Recent Calibration & Maintenance 483’s and Warning Letters
Discussion Topics:

1. GMP – Preventative vs Reactive
2. Regulatory Inspection Agencies
3. Regulatory Actions
4. Regulations
5. FDA 483’s and Warning Letters
6. Wrapup and Questions
GMPs

- Identify minimum requirements to produce and market a drug product or component
- Assure drugs and components meet requirements of FD&C Act as they relate to:
  - Safety
  - Identity
  - Strength
  - Purity
  - Effective
- State what must be done (NOT how to do it!)
Types of Inspections

- **Routine** – unannounced visit conducted periodically.
- **Pre-Approval** – Scheduled before approving a new facility or product.
- **For-Cause** – unannounced – Belief or evidence of something wrong at the facility.

What are they looking for

- Compliance with License Commitments and cGMP’s.
- Compare what was submitted in license app to reality.
- Evidence of wrong doing/fraud.
- Good Quality Systems: Change Control, Deviation Investigations, etc.

**CONTROL** of incoming goods, processes, final product.

What if they find something they don’t like

- Observations on 483 form.
- Warning Letter
- Consent Decree
- Injunction/Debarment/Criminal Charges.
What is a Form 483?

- Issued at the conclusion of a site inspection
- Details observations made by the inspector that may be in violation of Food Drug and Cosmetic (FD&C) Act and related Acts
- Response given by company with corrective actions
- Is this a final step?
  - Yes, if all corrective actions resolve all observations
  - No, if observations are not resolved, a Warning Letter may be issued.
What is a Warning Letter?

- Issued when significant violations of FDA regulations are observed and/or not resolved after Form 483
- Indicated problems to correct, directions to resolve and a timeframe
- Is this a final step?
  - Yes, if all corrective actions resolve all violations then a Close-out letter can be issued
  - No, if observations are not resolved, a Consent Decree may be issued.
What is a Consent Decree?

• A legal document issued by FDA and enforced by the Federal Court that forces a company to cease production and fix serious violations

• Includes fines, reimbursement to the government, due dates, penalties for non-compliance

• Is this a final step?
  ✓ Yes, usually this is a permanent resolution
  ✓ Very few companies have succeeded in removing the decree
Sec. 211.68  Automatic, mechanical, and electronic equipment.

(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be \textit{routinely calibrated, inspected, or checked according to a written program designed to assure proper performance}. Written records of those calibration checks and inspections shall be maintained. [43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]
(a) Equipment used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and shall perform in the manner for which it was designed so as to assure compliance with the official requirements prescribed in this chapter for blood and blood products.

(b) Equipment that shall be observed, standardized and calibrated with at least the following frequency, include but are not limited to...
Sec. 820.72 Inspection, measuring, and test equipment.

(a) Control of inspection, measuring, and test equipment. Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities shall be documented.

(b) Calibration. Calibration procedures shall include specific directions and limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on the device's quality. These activities shall be documented.
Title 21 – Food and Drugs

SUBCHAPTER H – MEDICAL DEVICES,
PART 820 -- QUALITY SYSTEM REGULATION

Subpart G--Production and Process Controls

Sec. 820.72 Inspection, measuring, and test equipment. 

(1) Calibration standards. Calibration standards used for inspection, measuring, and test equipment shall be traceable to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an in-house standard.

(2) Calibration records. The equipment identification, calibration dates, the individual performing each calibration, and the next calibration date shall be documented. These records shall be displayed on or near each piece of equipment or shall be readily available to the personnel using such equipment and to the individuals responsible for calibrating the equipment.
Comparison of Total 483s Issued

<table>
<thead>
<tr>
<th>Center Name</th>
<th>FY 2012</th>
<th>FY 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods</td>
<td>3057</td>
<td>2386</td>
</tr>
<tr>
<td>Devices</td>
<td>1090</td>
<td>1099</td>
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<tr>
<td>Drugs</td>
<td>787</td>
<td>690</td>
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<tr>
<td>Veterinary medicine</td>
<td>243</td>
<td>328</td>
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<tr>
<td>Bioresearch monitoring</td>
<td>283</td>
<td>273</td>
</tr>
<tr>
<td>Biologics</td>
<td>237</td>
<td>191</td>
</tr>
<tr>
<td>Human tissue for transplantation</td>
<td>138</td>
<td>121</td>
</tr>
<tr>
<td>Parts 1240 and 1250</td>
<td>110</td>
<td>91</td>
</tr>
<tr>
<td>Radiological health</td>
<td>18</td>
<td>32</td>
</tr>
</tbody>
</table>

Sum Product Area 483s from System  

| Sum Product Area 483s from System | 5963 | 5211 |

Actual Total in system 483s** (some 483’s had multiple centers in observation)  

| Actual Total in system 483s**         | 5797  | 5050  |

http://www.fda.gov/iceci/EnforcementActions/ucm250720.htm
## Top 12 Observations in Drugs Category

<table>
<thead>
<tr>
<th>RANK</th>
<th>Ref No.</th>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21 CFR 211.22(d)</td>
<td>155</td>
<td>Procedures not in writing, fully followed</td>
</tr>
<tr>
<td>2</td>
<td>21 CFR 211.192</td>
<td>131</td>
<td>Investigations of discrepancies, failures</td>
</tr>
<tr>
<td>3</td>
<td>21 CFR 211.100(a)</td>
<td>106</td>
<td>Absence of Written Procedures</td>
</tr>
<tr>
<td>4</td>
<td>21 CFR 211.160(b)</td>
<td>99</td>
<td>Scientifically sound laboratory controls</td>
</tr>
<tr>
<td>5</td>
<td>21 CFR 211.67(b)</td>
<td>77</td>
<td>Written procedures not established/followed</td>
</tr>
<tr>
<td>6</td>
<td>21 CFR 211.113(b)</td>
<td>76</td>
<td>Procedures for sterile drug products</td>
</tr>
</tbody>
</table>

[http://www.fda.gov/iceci/EnforcementActions/ucm250720.htm](http://www.fda.gov/iceci/EnforcementActions/ucm250720.htm)
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<tbody>
<tr>
<td>7</td>
<td>21 CFR 211.67(a)</td>
<td>71</td>
<td>Cleaning / Sanitizing / Maintenance</td>
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<tr>
<td>8</td>
<td>21 CFR 211.165(a)</td>
<td>66</td>
<td>Testing and release for distribution</td>
</tr>
<tr>
<td>9</td>
<td>21 CFR 211.110(a)</td>
<td>65</td>
<td>Control procedures to monitor and validate performance</td>
</tr>
<tr>
<td>10</td>
<td>21 CFR 211.166(a)</td>
<td>62</td>
<td>Lack of written stability program</td>
</tr>
<tr>
<td>11</td>
<td>21 CFR 211.100(b)</td>
<td>59</td>
<td>SOPs not followed / documented</td>
</tr>
<tr>
<td>12</td>
<td>21 CFR 211.68(a)</td>
<td>56</td>
<td>Calibration/ Inspection not done</td>
</tr>
</tbody>
</table>

http://www.fda.gov/iceci/EnforcementActions/ucm250720.htm
## Maintenance and Calibration Related Observations

<table>
<thead>
<tr>
<th>Division</th>
<th>Total 483 Observations</th>
<th>Maintenance Observations (including documentation, process, etc.)</th>
<th>Calibration Observations (including documentation, specifications, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods</td>
<td>2386</td>
<td>136</td>
<td>245</td>
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<td>15</td>
<td>51</td>
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<td>Biologics</td>
<td>191</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

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Regulation vs. Guidance

Guidance Documents - Benchmarking

ISPE GAMP Calibration Management (second edition)

ISPE GAMP Validation of Lab Computerized Systems

ISPE Good Practice Guide - Maintenance

NCSLI RP-6 Calibration Control Systems

ISO 17025 General Requirements for Calibration Labs

ISO 98 Guide for Measurement Uncertainties
Regulation vs. Guidance

*Regulation – Law*

CFR (or Code of Federal Regulations) Title 21
Calibration Observations
11. Control of Inspection, Measuring, and Test Equipment
Your calibration procedure and implementation is inadequate in that your procedures dictate calibration and you are performing verification, unless it falls out of your tolerances upon which you calibrate the equipment.
Routine calibration and checking of automatic and mechanical equipment is not performed according to a written program designed to assure proper performance.

Specifically, instrumentation for the following thermometers are not checked and calibrated to an NIST-traceable standard:

a. Incubators used for storage of environmental monitoring and media fills
b. Autoclave
c. Depyrogenation oven
d. Hot/stir plate in clean room adapted isolator used to mix all formulations
e. Freezer used for storage of products such as Bi-Mix and Tri-Mix.
f. Dry heat blocks used for biological indicator tests for autoclave
6. Failure to establish and maintain adequate schedules for the adjustments, cleaning, and other maintenance of equipment to ensure that manufacturing specifications are met. Maintenance activities including the date and individual(s) performing the maintenance activities, shall be documented as required by 21 CFR 820.70(g)(1). For example:

A. Your "Facility and Equipment -Maintenance and Housekeeping" procedure, S8016-0A, states that all maintenance tasks must be recorded in the Monthly Maintenance Form, F8016-0A, and performed with the frequency stated in F8016-0A. Instead, according to your firm's officials, maintenance activities have been performed "as needed" and have been recorded on a loose-leaf paper log in the production area.

B. Your firm does not calibrate equipment as required. Calibration stickers and documentation for the (b)(4) burst tester (Serial: cannot be determined), (b)(4), and (b)(4) (Serial: (b)(4)) state the equipment was due for annual calibration on “7/16/2008”, “8/9/2011”, and “1/29/2003” respectively however, there is no documentation to demonstrate this equipment was calibrated on or since those dates.
Delta Pharma  
September 2013, Ripley, MS

Routine calibration of equipment is not performed according to a written program designed to assure proper performance.
Specifically,
There are no written procedures or records which demonstrate the following equipment has been calibrated:

- (b) (4) a) the pressure gauge used for ________  
b) the digital thermocouple model # used in the depyrogenation oven  
c) the dial thermometer used in the depyrogenation oven.  
d) the glass thermometer in incubator with ID ###### which is used for incubation of environmental monitoring samples.

The above is a repeat observation from the previous FDA inspection ending on 09/17/2010.
Maintenance Observations
Adequate laboratory facilities are not maintained.

A) Our inspection of the QC analytical and microbiology laboratories found the facility to be in significant disrepair. Laboratory windows within the instrumentation (e.g. HPLC) rooms were found to be un-closeable, Too Numerous To Count (TNTP) flies were observed throughout the sample preparation room, and laboratory reagent/equipment/documentation storage cabinets were found to be broken and un-closable.

B) During our inspection of the QC analytical laboratory on 01/05/14, we found a pool of water directly under the working standard storage refrigerator # l0100204 maintained at 2-8 °C. Upon opening this refrigerator, a significant buildup of melting ice was observed, causing a pool of water to form at the base of the internal cavity where working standard sample containers were found to be stored.

THIS OBSERVATION WAS DISCUSSED WITH MANAGEMENT DURING THE PREVIOUS FDA INSPECTION CLOSEOUT MEETING IN 12/2012.
Analytical instruments are not calibrated, qualified, or maintained appropriately. Specifically, analytical instrumentation located within your firm's process development laboratory, which provides GMP testing support to the manufacturing department, has not been:

1) qualified
2) calibrated at regular intervals, and
3) maintained at regular intervals.
Records regarding the maintenance of manufacturing equipment are not completed. Specifically, during our inspection of the Unit manufacturing block on 01/08/14, we reviewed the "Maintenance Work Permit" records currently stored in the documentation room, and found that 43 of approximately 55 records reviewed were not signed by the responsible employee demonstrating that the work had been "completed" and a "satisfactory job done", as required per section 6.3.7 of SOP OP003748, "Maintenance of building and equipment".
FDA Action in the News

http://www.youtube.com/watch?v=SCweXoedWM8
Meridian Medical
March 2013, Brentwood, MO

Records are not kept for the maintenance of equipment. Specifically, you failed to document each preventive maintenance (PM) task individually performed on over (REDACTED) valves located on your (REDACTED) Systems and over (REDACTED) valves located on your (REDACTED) System.

In addition, your SOPs #'s MNT-PRM-00179 and MNT-PRM-00176 titled "Operation and Maintenance of the (REDACTED) System“ and “Operation and Maintenance of the (REDACTED) System” respectively, fail to instruct the technicians to record this information for each PM task performed. Your (REDACTED) produced in these systems is used during manufacturing operations of your sterile injectable drug products.
Meridian Medical  
March 2013, Brentwood, MO

Buildings used in the manufacturing, processing, and packing of a drug product are not maintained in a good state of repair.

1. At your "Base" facility used for Morphine Injectable assembly, labeling and packaging operations, the facility is not maintained in a clean and good state of repair. We observed at least 8 holes in the ceiling tile, at least 4 water spots in the ceiling tile, obvious dust on the ledges in the Morphine assembly Room and obvious dirt on the floors of the warehouse and Morphine assembly Room.

   Additionally, your cleaning record documentation for your Assembly Room and warehousing areas used to assemble your Morphine Drug units, along with finished packaging and labeling was not reviewed and approved after tasks were performed from the week of 11/7/2013 through 1/17/2013.

2. We observed rust on a pipe in your formulation suite used to compound all of your sterile injectable products.
Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition.

Specifically, the following was observed in the ISO 5 clean room areas on 08/06/13:

B.) Contract third party who certifies your clean room states in Report-dated 06/1-19/13 for horizontal flow hood where aseptic operations taken place states that "hood needs a good cleaning". There is no evidence that this document was reviewed or additional corrective actions were taken.

a. The prefilter from the ISO 7 clean room to the ante room was found visibly dirty on 08/06/13. Contract third party (Redacted) wrote in report-dated 06/19/13 that "clean room prefilters need to be changed". Your firm has no records to demonstrate the regular maintenance is performed on HEPA prefilters in ISO 5,7,8 areas.

b. Apparent brown splatter marks on the ceiling of the clean room
b. You did not appropriately maintain the deionized (DI) water system used for chemistry testing of OTC drug products in your main laboratory. The red light (indicating a filter change is needed) was on, the inside of the dispensing hose was discolored, there was a bronze-like color coating on the outside of the dispensing hose and connections to the hose. Given the lack of maintenance records, it was unclear how long the filter light had been on or if the filters had been replaced since installation in October 2010.

In your response, you state that the DI water filters have been changed and your staff has been instructed to keep the oven and the DI water system clean. Your response, however, is inadequate because it does not provide adequate assurance that you will clean and maintain the equipment at appropriate intervals to prevent the recurrence of these violations. Your response does not indicate whether your firm will implement new standard operating procedures (SOPs) or will make necessary changes to the existing SOPs outlining equipment cleaning and maintenance instructions, employee training, and documentation of cleaning and maintenance.
c. Your firm's Cleanroom Maintenance Procedure (SOP #823 Rev. 3) requires a HEPA filter velocity verification to be done (b)(4) for the Integra Suite, the site of the final manufacturing steps of the Integra artificial skin products. This requirement became effective May 4, 2011. Although your Integra Suite was operating in May 2011 and June 2011, the HEPA filter velocity verification was not performed. The Integra Suite was shutdown in July 2011 for remediation/renovation.

The adequacy of your firm's response cannot be determined at this time because implementation of the corrective actions will not be performed until the Integra Suite is restarted. Your firm initially stated that the intent of the HEPA filter velocity verification was to verify that there was flow across the HEPA filters between the (b)(4) month Integra suite cleanroom recertification. However, your firm later stated that no velocity specification should have been added in SOP #823, Rev. 3, and that the revised procedure, Rev. 4, deleted this specification. Your firm's root cause analysis determined that the procedure was implemented prematurely and without adequate training of the responsible operators.
Ideas and Thoughts:

✓ Read your Corporate Policy and or SOP’s routinely
✓ Get involved with fellow professionals and ask questions - Fun plus networking
✓ Benchmarking - Industry has great solutions
✓ Treat every deviation with an open mind
✓ Take advantage of relevant training sessions and even sponsored WebEx events
✓ Cross training (temporary shift of responsibilities)
✓ How proceduralized is your organization and are the procedures followed?
✓ Is there too much “Tribal Knowledge” in your area?
Final Thoughts

• 483’s happen everyday
• GAMP guidelines
• Be patient – No overnight turnarounds
• Questions?