Lessons from Pharmaceutical Laboratory related FDA Warning Letters

The Agilent Critical Compliance Seminar 2016

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Overview

- 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, check: **www.fdawarningletter.com**

What about Europe

- EMA launched new version of the EudraGMDP website
- Incudes 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

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.	Příbram 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 th validi
Discrepancies between electronic data and those results formally re
investigation raised by the company. The company provided comm
identified in process validation and release data. During on-going c
products. No satisfactory explanation was given for this discrepancy.

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

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.

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

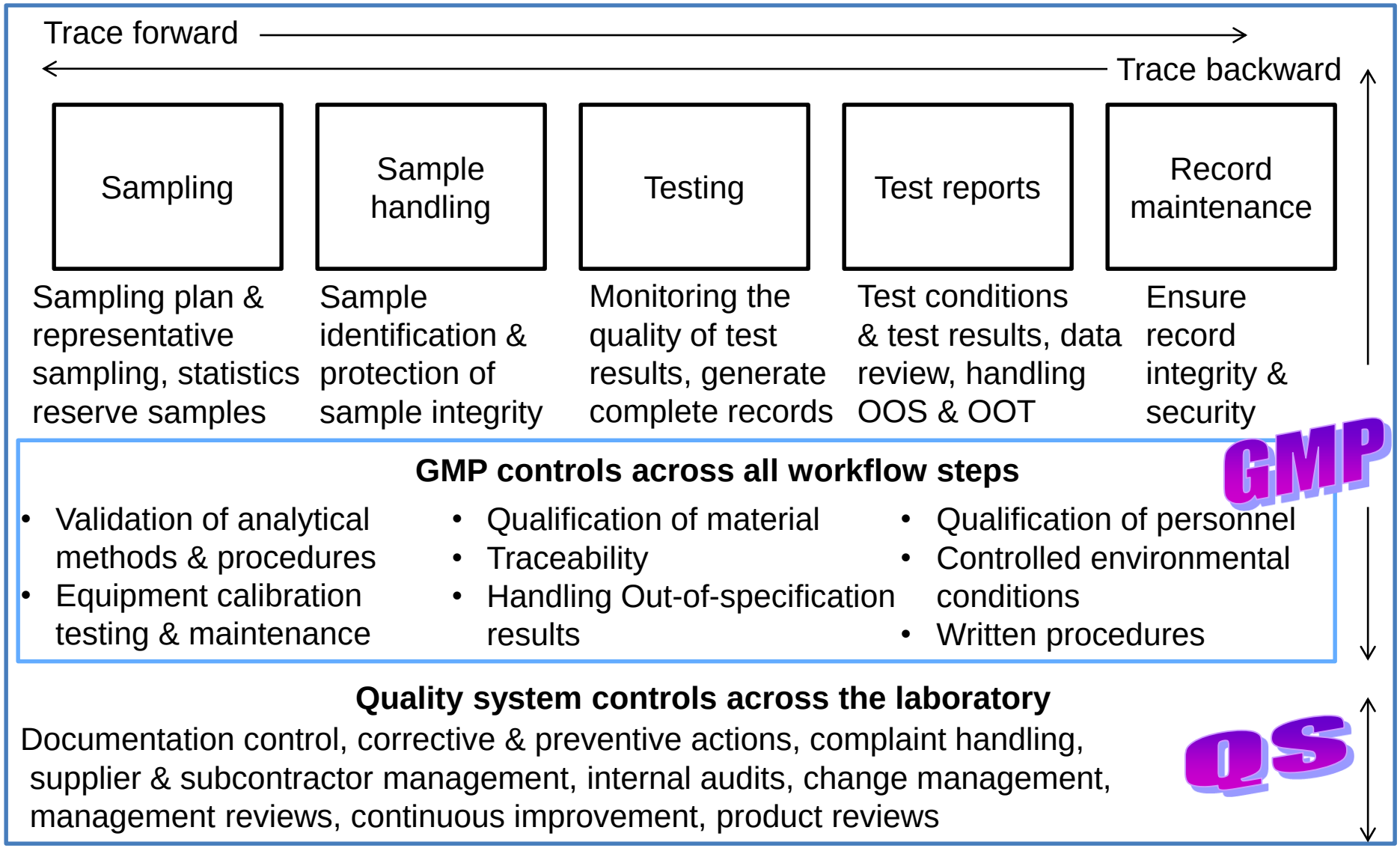
Missing Roles and Responsibilities

- **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 (242)

Compliance across the GMP Lab



Slide 8

Poor Quality System

FDA Warning

- It is apparent that you have not implemented a robust quality system at your firm.

FDA Advice

- 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)

Other Advice

- ✓ 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

No on-going GMP Training

- 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)

- ✓ 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

- 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).

Develop an SOP for assessment of material suppliers

✓ Include a list with quality requirements

✓ Develop and maintain a list of approved suppliers

Method Validation

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

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 t**hrough 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> and the EU GMP chapter 6 as a guidelines for transfer of analytical methods
- ✓ 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.
- ✓ Develop an equipment qualification master plan
- ✓ 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

- 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 manufacture**r. 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)

✓ 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

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 t**o 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)

Good Advice

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

No SOP for Inadequate Handling of Out-of-Trend Results

- 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)

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

Examples for Data Integrity Issues

FDA Observations

- Failure to maintain complete data derived from all lab tests
- Failure to record activities at the time they are performed
- Not reporting failing results
- Conducting unofficial testing (trial injections)
- Disabling electronic audit trails, unauthorized changes to data
- Backdating/postdating/missing signatures
- System access to groups/departments instead to individuals

ALCOA+: **A**ttributable, **l**egible, **c**ontemporenaous, **o**riginal (or accurate copy), **a**ccurate, **c**omplete

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 prodecure for integration and re-integration
- ✓ Define when special authorization is required

Trial Sample Injections not Recorded

FDA Warning

- Our investigators identified your practice of performing **trial sample injection**s 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 ana**lyzed.**
- **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 special system evaluation test runs
- ✓ Store all data in a sample folder and review the data

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

- 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)

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

- 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)

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

FDA Advice

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

Other Advice

✓ Use internal or external **data integrity specialists** to review and aprove critical records

✓ The specialists should also look at historical data

No Access to Information During Inspection

FDA Warning

- During the inspection, an analyst removed a USB thumb drive from a computer controlling an HPLC. **When asked to provide the drive, the analyst instead exited the room with the thumb drive.**
- After approximately 15 minutes, management provided our investigator with what they asserted was the USB thumb drive in question. **It is impossible to know whether management provided the same USB thumb drive that the analyst had removed**

FDA Advice

✓ Because of the findings of the FDA inspection described herein, your firm was placed on Import Alert on September 9, 2015

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 evaliate and follow-up on past shipments (historical data)

Resources

www.labcompliance.com/agilent
(available until April 30, 2016)

- **Agilent Primers**
  - Analytical Instrument Qualification and System Validation
  - Understanding and Implementing ISO/IEC 17025
  - **Compliance for BioPharmaceutical Laboratories Version 2 (2015)**
  - **Compliance by Design“ for Quality Control Laboratories: Learning from FDA Warning Letters**

Other Resources

- Tutorials (method validation, computer validation, Part 11, GLP) www.labcompliance.com/tutorial
- References to FDA Warning letters and 483s www.fdawarningletter.com
- **Free Labcompliance Newsletter http://www.labcompliance.com/newsletter/ordering/default.aspx**