclosed that there was no requirement for on-going CGMP training of employees.
- **The firm only had an initial CGMP training and did not provide regular CGMP training** to all employees involved in the manufacture of drug products.
- There is no reference to CGMP training of supervisors or directors. (W-219)

**Good  
Advice**

- ✓ Include in the training program a schedule for regular cGMP training
- ✓ Make sure everybody working under GMP attends all GMP trainings, including supervisors and directors, **and IT personnel**



# No Supplier Quality Agreement

**FDA  
Warning**

- Failure to establish and maintain the requirements, including quality requirements that must be met by suppliers.
- For example, your firm has not specified quality requirements for suppliers, maintained lists of approved suppliers and developed written procedures describing how suppliers are evaluated for quality acceptance requirements (W-048).

**Good  
Advice**

Develop an SOP for assessment of material suppliers

- ✓ Include a list with quality requirements
- ✓ Develop and maintain a list of approved suppliers



# Method Validation

**FDA  
Warning**

- The **accuracy, sensitivity, specificity, and reproducibility** of test methods have not been established and documented (W-187)

**Good  
Advice**

The FDA frequently mentions these four parameters as the only required validation parameters, They are listed in CFR 211 but not sufficient. You need to do more

- ✓ Study ICH Q2 and USP 1225 and develop an SOP accordingly
- ✓ Start looking at the new FDA Method Validation guidance from 2015, It has modern elements as Quality by Design, Design of Experiments, and integrated lifecycle management



# Compendial Methods not Verified

**FDA  
Warning**

- Method verifications for compendial tests are not performed. Any method, including compendial methods, must be verified as suitable under actual conditions of use (W-274).

**Good  
Advice**

- ✓ Demonstrate that your laboratory is **suitable to run compendial methods under actual conditions of use**
- ✓ Follow USP general chapter <1226> as a guideline for verification of compendial methods
- ✓ Repeat one to three validation experiments
- ✓ Using the risk based approach select validation studies that are most difficult to pass.

# No Formal Method Transfer

**FDA  
Warning**

- The firm failed to determine the acceptability of ten methods prior to using them in the QC laboratory **through formal method transfer procedures** (282)
- Methods that were validated at one facility and transferred to xxx site are being **used without a methods transfer or revalidation protocol**. (W-186)

**Good  
Advice**

- ✓ Demonstrate that the receiving laboratory is suitable to run the method under actual conditions of use
- ✓ Follow USP general chapter <1224> as a guideline for transfer of analytical method
- ✓ Unless there is any specific reason not to do so, use the comparative testing approach for the transfer .



# No Equipment Qualification Program

**FDA  
Warning**

- The **calibration procedure** for HPLC systems is **inadequate** in that it did not include the detector's linearity, injector's reproducibility, and accuracy of temperature settings for the column heater (W-097)
- Failure to have an adequate **qualification (calibration) program** for the QC laboratory instruments.(W-246)

**Our  
Advice**

- ✓ Use the USP <1058> approach for analytical equipment qualification and calibration.
- ✓ Use the equipment supplier's test procedures and/or qualification services to ensure FDA compliant testing

# No Failure Investigations for failed Calibrations

**FDA  
Warning**

- There was **no documentation that an investigation was conducted to determine the root cause of the failed calibrations** of the Gas Chromatograph.
- In addition, your firm failed to implement adequate corrective action to prevent re-occurrence..(W-240)

**Good  
Advice**

In case of failed equipment calibration

- ✓ identify the root cause why this happened
- ✓ develop and implement a corrective action plan
- ✓ develop and implement preventive action plan
- ✓ verify the corrective and preventive action plans for effectiveness

# No Computer Validation at the Users Site

**FDA  
Warning**

- During the inspection, I asked if the computer software has been validation to **assure that it performs for it's intended use.**
- I was told that the software was **validated by the manufacturer.** The managing director **provided me a copy of the letter** the received from (the vendor).
- **The letter indicated that the software was validated.** She also gave me a copy of validation information that was obtained from (the vendor) during the inspection. (W-191)

**FDA  
Advice**

- ✓ I told the managing director **I still need to see what they have done to validate the system** since the computer was making a decision to accept or reject potential donors



**FDA  
Warning**

## Trial Sample Injections not Recorded

- Our investigators identified your practice of performing **trial sample injections** for HPLC analyses.
- For example, **trial injections of stability samples were acquired in the “Test” folder** prior to official testing. Immediately after the trial injections were completed, the official samples were **analyzed**.
- **The trial injection raw data**, captured in the back-up files, **were deleted** from the test folder. (W-295)

**Good  
Advice**

Develop a procedure to determine instrument readiness

- ✓ Equilibrate the complete system without sample injections, but under real HPLC conditions
- ✓ Run system suitability test runs
- ✓ Store all data in a sample folder and review the data

# Excel Spreadsheets not Validated and Controlled

**FDA  
Warning**

- The calculation for residual solvent uses an Excel spreadsheet that has not been qualified. We are concerned about the data generated by your QC laboratory **from non-qualified and uncontrolled spreadsheets**
- The use of the Excel® spreadsheets in analytical calculations **are neither controlled nor protected** from modifications or deletion (W-286)

**Good  
Advice**

Develop an SOP: "Validation and Control of Spreadsheet Application with recommendations for

- ✓ Validation using the lifecycle approach (DQ/IQ/OQ/PQ)
- ✓ **Control focusing on security and integrity of records and spreadsheets**



# Inadequate System Suitability Testing

**FDA  
Warning**

- Methods **do not include system suitability tests** to ensure that the system is operating properly (W-162)
- **No System Suitability performance before running testing** (132)
- The SOP requirement for the assay analysis of xxx **was not followed** in that the HPLC system suitability test was only performed weekly per firm SOP, instead of the actual time of testing (W-133)

Develop a procedure for system suitability testing

- ✓ What needs to be tested – check USP chapter 621
- ✓ When should the test be done – what frequency
- ✓ Make sure the SOP is followed

**Good  
Advice**

# No Procedure for Chromatographic Peak Integration and Re-integration

**FDA  
Warning**

- The inspector documented that HPLC processing methods (including integration parameters) and **re-integrations** are executed without a pre-defined, scientifically valid procedure
- A QC operator interviewed during the inspection stated that integrations are performed and re-performed **until the chromatographic peaks are “good”**, but was unable to provide an explanation for the manner in which integration is performed.. (W-287)

**Good  
Advice**

- ✓ Optimize chromatography to avoid re-integration
- ✓ Develop a procedure for integration and re-integration
- ✓ Define when special authorization is required



# No SOP and Inadequate Handling of Out-of-Trend Results

**FDA  
Warning**

- There is **no standard operating procedure** in place that describes the steps to be followed during an Out-of-Trend (OOT) Investigation
- Besides, the "**OOT Investigation**" **performed was inadequate.** (W-241)

**Good  
Advice**

1. Study requirements for handling OOT results
2. Develop an SOP for FDA compliant handling OOT results

# Incomplete Raw Data

**FDA  
Warning**

- Your Quality Unit failed to **provide all spectra and raw data** associated to the reports. (W-248)
- The laboratory records do not include **raw data to support the evidence of sample preparation, standards preparation** and did not include a **statement of the weight or measure of the samples** used for each test (W-248)

**Good  
Advice**

Make sure that the laboratory raw data are complete either in paper or in electronic form

- ✓ Develop an SOP that defines what constitute complete raw data, check 21 CFR 211.194(a)
- ✓ For examples see above

# Electronic Raw Data not Saved

**FDA  
Warning**

- Operating parameters of the spectroscopy system were maintained with the relevant test records. **However, electronic raw data was not saved** (W-167).

*21 CFR Part 211: (e) requires that complete records shall be maintained of all stability testing performed in accordance with Sec. 211.194 (e)..*

**Good  
Advice**

- ✓ Develop a policy and procedure that for HPLC data electronic records must be saved and available for inspectors



# Missing Audit Trail

**FDA  
Warning**

- Data stored on the computer can be deleted, removed, transferred, renamed or altered (W-209)
- There is **no audit trail or log of data changes** that are made to the information in the database. (W-224)

**Good  
Advice**

Develop procedural and technical controls to ensure electronic audit trail

- ✓ Include audit trail in the URS
- ✓ Make sure that the audit trail function can not be switched off by the operator
- ✓ Validate audit trail function





# Electronic Audit Trail not Reviewed

**FDA  
Warning**

- Your firm's review of laboratory data **does not include a review of an audit trail** or revision history to determine if unapproved changes have been made.. (W-229)

**Good  
Advice**

Develop a procedure for reviewing electronic audit trail

- ✓ Inform you laboratory staff that audit trails are reviewed
- ✓ Include audit trail review as checklist item in regular data review and approval
- ✓ Ask software suppliers to handle creation and review of audit trail tables more user friendly

# Manipulation of Printed Raw Data

**FDA  
Warning**

- Your firm's laboratory analyst had **modified printed raw data** related to the IR Spectra test
- Your **quality control unit failed** to detect that IR spectra were being substituted by a laboratory employee and **detect the manipulation or alteration** of laboratory documents

✓ We highly recommend that you hire a third party auditor, with experience in detecting data integrity problems (W-230)

**FDA  
Advice**

- ✓ Use internal or external **data integrity specialists** to review and approve critical records
- ✓ The specialists should also look at historical data

**Other  
Advice**



# Responding to Inspection Deviations

- **Fully understand** the content of each deviation in the exit meeting
- Respond in time (**15 days for FDA Warning Letters and 483s**)
- Address each item separately in the response
- Start with a statement that you understand and accept the deviation
- If some deviations are already fixed, provide documented evidence
- For others write how you will correct the deviation: Who, how, when
- Attach preliminary documentation for the corrections, if available
- **Commit to train all affected personnel**
- Write how you will prevent the same of similar problem re-occurring (preventive action)
- Write how to evaluate and follow-up on past shipments (historical data)



# Resources

[www.labcompliance.com/agilent](http://www.labcompliance.com/agilent)  
(available until February 30, 2016)

- **Agilent Primers**

- Analytical Instrument Qualification and System Validation
- Validation of Analytical Methods
- Good Laboratory Practice and Good Manufacturing Practice
- Understanding and Implementing ISO/IEC 17025
- **Compliance for BioPharmaceutical Laboratories Version 2 (2015)**
- Qualification and Validation for Supercritical Fluid Chromatography
- Elemental Impurity Analysis in Regulated Pharmaceutical Laboratories
- **Compliance by Design“ for Quality Control Laboratories:  
Learning from FDA Warning Letters**

## **Other Resources**

- Tutorials (method validation, computer validation, Part 11, GLP)
- References to FDA Warning letters and 483s
- Free Labcompliance Newsletter