FDA’s New Inspection Methods and Alignment
Get Ready for Fewer…but Tougher Inspections

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About Your Presenter
John Avellanet
Trainer for FDA and Health Canada inspectors on advanced data integrity inspection techniques and detecting data fraud in clinical, laboratory, and manufacturing operations
Served on behalf of the US Department of Justice as the independent overseer for the five-year, multi-million dollar Dr. Comfort Corporals Integrity Agreement
Industry reviewer for the international standard, BSI 10008 Evidential Weight and Legal Admissibility of Electronic Information (2015)
Lead expert for the ISPE GAMP Data Integrity Working Group
Author of Get to Market Now! Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicine (2010); co-author of Pharmaceutical Regulatory Inspections (2014)
Prior to founding Cerulean, John spent more than 15 years designing, implementing, and being accountable for quality systems and data compliance programs for FDA, DEA, BIS, ICH, IMDRF, and ISO

Agenda
NIPP and MDSAP
quick review of 2016
forecast for 2017
Presentation Objectives

1) Understand how FDA's risk inspection focus is flowing into 2017
2) Recognize the business implications of FDA's anticipated 2017 enforcement priorities
3) Identify the real-world implications of FDA’s new inspection changes to your clients
4) Improve your business plans to help better prepare your clients for FDA initiatives in 2017 and beyond

“FDA is undergoing some of its biggest changes in **over 20 years**...and for some things, since the 1990’s”

- Alonzo Cruse, FDA, Office of Regulatory Affairs, December 2016
Program Alignment - Commitments
1. Establish Commodity-Based and Vertically Integrated Regulatory Programs
2. Increase Specialization
3. Enhance Training
4. Revamp Agency Work Planning
5. Improve Compliance Policy and Enforcement Strategies
6. Enhance Import Operations
7. Advance Lab Optimization
8. Address Delaying/Streamlining

ORA Operations - Future Structure

What does this mean for me?
- Inspectorate specializes by program
- Expanded technical expertise
- Increased ability to keep pace with changes in manufacturing
- Goal of reduced timeframes for decision-making through both streamlining as well as team-based approaches
New Inspection Methods

New Inspection Protocol Project (NIPP)
- NIPP leverages 10 years’ worth of historical data with annual data, plus predictive analytics
- Uses algorithm to sort site data into inspection priorities
- Replaces routine inspections for:
  - 50% PAI
  - 50% postmarket surveillance (e.g., PV) inspections
  - "for cause" will be one-offs
- Piloted in 2015 and 2016

Medical Device Single Audit Program (MDSAP)
- Covers 7 different subsystems
- Emphasis on risk management (risk to public safety)
- Aligns with ISO 13485:2016
- Allows harmonized global inspections:
  - Brazil, US, Japan, Canada, EU, Australia
  - Supplemented with specific unique national requirements
  - "for cause" will be one-off, unique
- Piloted in 2015 and 2016

So *theoretically* should NOT be inspected more than 1x every 2 years by ANY of these regulatory bodies

www.fda.gov/medicaldevices/internationalprograms/mdsappilot/
“So what?”

Previously on…

QSIT and CAPA+2

• Quality System Inspection Technique (QSIT)
• Covered 5 different subsystems
• Pharma investigators used a “CAPA+2” approach (“CAPA+Production+1”)
• Examine 10 CAPAs and 10 production records
• Examine 1-2 other area such as:
  – design control — changes, validation, etc.
  – raw material controls (incoming acceptance, supplier qualification, etc.)
  – outsourced production-related controls (control over CMO, etc.)
  – process validation
  – records controls (records retention, data integrity — includes Part 11, etc.)
  – distribution controls (anti-counterfeiting, etc.)
  –.pharmaceutical surveillance (PV) and complaint-handling/MDR
During a regulatory inspection, the investigator asks for a specific record. After 24 hours, you cannot find it. Which response is best?

a) Give us another 24 hours to locate the record

b) The record is at another site

c) We noted a discrepancy and opened a CAPA
Case Study from 2016

- Firm makes and sells 5 different OTC products
- Buys its APIs
- Onsite microbiology lab
- Onsite analytical chemistry lab
- Onsite distribution warehouse
- Runs two different shifts
- Approx. 350 personnel at site
- Had passed nine different FDA and Health Canada inspections since 2000

Pre-Arrival Requests

"Please complete the following three questions prior to our arrival onsite the week of [...]:

1. Do you have a policy on data integrity? Yes | No (no need to supply now)

Why would they ask this?

2. Please confirm that computerized system owners and personnel with administrative-level access will be made available for the duration of the inspection. Note: If a corporate or global function performs this then a communication channel with remote access and visibility to all systems will be sufficient.

And why would they need this?
Pre-Arrival Requests

3. Please complete the listing of computerized systems (e.g., ERP, LIMS, chromatography systems, MES, security control systems, spreadsheets with macros, eBMR, EDMS, etc.) used principally in regulatory activities in the table below as follows. Please highlight any stand-alone systems.

<table>
<thead>
<tr>
<th>Type</th>
<th>Area/Site</th>
<th>Product Name, Purpose &amp; Supplier</th>
<th>Version or Model</th>
<th>Last Validation Date</th>
<th>Most Recent Changes (within past year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Networked (on-site)</td>
<td>Labs (all)</td>
<td>Chromleon Chromatography Data System (Thermo Scientific)</td>
<td>v 6.9</td>
<td>Dec. 2014</td>
<td>Change controls #73, 76, 81</td>
</tr>
<tr>
<td>Hosted SaaS (Corporate (all sites))</td>
<td>TrackWise EQMS (Sparta)</td>
<td>v 8.1</td>
<td>Nov. 2015</td>
<td>Change controls #81, 111</td>
<td></td>
</tr>
<tr>
<td>Stand-alone (QC Lab)</td>
<td>Excel Sample Tracking Worksheet (Microsoft with custom macros)</td>
<td>v Office 2013</td>
<td>April 2016</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

Regulator’s Computerized System Inventory Format*

Initial Records Requested

- Site data integrity compliance plan showing progress to date
- Inventory list of computerized system validations performed (completed) since last inspection
- List and copies of the CSV and data integrity policies the site trains on and enforces
  - Good data integrity practices (or Good documentation practices)
  - Computerized system validations
  - Change control
  - Records retention and archiving
  - Computerized system security
  - Backups and disaster recovery
- The most recent change controls related to validated systems
- 18 months’ worth of CAPAs involving the validated systems, the word “data” and other key phrases

Does everyone see what this request forces...?
What FDA was Looking for….

1) **Data fraud** - backdating, re-running samples until they passed, etc.
2) **Data loss** – inadvertent or intentional, active data, historical data
3) **Ongoing oversight** and verifications by site business management AND by Quality Unit
4) **Consistency of controls** – proof of a “consistent state-of-control” around data

What FDA was NOT Looking for….

• Perfection
• Use of the “right” risk methodology
• Detailed computerized system validations
• Comprehensive set of the “right” SOPs

Within One Day….

- No periodic verifications of data archives to prove maintained records as per 21 CFR §§211.68, 211.180, 211.188, and 21 CFR §11.10(c)
- No data integrity related SOPs or policies as per 21 CFR §§211.22, 211.180, 211.188, and 21 CFR §11.10(j)
- No documented data reviews as per 21 CFR §§211.22, 211.68, 211.100, 211.180, and 21 CFR §11.10(e)
- No investigations for failed backups as per 21 CFR §§211.132, 211.180, 211.188, and 21 CFR §11.10(b)(1)
- Stand-alone lab machines and factory floor machines have no backups as per 21 CFR §§211.68(b) and 21 CFR §11.10(c)
- Validations were not “fit for use” (no PQ) as per 21 CFR §§211.68, 211.110, 211.113(b) and 21 CFR §11.10(a)
NIPP and MDSAP Realities

- Team-based inspections (at least 1 Quality System/Data Integrity expert and 1 Product Specialist)
- Heavy reliance on “live” access to the firm’s digital records and systems (no time for “war room” reviews)
- Long-term goal is for ALL members of the ICH and IMDRF to use these methodologies by 2020
- Significantly increased likelihood of getting a FDA-483 observation (wouldn’t be inspecting your site if not flagged as risk OR as part of a one-off “for cause”)
- All FDA CPMs, Inspection Guides, etc. are being re-written (including inspection policies....)

MDSAP v QSIT

<table>
<thead>
<tr>
<th>MDSAP Structure</th>
<th>QSIT Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management Oversight and Involvement</td>
<td>Management Controls</td>
</tr>
<tr>
<td>Marketing Authorization and Facility Registration</td>
<td>--</td>
</tr>
<tr>
<td>Measurement, Analysis and Improvement</td>
<td>Corrective and Preventative Actions</td>
</tr>
<tr>
<td>Adverse Events and Reporting</td>
<td>Design Controls</td>
</tr>
<tr>
<td>Device Design and Development</td>
<td>Production and Process Controls</td>
</tr>
<tr>
<td>Production and Servicing Controls</td>
<td>--</td>
</tr>
<tr>
<td>Purchasing Controls</td>
<td>--</td>
</tr>
</tbody>
</table>
FDA Implementation Timeline
For both MDSAP (devices) and NIPP (drugs)

In December 2016, Health Canada ended its own internal device assessment program in favor of "just" having MDSAP as the one regulatory approved method.

Three Implications to Consider

Greater 483 chance
lose touch
laxity

QUICK REVIEW OF 2016

enforcement recap for medical devices
enforcement recap for pharmaceuticals
FDA, Risk and Enforcement

- **High benefits to patients with little risk to public safety**
- **FDA exercises enforcement discretion**

- **Low benefits to patients with high risk to public safety**
- **FDA takes enforcement action**

Overall Summary Statistics

<table>
<thead>
<tr>
<th>Enforcement Action</th>
<th>Total Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-483 Observations</td>
<td>7,135</td>
</tr>
<tr>
<td>FDA Warning Letters</td>
<td>118</td>
</tr>
<tr>
<td>Recalled Products</td>
<td>246</td>
</tr>
</tbody>
</table>

CDER Top 6 Issues (drugs)

01 Procedures Not Fully Followed
Responsibilities and procedure applicable to [quality unit] are not fully followed, not in writing, et al

02 No Scientifically Sound Laboratory Controls
Laboratory controls do not include scientifically sound and appropriate specifications, sampling plans, test procedures, et al

03 Failure to Investigate Discrepancies
There is a failure to review any unexplained discrepancy; the failure of a batch to meet any of its specifications, et al
CDER Top 6 Issues (drugs)

04 Absence of Written Procedures
There are no written procedures designed to assure that the drug product has the identity, safety, quality, and purity expected

05 Environmental Monitoring System
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions to ensure drug product safety, quality, et al

06 Calibration and Inspection Maintenance Not Done
Routine calibration, maintenance, inspection of equipment is not performed in order to assure proper performance

CDER Numbers (drugs)

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Issue</th>
<th>No. of FDA-483</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 CFR 211.22(d)</td>
<td>Procedures not fully followed</td>
<td>147</td>
</tr>
<tr>
<td>21 CFR 211.160(b)</td>
<td>No scientifically sound laboratory controls</td>
<td>133</td>
</tr>
<tr>
<td>21 CFR 211.192</td>
<td>Failure to investigate discrepancies</td>
<td>126</td>
</tr>
<tr>
<td>21 CFR 211.100(a)</td>
<td>Absence of written procedures</td>
<td>85</td>
</tr>
<tr>
<td>21 CFR 211.42(c)(10)(v)</td>
<td>Environmental monitoring system for aseptic production</td>
<td>78</td>
</tr>
<tr>
<td>21 CFR 211.68(a)</td>
<td>Calibration and inspection maintenance</td>
<td>76</td>
</tr>
<tr>
<td>21 CFR 211.165(a)</td>
<td>Failure to test products before release</td>
<td>73</td>
</tr>
<tr>
<td>21 CFR 211.113(b)</td>
<td>Failure to prevent contamination of drug product</td>
<td>70</td>
</tr>
<tr>
<td>21 CFR 211.67(a)</td>
<td>Failure to clean, sanitize equipment and utensils</td>
<td>65</td>
</tr>
<tr>
<td>21 CFR 211.166(a)</td>
<td>Lack of a stability program</td>
<td>65</td>
</tr>
</tbody>
</table>

Translation:
FDA is increasingly citing drug firms for fundamental, basic failures
Implications for Drug Firms

CDRH Top 6 Issues (devices)

01 Lack of or Inadequate CAPA Procedures
   Procedures for corrective and preventative actions (CAPA) are not adequately followed, enforced, documented, et al

02 Lack of or Inadequate Complaint Handling Procedures
   Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit are not established, followed, enforced, et al

03 Lack of MDR Procedures
   Procedures for when a device error or adverse event needs to be reported to the FDA have not been written, followed, enforced, et al

04 Lack of Non-Conforming Product Procedures
   Procedures to control products that do not meet specifications have not been written, are not enforced, followed, et al

05 Lack of or Inadequate Purchasing Controls Procedures
   Procedures to ensure that all purchased or otherwise received product and services conform to requirements are not established, enforced, et al

06 Lack of or Inadequate Process Validation
   A process whose results cannot be fully verified by inspection and testing has not been validated according to established procedures
CDRH Numbers (devices)

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Issue</th>
<th>No. of FDA-483s</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 CFR 820.100(a)</td>
<td>Lack of or inadequate CAPA SOPs</td>
<td>344</td>
</tr>
<tr>
<td>21 CFR 820.198(a)</td>
<td>Lack of or inadequate complaint handling SOPs</td>
<td>264</td>
</tr>
<tr>
<td>21 CFR 803.17</td>
<td>Lack of or inadequate MDR procedures</td>
<td>146</td>
</tr>
<tr>
<td>21 CFR 820.90(a)</td>
<td>Lack of non-conforming product procedures</td>
<td>135</td>
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<tr>
<td>21 CFR 820.50(a)</td>
<td>Lack of or inadequate purchasing controls SOPs</td>
<td>122</td>
</tr>
<tr>
<td>21 CFR 820.75(a)</td>
<td>Lack of or inadequate process validation</td>
<td>119</td>
</tr>
<tr>
<td>21 CFR 820.100(b)</td>
<td>Inadequate documentation and follow-ups</td>
<td>99</td>
</tr>
<tr>
<td>21 CFR 820.30(i)</td>
<td>Lack of or inadequate design control procedures</td>
<td>78</td>
</tr>
<tr>
<td>21 CFR 820.22</td>
<td>Lack of or inadequate quality audit procedures</td>
<td>76</td>
</tr>
<tr>
<td>21 CFR 820.181</td>
<td>Failure to maintain device master record</td>
<td>65</td>
</tr>
</tbody>
</table>

Translation:

Failure to follow SOPs leads to FDA-483s and Product Recalls

Implications for Device Firms

Audit Actions

SOPs

Supplier Oversight
Device Cybersecurity

Device Cybersecurity in 2017

FDA finalized Cybersecurity postmarket guidance

Companies will struggle to adapt

Hacking will grow

“Ransomware will become increasingly targeted and personal in 2017”

Source: Malwarebytes, Security Predictions 17 January 2017
Device Piggybacking

- June 2015 – Blood gas analyzer, MRI and ultrasound devices arrived at 3 hospitals infected with malware directly from the US device manufacturer; these devices were used by hackers to steal private health and patient identity records that were then sent to an encrypted address in Guiyang, China

- April 2016 – VA hospitals report that 2 devices arrived at VA hospitals infected with malware directly from the device manufacturer

Sources:
- InformationWeek, Hospital Medical Devices Used as Weapons in Cyberattacks, June 2015

Two Questions to Consider

From the April 2016 VA hospital report to Congress, the two devices arrived from the device manufacturer already infected with malware that could've taken over hospital within hours if not caught as part of the hospital's incoming acceptance testing process.

- What cybersecurity quality control testing do you do as part of device final release?
- What cybersecurity testing do you do as part of incoming component acceptance?

“For firms to have a sliver of a chance in cybersecurity-based product liability litigation, they must be able to prove they took all the appropriate steps – and continuously and quickly acted on new information.”

- Dan Wittenberg, Esq., Snell & Wilmer, Hot Topics in Device Product Litigation, 10 February 2017
Implications to Consider

1) Firms will **not** be able to stop hacking
2) Product liability litigation **will increase**
3) Firms will **confuse** technology’s quick timeframe expectations with FDA’s more lax analog timeframes, and suffer as a result
4) FDA may step up its cybersecurity handling enforcement by YE – **too little, too late**

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Consider Scrutinizing…

- **Postmarket complaint handling and investigation process (SOP)**
  - do investigations consider cybersecurity design flaws...?
  - how rapidly can the firm update its software/firmware...?

- **Risk assessment process (SOP)**
  - does this include cybersecurity risks...?
  - was this process cross-functional (w IT) or just engineers...?
  - how did they address the likelihood of hackers attacking individual patients (implants) or diagnostic devices...?

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Drug Enforcement in 2017

- Warning Letters likely to decline
- FDA-483s will likely increase
Implications to Consider

1) FDA will be pushed publicly to reduce enforcement

2) FDA will likely continue to issue the same or greater amount of FDA-483s (private except through FOIA) and use risk/benefit to justify public perception

3) Firms will incorrectly conclude that FDA is getting lax

4) Many firms will be ripe for product liability litigation and out-of-court settlements

Remember, the minute something publicly bad happens, Congress will turn on FDA – so FDA-483s can be CYA for the agency

Agenda Recap

NIPP and MDSAP
quick review of 2016 forecast for 2017

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