FDA Inspectional Tactics

cerulean associates LLC
lean compliance + FDA consulting

FDANEWS

Agenda

how FDA prepares for an inspection
inspection walkthrough (from FDA's perspective)
closeout meeting and 483s (from FDA's perspective)
case study
new FDA inspection tactics
real-world business implications

Overall FDA Expectations

FDA Investigators

- Conduct themselves reasonably and professionally
- Conduct the inspection with as little disruption to a firm's operations as possible
- Openly communicate the scope of the inspection and potential findings at least daily
- For contentious issues to arise

Industry

- Welcome the investigator professionally and courteously
- Facilitate an efficient inspection
- Provide records, information, and interviewees as *swiftly* as possible (more on this shortly)
- Provide access to all locations and records (e.g., no hidden or "off limit" areas)

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Investigator training
Internal FDA guidelines
Overall tactics to choose from
Specific firm preparation

HOW FDA PREPARES

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Investigator Training

Regulations and preambles

Internal FDA documents (QSIT, CPG, etc.)

FDA guidance documents (var.)

Harmonized guidelines

- ICH
- IMDRF (especially for suppliers)
- PIC/S (aide-memoires, FAQs)

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Internal FDA Guidelines

- Investigations Operations Manual
  www.fda.gov/ICECI/Inspections/IOM/default.htm
- Compliance Program Guidance Manuals
  www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/default.htm
- Inspection Guides
  www.fda.gov/ICECI/Inspections/InspectionGuides/default.htm
- Inspection Technical Guides
  www.fda.gov/ICECI/Inspections/InspectionGuides/InspectionTechnicalGuides/default.htm
- Guide to International Inspections and Travel
  www.fda.gov/ICECI/Inspections/ForeignInspections/default.htm
- Quality System Inspection Technique
  www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm

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Specific Firm Preparation

Investigator reviews:

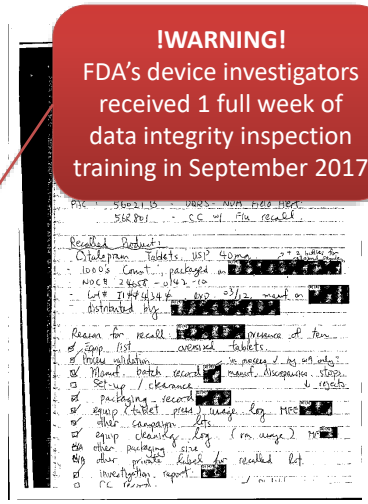
- Firm's compliance history (483s, WLs, EIRs, etc.)
- Firm's registration and production listing information (if any)
- Critical suppliers identified in any FDA registration listing (e.g., CMOs) or previous inspection EIRs
- Submission-specific information (incl. any specific commitments to FDA)
- Product recalls and adverse events (AE/MDR) filed with FDA (if any)
- Complaints about firm's products filed with FDA (if any)
- Public records (SEC filings, firm's press releases and website, firm's social media presence, other google-able information, online product reviews)
- Other information provided by the Center (such as any cross-agency information obtained by other US agencies – OSHA, CMS, HHS, etc. – and information from international sister agencies – EMA, MHRA, etc.)

Specific Firm Preparation

Investigator then prepares:

- Any needed equipment
- Any sample collection equipment
- Preprinted seals
- Form FDA-482
- Other items as relevant
- Inspection plan (usually in diary form)
- And his/her plan to address electronic record integrity and Part 11 compliance
  - data integrity in production
  - data integrity of labs
  - data integrity of record archives
  - overall plan and progress-to-date

!WARNING!
FDA's device investigators received 1 full week of data integrity inspection training in September 2017



FDA's Data Integrity Instructions

If a firm is keeping electronic records, determine if they are in compliance with 21 CFR Part 11. At a minimum, ensure that:

(1) the **firm has prepared a plan for achieving full compliance with part 11** requirements and is making progress toward completing that plan in a timely manner

(2) accurate and complete electronic and human readable copies of electronic records, suitable for review, are made available

(3) employees are held accountable and responsible for actions.

If initial findings indicate the firm's **electronic records may not be trustworthy and reliable**, or when electronic recordkeeping systems inhibit meaningful FDA inspection, a more detailed evaluation may be warranted.

- FDA Enforcement Compliance Policy Manual, Attachment A
http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133927.htm

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Notice of inspection
Investigator arrival
Opening meeting
Facility tour
Three common inspection pathways
Record collection
Commonly requested records and questions
Closeout meeting
Form FDA-483
Investigator departure
Post-Inspection Activities

INSPECTION WALKTHROUGH
(from FDA's perspective)

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Notice of Inspection

Telephone call (for short notice)

Letter of intent

- date is not (very) negotiable in US
- identifies purpose behind inspection
- may (for co-inspection agreements) identify the other regulatory agency (EMA, Health Canada, etc.) involved
- may (for non-US inspections) identify non-FDA accompanying personnel

Note:
FDA has signed several agreements with sister RHA's allowing their inspections to stand-in for an FDA inspection

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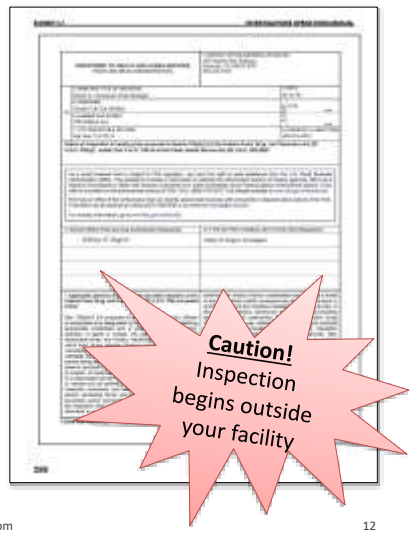
Investigator Arrival (to FDA)

Upon initial arrival…

- Present credentials (all individuals on team)
- Issue written notice of inspection (FDA Form-482) to most responsible person
- Identify general nature of inspection
- Request opening meeting
- Get a feel for how firm responds to FDA's arrival



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Opening Meeting (to FDA)

- Present overview of inspectional plan
- List specific products/operations to be covered
- Verify company profile
  - registration status
  - key personnel
  - site activities (products produced, critical suppliers in use, etc.)
  - any recent recalls from site (if any)
- Identify initial set of records to review
  - quality policy/manual
  - list of relevant SOPs/policies
- Request site tour

!CAUTION!
this list is *really* changing

Five New Record Sets Requested

- Site **data integrity compliance plan** showing progress to date
- An **inventory list** of cGXP computerized systems and any validations performed (completed) since last inspection
- A **list and copies of** the CSV and data integrity-related SOPs and policies the site trains on and enforces, such as….
  - 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

Facility Tour (to FDA)

- Preliminary walkthrough
  - this is **NOT** a dry run or a visitor show-and-tell
- Investigator's Goals
  - verify site layout and workflows
  - refine inspectional plan
  - gather initial impressions of operations and culture
  - verify personal safety and emergency exits
  - gather initial impressions of facility cleanliness and upkeep, equipment status, overall physical controls

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Example Inspection Pathway

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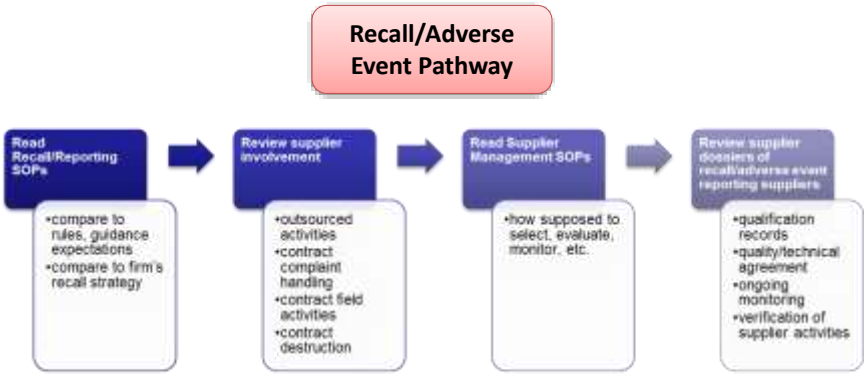
Example Inspection Pathway



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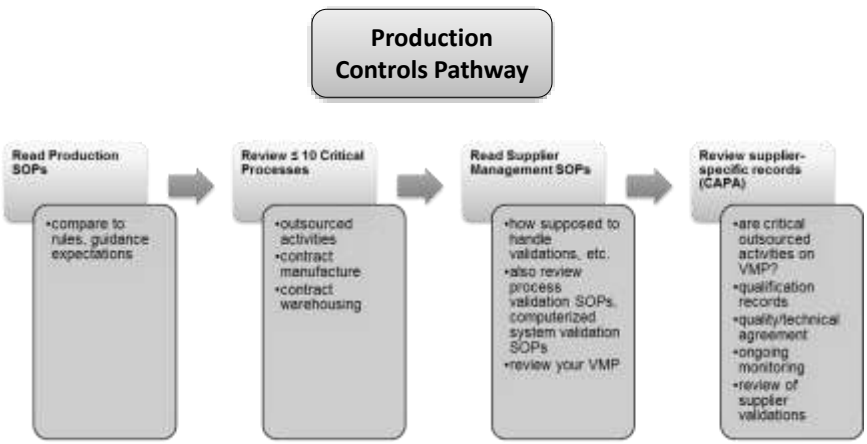
Example Inspection Pathway



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Record Collection (to FDA)

- Request specific records
  - always verify request in firm's lingo (SOP = "task guide")
- Collect copies of records to substantiate observations
  - do **NOT** ask to take original documents
  - do **NOT** ask for confidential/trade secret documents without clear demarcation on the records
  - records are to be treated as evidence
- Ask for print-outs or screenshots of audit trails
- Obtain digital files on USB "thumb drive"
  - ask if e-files have been scanned with anti-virus

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Record Collection (to FDA)

- Use camera where needed to document evidence
  - always request permission to see firm's response
  - explain what you are photographing and why
- Collect samples for laboratory review if needed
  - do **NOT** accept company-provided samples unless absolutely necessary (e.g., limited items)
- Use mobile tools to analyze materials
  - as with photographs, ask permission to gauge response
  - explain what you are analyzing, why and results
  - show results as necessary

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Commonly Requested Records

- Organization chart
- Production floor diagrams (room classifications, workflow, etc.)
- List of SOPs and policies (index, table of contents, etc.)
- List of all products/sizes made vs. distributed at site
- Recent product shipping records (speaks to interstate commerce)
- List of suppliers ("important" suppliers – API, CMO, CRO, etc.) and names/addresses
- List of recent OOS and OOT's related to specific products (or reason for inspection)
- List of any outstanding complaints and adverse event reports
- List of any open (e.g., in process) recalls and field alerts
- List of any recent sterility/environmental failures and investigations
- (*since 2010*) Overall site data integrity compliance plan showing progress to date
- (*since 2015*) CSV inventory template for firm to complete

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Commonly Requested Records

- Overall quality policy
- Recordkeeping and retention policy
- Overall quality manual
- Internal quality audit schedule (not the audit reports themselves, although…)
- Specific SOPs:
  - CAPA
  - Change control (looking to see if you have two different change control processes)
  - Complaint Handling
  - MDR/AER
  - Recall Handling
  - Process Validation
  - Equipment Maintenance/Calibration (critical equipment only…usually)
  - How to make each product (for clinical and laboratory – how data is collected/entered)
  - Management responsibility/accountability

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Typical Investigator Questions

- Does the firm have a written **quality policy**?
- Is the quality policy supported by **measurable objectives**?
- Is the scope of the "management representative" defined?
- How are QSMRs or APRs tied to the quality policy? What continuous improvement actions stem from the QSMR or APR?
- Is a firm's management familiar with the specific FDA regulations under which the firm operates?
- How is **training tracked** and documented? How many trainings does firm allow to take place in one (1) day?
- How is the need for training assessed?
- Are personnel trained on regulations as well as the firm's SOPs and policies?
- Do supervisors evaluate the training effectiveness of employees in key operations?

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Typical Investigator Questions

- For critical **supplied components/ingredients**, does the firm know its own supply chain?
- Does the firm have a supply chain map or other document showing its various suppliers and distributors (ideally through tier 2 suppliers)?
- Does the firm obtain **periodic independent testing** of supplied materials and/or finished product?
- Does a contract or quality agreement with the supplier define the specific responsibilities of each party? Does this include **data integrity controls**?
- How does the firm consistently oversee and monitor those suppliers whom it cannot audit?
- How often does the firm audit or **qualify its suppliers?** Are re-evaluation triggers identified in any supplier/purchasing-related SOPs or policies?

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Typical Investigator Questions

- Does the firm have a **records retention policy** and/or schedule? How current is the schedule?
- How is record destruction documented for expired required records?
- Review equipment calibration and **maintenance records** – are these consistent?
- Review at least 10 complaints over the past 2 years or all complaints related to the matter at hand. Does the **complaint documentation** show how the complaints were tracked? were investigated? were followed-up upon? were appropriately closed?
- Are there written explanations of any missing information, unexplained inconsistencies, incomplete records, etc.?
- How does the firm **track and trend complaints**? Act upon any trends?

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Typical Investigator Questions

- For computerized systems, are there current and historical **lists** of who is authorized to access the system and enter/change data?
- Are there written procedures for system and software validation, data collection, and data backups? Does the firm have a **good data integrity practices** policy or otherwise conduct such training?
- How are system and software changes controlled? Is there documentation of changes occurring? Is it consistent? Compare dates, reviews and approvals along with change timing.
- Are original **data entered directly** into an electronic record at the time of collection or are **data transcribed** from paper records into an electronic record? How are scans of paper records controlled and validated?
- How are **data transmitted** from the firm to/from its suppliers (sponsors, business partners, etc.) in a controlled manner?

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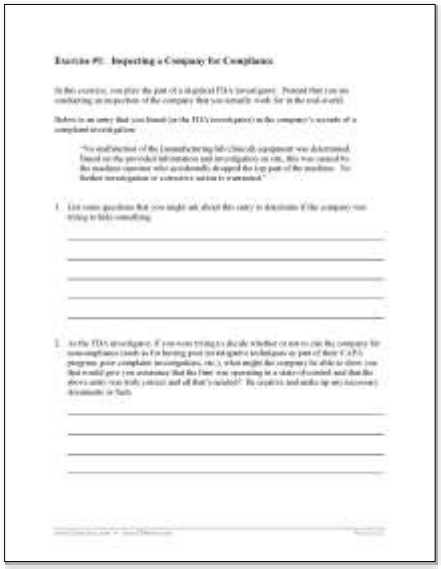
Interactive Exercise



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Ongoing Discussions (to FDA)

- Have open, running dialogue
  - do **NOT** play "gotcha"
  - there should be no surprises or misunderstandings for firm at closeout meeting (and on the Form FDA-483)
  - expect disagreement on some issues (remember that ORA or Center will make final determination)
  - avoid providing assurances of any official actions (e.g., ORA or Center will make final determination)
- Provide opportunities for firm to close any gaps
  - evidence must be provided to accept closure
  - firm must be able to show systemic-level corrections (and preventative actions), not just one-off fixes
  - do not allow fixes to unreasonably delay the inspection or closeout

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> “ Industry may use this opportunity to ask questions about observations, request clarification, and inform the inspection team what corrections have been or will be made during the inspection process. **Investigators are encouraged to verify the establishment's completed corrective actions** as long as the verification does not unreasonably extend the duration of the inspection.”

FDA, *Inspection Operations Manual, § 5.2.3*
http://www.fda.gov/ICECI/inspections/IOM/ucm122530.htm

Common Inspection **Red** Flags

- CAPA **evaluations are incomplete**, missing, not conducted or closed upon specified time expirations
- No **documented internal quality audit plan** or schedule
- Multiple **aborts, interrupts, errors in laboratory testing** – especially if data and audit trail reviews are insufficient
- Supplier-provided **COA/COC contain similar test values** across batches/lots
- Firm claims **no usage of electronic records** in any regulated process or decision-making
- Firm has **no data integrity compliance plan** and timeline
- Company has **no records retention or recordkeeping policy**

Closeout Meeting (to FDA)

- Expect top management with authority to attend
  - ability to commit company resources, time, money
  - at least one senior management representative
- Any final claims of corrections must have proof
  - remember: SOPs are "written intents" only
  - documents, samples, completed forms, etc. are proof
- Non-compliance findings issued on Form FDA-483
- Opportunity for questions and clarifications
- Discuss response options and requirements

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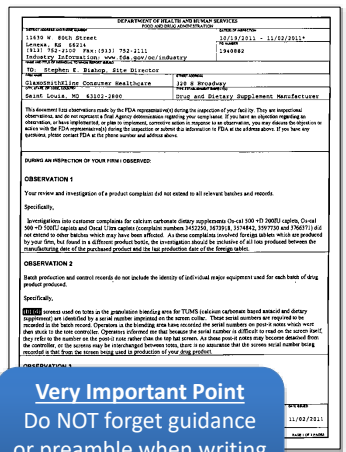
Form FDA-483

- Used to document regulatory deviations
  - correlate to regulated products or processes
- Observations are listed in descending order of importance
- Is not an "all inclusive list" of deviations or problems (snapshot in time)
  - other problems will be listed in final inspection report
- Presented during closeout
  - reflects judgment of investigator(s) only
  - cites specific examples
  - observations quote from regulations
  - commentary can reference guidance deviations



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

11430 W. 80th Street
Lenexa, KS 66214
(913) 752-2100 FAX:(913) 752-2111
Industry Information: www.fda.gov/oc/industry

10/13/2011 - 11/02/2011*
1940882

TO: Stephen E. Dialyp, Site Director

GlaxoSmithKline Consumer Healthcare
320 W Broadway
Saint Louis, MO 63102-2890
Drug and Dietary Supplement Manufacturers

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

Your review and investigation of a product complaint did not extend to all relevant batches and records.

Specifically,

Investigations into customer complaints for calcium carbonate dietary supplements Os-Cal 500 +D 200IU caplets, Os-cal 500 +D 500IU caplets and Oscal Ultra caplets (complaint numbers 3452250, 3473918, 3474842, 3597730 and 3706371) did not extend to other batches which may have been affected. As these complaints involved foreign tablets which are produced by your firm, but found in a different product bottle, the investigation should be inclusive of all lots produced between the manufacturing date of the purchased product and the last production date of the foreign tablet.

OBSERVATION 2

Batch production and control records do not include the identity of individual major equipment used for each batch of drug product produced.

Specifically,

[illegible] screens used on totes at the granulation blending area for TUMS (calcium carbonate based antacid and dietary supplement) are identified by a serial number imprinted on the screen collar. These serial numbers are required to be recorded in the batch record. Operators at the blending area have recorded the serial numbers on post-it notes which were then stuck to the tote controller. Operators informed me that because the serial number is difficult to read on the screen itself, they refer to the number on the post-it note rather than the top hat screen. As these post-it notes may become detached from the controller, or the screens may be interchanged between totes, there is no assurance that the screen serial number being recorded is that from the screen being used in production of your drug product.

OBSERVATION 3

11/02/2011

NAME OF LEADER

Very Important Point
Do NOT forget guidance or preamble when writing response!

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Form FDA-483 (to FDA)

FDA investigators are law enforcement officers – gathering defensible evidence

- Useful and credible observations:
  - clearly written with specific examples
  - not repetitious
  - correlate to FDA-regulated products and/or processes (including records)
  - ranked in order of significance (e.g., often the immediacy of risk to public health and safety)
  - legible
- Identify any known repeat findings
- Avoid identifying any individuals by name (if possible, avoid naming suppliers and distributors and other consignees on form)
- Do not minimize the importance of issues identified that were NOT written onto the 483
  - non-483 documented issues will be included in the inspection report
  - as will any discussion with management during the closeout meeting

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Investigator Departure (to FDA)

- Use the time for final facility review
- Be alert for discrepancies
- Handwrite any additional notations on the form
  - try to obtain any previously provided 483 and replace with copy of annotated form

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"Hidden" 483 Triggers

- Confining yourself to just the QSR or just the cGMPs
  - do not forget 21 CFR 11, GLP for QC labs in GMP environs, etc.
  - do not forget the interrelationship between cGCPs and cGMPs
- Lack of or incomplete documentation
- Decisions "without justification"
- Inconsistent (or lack of) records retention program
- Poor electronic data integrity controls (Part 11)
- Unqualified laboratory/clinical site facility management
- Calibration programs are not followed (or don't exist)
- Management is clearly not engaged/involved in QS

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Post-Inspection Activities (to FDA)

- Prepare final Establish Inspection Report (EIR)
  - recommend inspection classification (NAI, VAI, OAI)
  - any repeat findings cause OAI recommendation
- Send to Center and ORA for final review and determination of follow-up actions

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EIR (to FDA)

- Details inspectional findings
  - narrative format
  - lists individuals interviewed, records reviewed, etc.
  - summarizes discussions with management
  - may include investigator's overall impressions
- Exhibits attached
  - samples collected (if any)
  - record copies collected (SOPs, schematics, etc.)
  - original Form FDA-483
- Classification recommendation

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"As a general rule, a Warning Letter should **not** be issued if the agency concludes that a **firm's corrective actions are adequate and that the violations** that would have supported the letter **have been corrected**."

FDA, *Regulatory Procedures Manual, § 4-1-3 #3*
http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm

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Issue a Warning Letter…?

- The **firm's compliance history**, e.g., a history of serious violations, or failure to prevent the recurrence of violations;
- The **nature of the violation**, e.g., a violation that the firm was aware of (was evident or discovered) but failed to correct;
- The **risk associated with the product** and the impact of the violations on such risk;
- The **overall adequacy of the firm's corrective action** and whether the corrective action addresses the specific violations, related violations, related products or facilities, and contains provisions for monitoring and review to ensure effectiveness and prevent recurrence;
- Whether **documentation of the corrective action was provided** to enable the agency to undertake an informed evaluation;
- Whether the **timeframe for the corrective action is appropriate and whether actual progress has been made** in accordance with the timeframe; and,
- Whether the **corrective action taken ensures sustained compliance** with the law or regulations.

FDA, *Regulatory Procedures Manual, § 4-1-3 #2*
http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm

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Issue a Warning Letter…?

- The **firm's compliance history**, e.g., a history of serious violations, or failure to prevent the recurrence of violations;
- The **nature of the violation**, e.g., a viola
evident or discovered) but failed to corr
- The **risk associated with the product** an
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action addresses the specific violations,
facilities, and contains provisions for mo
effectiveness and prevent recurrence;
- Whether **documentation of the corrective**
agency to undertake an informed evaluation;
- Whether the **timeframe for the corrective action is appropriate and whether actual progress has been made** in accordance with the timeframe; and,
- Whether the **corrective action taken ensures sustained compliance** with the law or regulations.

This is why it is IMPERATIVE to have 2+ corrective timeframes for every observation:
[1] short-term (next 10 days), and
[2] longer-term activities

FDA, *Regulatory Procedures Manual, § 4-1-3 #2*
http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm

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Example Enforcement Actions

- Correspondence
  - Untitled Letter
  - Warning Letter
- Regulatory Meeting
  - with hand-delivered Warning Letter
- Injunction
- Product seizure (product is "arrested")
- Revoke/terminate research permit, marketing permit
- Civil penalties
- Import alert
- Debarment (for individuals)
- Consent decree/corporate integrity agreement

"Do **not** forget, above all else, the FDA is a **Law Enforcement agency**."

- former FDA Associate Chief Counsel, Mark Brown, Esq., December 2010

from investigator diary to FDA-483 to EIR

INSPECTION CASE STUDY

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InvaGen Pharmaceuticals*

- Conducted recall in August & September 2010
- Super-potent, oversized tablets
- Inspection (and recall) resulted from a customer complaint
- For cause inspection (narrow scope)

**Note:* we are only looking at these FDA historical documents for learning purposes only

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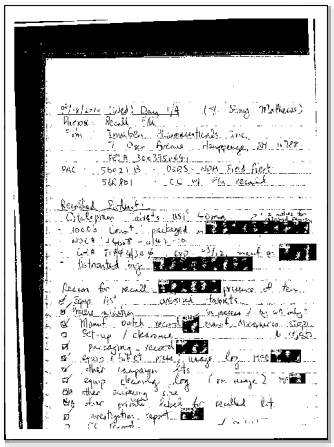
InvaGen FDA Investigator Diary

From FDA's Investigator Diary:

12 pages long – various lists of records to obtain and/or review, including:

- Org chart
- Equipment list
- Process validation SOP
- Process validation report
- OOS and OOT's associated with product over past 2 years
- Packaging records
- Equipment pressure logs
- Different tablet size batch records (for comparison)
- Internal investigation reports
- Any private labels
- Rejected batches – documentation
- Disposal SOP for rejected product
- Qualification of equipment involved
- Shelf life analysis report
- Equipment start-up SOP
- Stability data for 3-month, 6-month
- Workflow diagram for site



FDA Inspection Routine

Day 1 – Review of OOS & OOTs, CAPAs, other deviations

Day 2 – Site tour; product quality complaint handling

Day 3 – Documentation reviews of deviations and other CAPAs (now that have seen site, factory, labs, etc.)

Day 4 – More detailed tour of laboratories (including reviewing data integrity controls on various lab systems)

Day 5 – Warehouse controls vis-à-vis information filed with FDA around product sensitivities (e.g., humidity, etc.)

Day 6 – Documentation reviews, interviews

Day 7 – FDA writes draft Form FDA-483 (e.g., offsite)

Day 8 – Final verification of documentation, one-off clarifications

Day 9 – Closeout meeting

InvaGen FDA-483

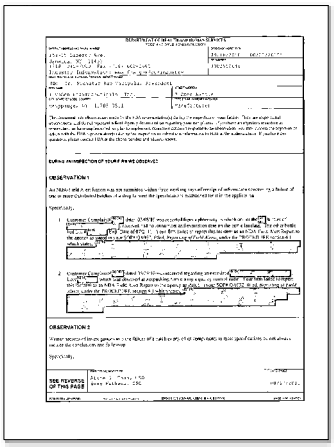
From FDA's Form FDA-483:

2 ½ pages long

Three observations

Records Referenced:

1. Customer log
2. Three customer complaints
3. SOP# QA032 Reporting of Field Alerts
4. Batch making instructions (*not listed in the EIR*)
5. Equipment usage and cleaning log for dedusters
6. Two batch records
7. One investigation (*not listed in the EIR*)

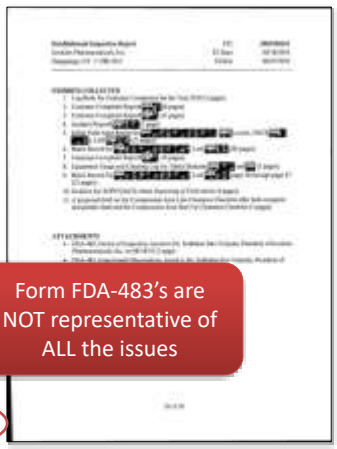


InvaGen EIR

From FDA's Establishment Inspection Report, p. 10:

List of Records Collected:

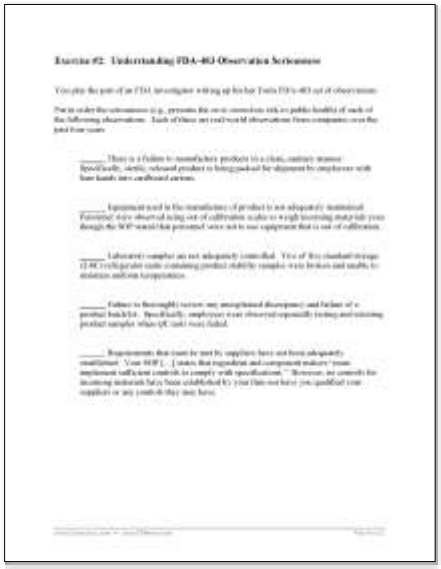
1. Log book for customer complaints for 2010
2. Customer complaint report
3. Customer complaint report
4. Incident report
5. Initial field alert report
6. Batch record
7. Customer compliant report
8. Equipment usage and cleaning log for deduster
9. Batch record
10. SOP# QA032 Reporting of Field Alerts
11. Proposed drafts of two checklists



Form FDA-483's are NOT representative of ALL the issues

196 total pages for a narrow inspection!

Interactive Exercise



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EMERGING FDA ACTIVITIES

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E-Inspections under FDASIA 2012

"Sec 706 Records for Inspection. (4)(A) Any records or other information that the Secretary may inspect under this section from a person that owns or operates an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a drug shall, upon the request of the Secretary, be provided to the Secretary by such person, **in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, and in either electronic or physical form, at the expense of such person**."

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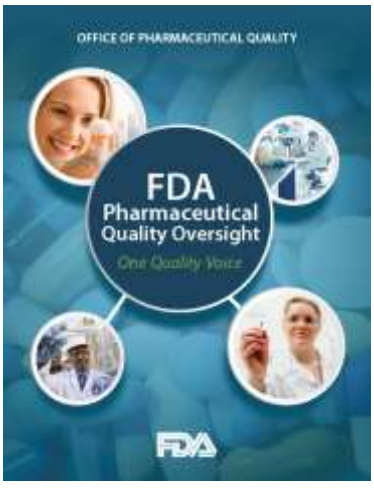
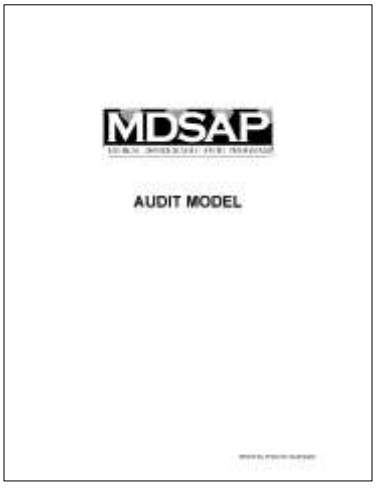
New Inspection Methods





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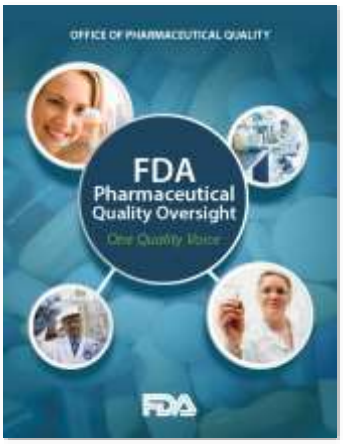
New Inspection Protocol Project

- Leverages up to 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 (within 3 years of NDA and 5 years of ANDA)
  - "for cause" will be one-offs
- Piloted in 2015 and 2016; formal rollout through 2018



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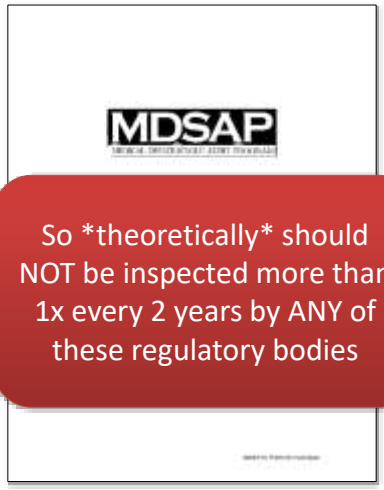
Medical Device Single Audit Program (MDSAP)

- 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, China
  - 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

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"So what?"
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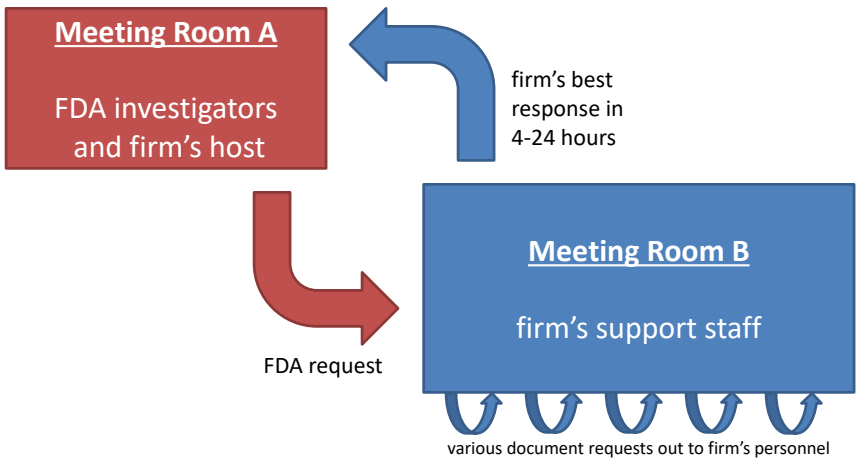
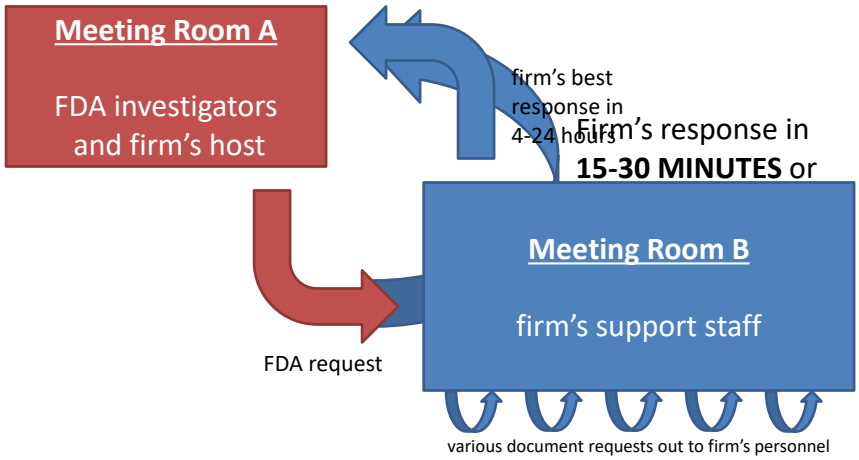
QSIT and CAPA+2

- 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.)
  - postmarket surveillance (PV) and complaint-handling/MDR

Inspection War Room Setup



Inspection War Room Change



NIPP Tactics

- Select a system used principally for regulat
- Identify the personnel with administrative access
  - how were they qualified/trained to be administrators?
- Ask an individual with administrative access to walk through the system in real-time and its various data integrity controls – security settings, audit trail settings, data storage controls, user access control lists, etc.
- Sample various digital data files using binomial sampling – review each data file's properties and an end-user's ability to change, edit, delete the data – along with corresponding audit trail documentation

Be very cautious if you're not training your SMEs and IT admins on FDA inspection handling

There is NO time to preview data in the war-room – it's all live in front of the investigator

Commonly Requested "Live"

- CAPA/deviation management and tracking system
- EDMS (for approved controlled docs)
- LIMS
- Electronic lab notebooks
- Complaint and AE management and tracking system
- Automated production systems (SAP, etc.)

Other Possibilities (not as frequent)

- Change control management and tracking system
- Facility (or equipment) monitoring (for temp, humidity, etc.)
- Network file storage locations (including SharePoint)

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NIPP Tactics

- On the system, check for folders commensurate with data fraud findings to date
- On the system, try to delete data:
  - use the application functionality
  - use Windows operating system capability (e.g., ctrl+D)
- On the system, try to change time and date
  - within the application
  - within Windows
- On the system, look for:
  - files in the desktop's Recycle Bin
  - failed/paused print jobs in the printer queue
  - files in the Temp folder (e.g., Run→%temp%)

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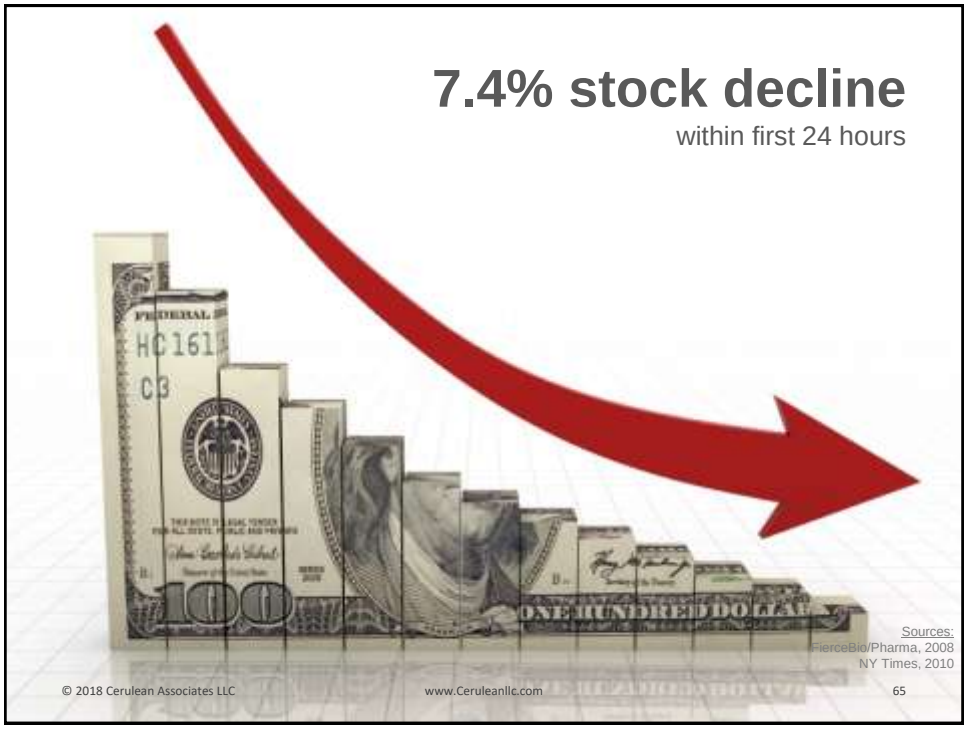
NIPP Tactics

- Request a copy on USB of the past X-years of data associated with a particular product (e.g., complaint files, batch files, SUSARs, CAPAs, etc.)…including any audit trails
  - make sure to capture any user-specific data if multiple logins on one computerized system
- Ask the firm to provide a summary table of all such data (and compare their summary to actual data)
- Offsite, examine the files provided:
  - look for data runs conducted or interrupted but not reported
  - look for file annotations, multiple file saves and “last edited” dates

bottom line costs of a Warning Letter

REAL-WORLD BUSINESS IMPLICATIONS


7.4% stock decline
within first 24 hours
Sources:
FierceBio/Pharma, 2008
NY Times, 2010
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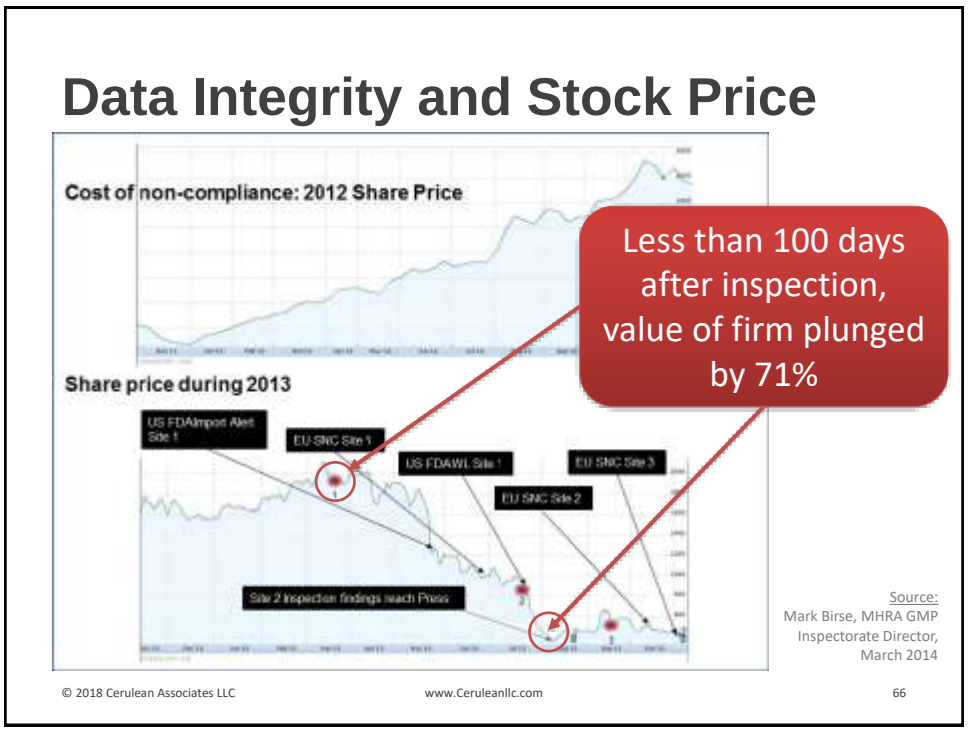
Data Integrity and Stock Price
Cost of non-compliance: 2012 Share Price
Share price during 2013
US FDAImpost Alert Site 1
EU SNC Site 1
US FDAWL Site 1
EU SNC Site 3
EU SNC Site 2
Site 2 inspection findings reach Press
Less than 100 days after inspection, value of firm plunged by 71%
Source:
Mark Birse, MHRA GMP Inspectorate Director, March 2014
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8% revenue loss in first year

Source:
Wall Street Journal, 2011

66 hours per employee each year

to resolve each 483 observation

Source:
ARMA International, 2010

- $480,000 in consultant and legal fees to respond to a Warning Letter

Source:
BioPharm International, 2004

Other Bottom Line Impacts

- Disgruntled investor lawsuits are "green-lighted"
  - after initial Warning Letter, J&J received a securities fraud class-action lawsuit in 2010
  - KV Pharma executives also cited in securities fraud and civil litigation
  - Chelsea Therapeutics executives cited in securities fraud class-action lawsuit in 2015
- States bring suit under unfair trade practices
  - Ortho-McNeil levied $327 million by South Carolina within ten months of a public Warning Letter
- Product liability settlements worsen
  - settlement costs jumps to $1.2 million per settlement
- Additional overhead slows new/revised product commercialization
  - productivity slows time to market by 30-90 days (approx. $33-99K per year)
  - lost opportunity cost (e.g., allow competitor more time to enter market)
- Each facility import alert reduces company revenue by $3M per product

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