AUDITING STABILITY PROGRAMS

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December 8-10, 2015
Freezer damages brain samples for autism study

BY STEVE LE BLANC
Associated Press

BELMONT, MASS. | A freezer malfunctioned at a Harvard-affiliated hospital that oversees the world’s largest collection of autistic brain samples, damaging a third of the scientifically precious specimens and casting doubt on whether they can be used in research.

The director of the Harvard Brain Tissue Resource Center said the loss was “devastating,” particularly in light of the increasing demand for brain samples among scientists searching for the cause of autism and potential treatments.

“Over the last 10 years, the autism tissue program has been working very hard to get the autism community to understand the importance of brain donation,” Dr. Francine Benes said. Now many of those samples have been compromised.

The freezer failed sometime late last month at the center, which is housed at McLean Hospital in the Boston suburb of Belmont. At least 54 samples earmarked for autism research were harmed. Many of them turned dark with decay.

However, an initial review indicates that the DNA in the samples is intact and can still be used for genetic research.

It’s unclear, however, whether the samples could be used for the full range of neuroscience needs.

Thirty-two of the brains had been cut in half, with one side placed in a formaldehyde solution and the other placed in the freezer. The samples in the solution remain available for all research projects, the hospital said.

The frozen tissue samples are normally maintained at about minus 80 degrees Celsius, but the temperature had reached about 7 degrees – the temperature of a common refrigerator – when the failure was discovered, Benes said.

Dr. Fred Volkmar, an autism researcher and director of the Child Study Center at Yale University, said the damage is even more disheartening given recent advances in autism research.

Some of that research, including autism studies involving stem cells, wasn’t even possible at the time when some of the brains were donated.
FIRST: KNOW THE FDA

- Understanding the position from which the Investigator comes can lead to a more successful FDA inspection
FDA’S CHARTER

- The FDA is a regulatory Agency that is established primarily to implement and enforce regulations consistent with laws passed by the US Congress and signed into law by the US President.

- To better understand FDA’s goals, especially if they are auditing you, it helps to understand this process.
LAWS AND REGULATIONS

- In the US, the LEGISLATIVE BRANCH (Senate and House of Representatives = Congress) crafts **laws** (e.g. The Federal Food, Drug, and Cosmetic Act)

- The EXECUTIVE BRANCH (under the leadership of the President and the Departments in the Cabinet) crafts **regulations** to implement the laws (e.g. Good Manufacturing Practice regulations) and enforce them (inspections, 483s, Warning Letters)

- The JUDICIAL BRANCH (the courts) rule on constitutionality and interpretation of both laws and regulations (e.g. the “Barr” Decision regarding out-of-spec findings, Consent Decrees)
The Executive Branch communicates its activities (proposals, final rules, guidelines, etc.) via the Federal Register (FR) which is published every day and available online.

Once they become final, regulations are published in the Code of Federal Regulations (CFR) which is available online.

Final FDA regulations are found in Title 21 of the CFR (e.g., the pharmaceutical GMPs are in Title 21 CFR Part 211).
FDA’s mission is based in laws for example:

- Biologics Control Act (1902)
- Pure Food and Drug Act (1906)
- Federal Food, Drug and Cosmetic Act (1938) *(NDAs for safety, Facility Inspections, Advertising)*
- Pesticide, Food and Color Additive Amendments (1950s)
- Efficacy Amendments (1962) *(NDAs for safety and efficacy, GMPs, Record Keeping)*
- Radiation Control for Health and Safety Act (1968)
- Medical Device Amendments (1976)
- Orphan Drug Act (1983)
- Generic Drug Enforcement Act (1992) *(Debarment)
- Dietary Supplement and Health Education Act (1994)
- Food and Drug Modernization Act (1997) (user fees; no ELAs; easier mfging changes; off-label use; pharmacy compounding; risk-based regulation decision-making)
- Bioterrorism Response Act (2002 and added to in 2004)
- Device User Fee and Modernization Act (2002)
- FDA Amendments Act (2007) (user fees, pediatric studies)
- Food Safety Modernization Act (2011)
- Generic Drug User Fee Act (2012)
LAWS TRIGGER REGULATIONS
EXAMPLES IN CFR TITLE 21:

- Recalls (CFR Part 7)
- Electronic Records (Part 11)
- Informed Consent (Part 50)
- GCPs (proposed Part 54)
- IRBs (Part 56)
- GLPs (Part 58)
- Patent Restoration (Part 60)
- Colors (Part 70)
- Foods (Parts 100 -)
- Food Additives (Part 172)
- GRAS Substances (Part 184)
- Drug Labeling (Part 201)
- Drug Advertising (Part 202)

- Drug GMPs (Parts 210-211)
- Drug Labeling (Part 201)
- INDs (Part 312)
- NDAs/ANDAs (Part 314)
- Drug Monographs, Standards and Tests (Parts 330-460)
- Biologics (Parts 600 -)
- Radiological Health (Parts 1000 -)
- Cosmetics (Parts 700 -)
- Medical Devices (Parts 800 -)
- Controlled Substances (Parts 1300 -)
THE LAW DEFINES A “DRUG”

- Articles recognized in the official USP, official Homeopathic Pharmacopeia, or official National Formulary.

- Articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals.

- Articles other than food intended to affect the structure or any function of the body of man or other animals.

- Articles intended for use as a component of any articles above.

FD&C Act Sec 201 (g)
THE LAW LISTS PROHIBITED ACTS, FOR EXAMPLE:

The introduction or delivery for introduction into US commerce of any food, drug, device, or cosmetic that is *adulterated or misbranded* is specifically prohibited by Section 301(a) of the FD&C Act.
"A drug or device shall be deemed adulterated if...the methods used in, or the facilities or controls used for its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current Good Manufacturing Practice"

FD&C Act Sec 501 (a)
THE REGULATIONS DEFINE THE GMPs

Title 21 in the Code of Federal Regulations Parts 210 and 211 (21CFR210/211): Current Good Manufacturing Practice in Manufacturing Processing, Packing or Holding of Drugs says:

The drug GMPs are the *minimum current* methods to be used in, and the facilities and controls to be used for the manufacture, processing (includes testing), packaging (includes labeling) and holding of a drug (bulk and finished) to assure it meets the requirements for safety, identity, quality, purity, strength and other characteristics it is represented to possess.
FDA’S MISSION

FDA is charged with assuring that drugs sold in the US are in compliance with the law......

Among other things, this means they cannot be adulterated......

Therefore, they must be made in compliance with GMPs
INSPECTIONS

FDA’s primary tool for assessing compliance with GMPS is an inspection.

But before we talk about WHAT FDA does - inspections - let’s look a little more about WHO FDA is ....
THE EXECUTIVE BRANCH
15 DEPARTMENTS ("CABINET"): 

- Agriculture
- Commerce
- Defense
- Education
- Energy
- Homeland Security
- Housing
- Interior
- Justice
- Labor
- State
- Transportation
- Treasury
- Veterans Affairs
- Health and Human Services
HEALTH AND HUMAN SERVICES

Includes the US Public Health Service, currently 8 agencies including:

- National Institutes of Health (NIH)
- Centers for Disease Control (CDC)
- Food and Drug Administration (FDA)
FDA
About 15,000 employees (1/3 in ORA)

A budget of about $4.5 billion

About $2.2 billion from user fees

Headed by a Commissioner appointed by the President and confirmed by Congress

Certain senior executives also may be political appointees
“CORPORATE” MANAGEMENT

- Commissioner
- Chief Counsel
- Chief Scientist
- External Affairs (industry, health, consumers)
- Policy
- Planning
- Legislation
- International Programs
- Finance and Budget
- Human Resources
- Information Management
OPERATIONS ARE ORGANIZED IN CENTERS BY PRODUCT

- Drug Evaluation and Research
- Biologics Evaluation and Research
- Veterinary Medicine
- Devices and Radiological Health
- Food Safety and Applied Nutrition
- Toxicological Research
- Tobacco Products (added in 1995)

And the Office of Regulatory Affairs
THE OFFICE OF REGULATORY AFFAIRS DOES INSPECTIONS

- Currently 5 Regions: ① Pacific, ② Southwest, ③ Central, ④ Northeast and ⑤ Southeast
- 20 Districts
- 13 Labs
- 150 Resident Posts
- 8 Ex-US Offices

But regions being “dissolved” with new ORA overhaul and further integration of the inspections Programs between HQ and the Field.

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FDA EX-US OFFICES

- Mexico City, Mexico
- San Jose, Costa Rica
- Santiago, Chile
- London, England
- Brussels, Belgium
- New Delhi, India
- Mumbai, India
- Beijing, China
OFFICE OF REGULATORY AFFAIRS
(THIS INCLUDES INTERNATIONAL)

- About 5,000 employees (1/3 of FDA)
- About 1,700 Investigators, 650 Lab Analysts, Compliance Officers and support staff
- About 150 employees now located ex-US
- In 2014, ORA conducted 15,400 inspections (3,067 ex-US) and analyzed 37,000 samples
- In 2015, ORA conducted half of all drug inspections OUTSIDE of the US
FDA IS A REGULATORY AGENCY

REGULATORY TOOLS INCLUDE:

- Product Review
- Deficiency Letters
- **INSPECTIONS**
- FDA 483s
- Warning Letters
- Consent Decrees (requires the Courts)
- Suspension of Approvals (Press Coverage)
- Recalls
- Import Detentions
- Seizures (focused on products)
- Injunctions (focused on business)
- Prosecutions (focused on people)

In 2014, FDA’s Office of Criminal Investigations alone secured $2.1 billion in fines.

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The overall objective of an FDA inspection is to determine compliance with appropriate “Good Practices” (GMPs, GLPs, GCPs) and other regulatory requirements (e.g. in INDs, NDAs, ANDAs) and current expectations (e.g. FDA and ICH guidelines)
REMEMBER: INSPECTIONS ARE FOR ENFORCEMENT

- To determine compliance status
- To obtain facts
- To obtain evidence
- FDA Investigators are REGULATORS
FOUR MAJOR GMP INSPECTION TYPES

- Pre-Approval (Compliance Program 7346.832)
- Post-Approval (Compliance Program 7346.843)
- Surveillance (Compliance Program 7356.002)
- For Cause (unscripted)
The purpose is to establish assurance that facilities named in a regulatory filing (e.g. DMF, NDA, ANDA) are capable of doing what they said in the filing and that the information submitted is accurate and complete.

- Readiness
- Conformance with Application
- Data Integrity
POST-APPROVAL

- Covers products already marketed under an approved application
- To monitor for changes in production and controls that occurred AFTER approval (generally at least 6 months after)
- Scheduled based on recommendations and risk
- What is covered may be based on PAI findings and past history

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SURVEILLANCE

- Surveillance = A “routine” GMP inspection
- Applies equally to domestic and international
- The focus is SYSTEMS
THE 6 SYSTEMS = THE GMPS

- Quality
  - GMPs – Organization and Personnel
- Facilities/Equipment
  - GMPs – Buildings, Facilities, Equipment
- Materials/Components
  - GMPs – Components and Container/Closures
- Production
  - GMPs – Production and Process Controls
- Packaging/Labeling
  - GMPs – Packaging and Labeling
- Lab Controls
  - GMPs – Laboratory
FOR-CAUSE INSPECTIONS

- Anything other than a PAI, Post-Approval or Surveillance inspection
- To investigate a specific problem
  - NDA Field Alert report
  - Recall
  - Complaint
  - Adverse events
- Focus is on something *specific*
FDA'S INSPECTION AUTHORITY

FDA has the authority to inspect all companies that manufacture, process, pack or hold any FDA-regulated products for the US market. This includes contract service providers (e.g. labs), animal test facilities, drug substance manufacturers, product manufacturers, packagers, warehouses, shippers (e.g. FedEx), and clinical study sponsors, facilities, investigators and Institutional Review Boards.
FDA has no legal authority outside of the United States. However, they can prohibit products from being imported into the US.

Since today’s commerce is global, FDA now seeks to inspect BEFORE the border. You can say “no” … but then FDA can say no to your product coming into the US.
FDA APPLIES ITS US AUTHORITY IN EX-US INSPECTIONS

- US law says FDA may inspect records, files, papers, processes, controls and facilities bearing on whether drugs are adulterated or misbranded and that FDA is permitted to have access to and to copy and verify such records.

- In the US, FDA inspections DO NOT require advance notice, a warrant or consent. With the cooperation of foreign government officials and regulatory agencies, FDA is now applying the same standard outside of the US.
DON’T SAY NO

- In the US, it is a _criminal offense_ to refuse an FDA inspection.

- The law says FDA may conduct inspections:
  - At reasonable times
  - Within reasonable limits
  - In a reasonable manner
  - With reasonable promptness

- If you say “no”, FDA can say no to your products.
NOT FDA AUTHORITY

- Financial Data
- Sales Data
- Pricing Data
- Personnel Data (other than qualifications)
- Records pertaining to the practices of medicine or pharmacy (unless directly connected to an Application or an “outsourcing” compounding pharmacy per the Compounding Quality Act of 2013)

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INSPECTIONAL TEAMS

- FDA may utilize a team approach
- Lead Investigator
- Other Investigators
- Chemistry
- Micro
- Engineering / facilities
- Formulations
FDA PREPARES A PLAN BASED ON

- Previous Establishment Inspection Reports (EIRs)
- Previous 483s observations, Warning Letters, responses and commitments
- The company’s website, product literature, press releases, products, etc.
- Applications, DMFs, Complaints, ADEs, Recalls, FARs, etc.
PREPARATION MATERIALS

- Filings - NDAs, ANDAs, DMFs
- Regulations - GMPs, other as applicable
- FDA Compliance Programs
- Investigations Operations Manual (IOM)
- Guidance documents (FDA, ICH, PIC/s. WHO, etc.
- USP
FILINGS

- If FDA is there to audit per a DMF, NDA, ANDA or other filing, you should assume the Investigator has reviewed the filing and may even have copy with him/her.

- You should also have a copy available during the inspection - especially CMC information.

- You should be very familiar with the content of the filing, and have supportive documentation readily available and personnel equipped to answer questions regarding the filing.
COMPLIANCE PROGRAM GUIDANCE

Found on FDA's website at:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm

- 7346.832 Pre-Approval Inspections
- 7346.843 Post-Approval Inspections
- 7352.002 Unapproved New Drugs
- 7352.004 In Vitro MD/MV, Generic Drugs
- 7353.001 Post-Marketing ADE Reporting
- 7356.002 Drug Manufacturing Inspections

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7356.002A Sterile Drugs
7356.002B Drug Re-packagers/Re-labelers
7356.002C Radioactive Drugs
7356.002E Compressed Medical Gasses
7356.002F Active Pharmaceutical Ingredients
7356.002M Licensed Biological Drugs
7356.002P Positron Emission Therapy Drugs
7356.008 Drug Quality Sampling and Testing
FDA “GUIDES TO INSPECTIONS OF”

Found on FDA’s website at:
http://www.fda.gov/iceci/inspections/inspectionguides/default.htm

- Lyophilization of Parenterals (1993)
- Micro Pharmaceutical QC Labs (1993)
- Pharmaceutical QC Labs (1993)
- Validation of Cleaning Processes (1993)
- Dosage Form Drug Manufacturer cGMPs (1993)

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Oral Solid Dosage Form Pre and Post-Approval Issues (1994)

Sterile Drug Substance Manufacturers (1994)

Topical Drug Products (1994)

Oral Solutions and Suspensions (1994)

Computerized Systems in Drug Establishments (1983)

Foreign Pharmaceutical Manufacturers (1996)
ICH GUIDES COMMONLY USED DURING FDA GMP INSPECTIONS


- Q1A-F, Stability
- Q2, Analytical Validation
- Q3A-D, Impurities
- Q4-Q4B and Annexes, Pharmacopoeias
- Q5A-E, Biotech Product Quality
- Q6A-B, Specifications
ICH GUIDES COMMONLY USED DURING FDA GMP INSPECTIONS

- Q7, GMP for APIs
- Q8, Pharmaceutical Development
- Q9, Quality Risk Management
- Q10, Pharmaceutical Quality System
- Q11, Development and Manufacture of Drug Substances
- Q12, Life Cycle Management
FDA “GUIDANCE FOR INDUSTRY”

Found on FDA’s website at:

- Quality Systems Approach to Pharma cGMPs (2006)
- Investigating OOS Test Results (2006)
MORE “GUIDANCE FOR INDUSTRY”

- Process Validation: General Principles and Practices (2011)
- Non-Penicillin Beta-Lactam Drugs: A cGMP Framework for Preventing Cross-Contamination (2013)
- Analytical Procedures and Methods Validation for Drugs and Biologics (2015)
INVESTIGATIONS OPERATIONS MANUAL (IOM)

Found on FDA’s website at:
http://www.fda.gov/iceci/inspections/iom/default.htm

- Primary source of information regarding Agency administrative and general procedures for FDA Investigators
- Chapters on Administration, Regulatory, Sampling, Inspections, Imports, Recalls and Investigations
- Also includes an FDA ORA Directory
THE INSPECTION BEGINS

- May be un-announced
- FDA says if operations are going on, they are subject to inspection
- FDA Credentials (picture ID, badge)
  - Cannot photocopy
- Notice of Inspection (FDA 482)
  - Not required for foreign inspections
- Introductions to the most senior level person
KICK OFF MEETING

- Introductions of inspection team
- Introductions of firm management
- Lead Investigator should state purpose of inspection
- General agenda for the inspection
- Company presentation
COMPANY PRESENTATION

- Have a hard copy to hand out
- Include *current* overall organization chart(s) with names and titles
- Present an overview of the company, but be brief
- List products
- Overview of the site and operations
- Regulatory history - audits by other agencies
- If a follow-up to a previous audit, a list of commitments and status of CAPA
PLANT TOUR

- It is typical for an inspection to start with a tour of the overall site operations. Most tours follow the process from incoming materials through development, production, packaging, labeling, testing (includes stability) and finished product warehousing.

- If you see something wrong, especially if FDA notes it, can you address it?
SETTING THE TONE

- Investigators should be impressed with your company from the moment they arrive on site.
- Is gate house responsive?
- Is reception responsive?
- Is company professional, organized, responsive, cooperative.
- Is there a place for the FDA team to work?
THE 6 SYSTEMS = THE GMPS

- Quality
  - GMPs - Organization and Personnel
- Facilities/Equipment
  - GMPs - Buildings, Facilities, Equipment
- Materials/Components
  - GMPs - Components and Container/Closures
- Production
  - GMPs - Production and Process Controls
- Packaging/Labeling
  - GMPs - Packaging and Labeling
- Lab Controls
  - GMPs - Laboratory
STABILITY IS A WINDOW INTO EVERY QUALITY SYSTEM

- Quality
  - GMPs – Organization and Personnel
- Facilities/Equipment
  - GMPs – Buildings, Facilities, Equipment
- Materials/Components
  - GMPs – Components and Container/Closures
- Production
  - GMPs – Production and Process Controls
- Packaging/Labeling
  - GMPs – Packaging and Labeling
- Lab Controls
  - GMPs – Laboratory
Credit for these next few slides for discussion regarding GMPs and stability operations goes to Michael Barron, one of our industry’s stability gurus.

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TOP REASONS FOR RECALLS

- Cross contamination
- Lack of sterility assurance
- Subpotency
- Failed dissolution specs
- *Stability data fails to support expiration dating*
- Particulate matter
- cGMP deviations
TOP REASONS FOR NON APPROVALS

- Lab controls
- Process validation
- *Stability issues*
- Process controls
- Equipment cleaning
- Application deviations
AUDIT QUESTIONS

1. I was reviewing the batch record and want to trace samples from lot # abc123 through your facility to the final test report.

2. I was reviewing your submission and want to trace the test results for lot # abc123 at the 12 month timepoint through your facility back to the batch record.
AUDIT ANSWERS

1. “We store the right quantity of the right lots in the right storage conditions, the first time, every time according to an approved protocol.”

2. “Samples are stored in well controlled, continuously monitored, qualified storage chambers under a perpetual inventory system”

3. “We pull the right quantity of the right lots from the right storage conditions at the right time, every time”
Question:

- What guiding principle does one use to build systems and procedures for a stability storage operation?

Answer:

- Sample Traceability...
ACHIEVING TRACEABILITY

Achieving Sample Traceability

- **CAPA**: common and required
- **Quality Systems**: e.g. Quality by Design, Lean Six Sigma, Total Quality Management, etc. ... common but none specifically required
- **Common Sense**: not necessarily common, but required
- **Poka-Yoke**: not common in pharma, but principles are required
  - Mistake proof, reduce or eliminate human error, fail-safe

http://www.mistakeproofing.com,
http://www.campbell.berry.edu/faculty/jgrout/pokayoke.shtml
POKA-YOKE

Poka-yoke (ポカヨケ) is a Japanese term that means "mistake-proofing". A poka-yoke is any mechanism in a lean manufacturing process that helps an equipment operator avoid (yokeru) mistakes (poka). Its purpose is to eliminate product defects by preventing, correcting, or drawing attention to human errors as they occur. The concept was formalized, and the term adopted by Toyota. More broadly, the term today is used to any behavior-shaping constraint designed into a process to prevent incorrect operation by the user.
POKA-YOKE

What are at least three mistake-proof devices in this picture?

Hints:
- You can’t necessarily see them
- Uses unleaded gas
POKA-YOKE

1. Filling pipe insert keeps the larger leaded-fuel nozzle from being inserted.

2. Gas cap tether does not allow the motorist to drive off without the cap.

3. Gas cap is fitted with ratchet to signal proper tightness and prevent over-tightening.
Many gas pumps are equipped with hose couplings that break-away and quickly shut-off the flow of gasoline.
MISTAKE PROOFING STABILITY

- Protocol generation and approval
- Determining quantities for storage
- Sample set-up
- Stability pull calendar
- Sample pulls
- Inventory
- Storage chamber qualification
- Storage chamber monitoring
- Redundant systems

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START WITH SOPS

- Marriage of compliance and common sense
  - Clear and specific (sample traceability assured)
  - Risk management considered (applying wisdom taught by experience)
- Encourage the right behaviors, do not just try to prevent the wrong ones
  - Mistake-proof principles applied
  - Fail-safe provisions considered
PROTOCOL GENERATION

- Supporting documentation identifying:
  - Regulatory status (US, EU, Global, R&D, Marketed, Rx, OTC, Large Molecule, Medical Device, etc.)
  - Batch selection, batch numbers
  - Dosage forms, delivery systems, packaging
  - Storage conditions and timepoints
  - Test methods and specifications
  - Sample requirements
  - Bracketing and/or matrixing rationale
  - Statistical evaluation
- Required signatures, change control

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DETERMINING STORAGE QUANTITIES

- Number and type of tests
- Number of samples per test
- Dosage form
- Packaging (unit dose, multi-dose, primary, secondary)
- How shared within labs (sub-dividing, multiple analysts, microbiology, etc.)
- Available supply and cost of materials
- Storage conditions
- Number of timepoints per storage condition
- Surplus pulled per timepoint
- Back-up/retention samples
SAMPLE SET UP

- Define storage labeling
  - Place on bin or box for storage?
    - almost always yes
  - Place on individual samples?
    - possibly, but adds a potential variable of a leachable in some cases
    - be careful not to “over-label”
  - Pre-label timepoint and/or condition on each sample?
    - possibly, but same issue as above and does the extra work add real value?

- Prevent co-mingling with other products or labels
  - Staging area clearance
  - Prevent co-mingling with other lots
    - One lot per staging area at a time

- Pre-storage approval
  - Second person verifies count and labeling

- Storage verification
  - Second person verifies placement of correct bins into chambers
PULL CALENDAR

- Well controlled, consistent, SOP driven
  - define month and/or year
  - define pull window(s), if any
  - account for weekends and holidays
- Manual or electronic?
  - both are acceptable but both should be “mistake-proof”
  - electronic is preferred in most circumstances due to better controls and it’s validatable
- input verification
- controlled access
- change control
- Regular “pick-list’, e.g. daily, weekly, monthly
SAMPLE PULLS

- Prevent co-mingling of same lot, different storage conditions
  - One lot, one storage condition at a time
- Labeling samples after the pull
  - Individual samples prevents mix-ups downstream in sample handling areas and lab
  - zip-loc bags, etc. for holding multiple samples from same lot and storage condition
  - both?....recommended
- How are they transferred to the laboratory?
  - Same building, different building, different site, contract lab?
  - Time in transition?
  - Temperature conditioning/monitoring required?
  - How do you protect from courier taking lunch or running errands with your samples?
INVENTORY CONTROL

- Receiving records
- Record for each upon setting study
  - Lot number, strength, and package configuration
  - Storage condition (chamber ID for sure and possibly shelf number)
  - Storage position (upright, inverted, random, etc.)
- Transaction history
  - Set, pulls, transfers, in/out
- Physical inventory
  - Periodic
  - Statistical sample Vs. complete inventory
- Bar codes or RFID?
FACILITIES

- Assess major risks
  - Flooding
    - From above (roof leaks)
    - Fire suppression equipment (know your local fire code)
    - Floor up (water main break, local bodies of water)
  - Hazardous weather
    - Hurricanes and/or tornadoes, Earthquakes, Snow and/or ice storms
  - Explosions
- Control access
  - Physical Security
    - security guards, access codes, keypads, keyed locks
  - Electronic Security
    - CCTV, motion detectors, swipe cards
- Preventative maintenance
CAN WE MISTAKE PROOF?

- **Power**
  - Separate electrical grid supply (expensive)
  - Generator for electrical power interruptions
    - Routine testing - frequency? under electrical load or not?
    - Fuel supply - What kind? How much is enough?
  - UPS with battery back-up for computers and %RH transmitters

- **Water**
  - Redundant water feed (expensive)
  - Reserve water supply - (how much is enough?)
  - Emergency by-pass of water filtering/conditioning system
  - Monitoring the quality of the water supply
MORE

- Protect against data gaps produced by primary system
  - Monitoring the monitoring system
    - Human intervention, e.g. security guards after hours
    - Automated system monitoring computer functions
  - Secondary?, Tertiary?
    - Back-up computers, UPS with battery
    - Secondary systems, e.g. data loggers or circle chart recorders
    - Automated phone/pager/e-mail/text notification 24/7/365
    - Secondary data sets, what do you do with them?

- Chamber space
  - How much excess capacity is enough?
  - At which storage conditions?

- Disaster recovery plan
  - Emergency contacts - readily accessible
  - Off-site storage?
CHAMBER QUALIFICATION

- **DQ** (Design Qualification)
  - e.g. User requirements

- **IQ** (Installation Qualification)
  - e.g. Equipment specifications, critical components identified, utilities requirements including power supply, water supply, the operating environment, and weight bearing capacity of flooring, maintenance accessibility, checklist of installation activities.

- **OQ** (Operation Qualification)
  - e.g. What you plan to do laid out in stepwise format to validate functionality

- **PQ** (Performance Qualification)
  - e.g. monitoring system data review, chamber maintenance and repair log review

- Qualification Vs validation
DOING IT

- Have user defined requirements
  - Full range of temperature and %RH vs. set point only
- Temperature/Humidity mapping
  - Duration of data collection
  - Operating environment
  - Door open test
  - Power down and re-start
  - Empty (with shelving)
  - Simulated full
- Approvals before and after execution of protocols
- Compose an executive summary, or cover letter, that includes:
  - Location of continuous monitoring devices based on data evaluation
  - “All specifications were met”
  - “This chamber is approved for use”
DOING IT AGAIN?

- Remapping
  - Variability across the industry, some examples include:
    1. Not unless a critical component changes or the set-point changes
    2. Annual; full and empty chamber
    3. Annual with current load
    4. Continuous mapping with multiple sensors
    5. Reduced remapping after a significant body of data supports it
  - Imperative that you have a procedure and documented evidence you follow it
- Performance history review
  - Equipment repair and adjustment log
  - Monitoring system data review
MONITORING

- Determine frequency of data capture
  - Computerized systems (every few seconds)
  - Electronic data loggers (every few minutes)
  - Circle chart recorders (continuous?)
  - Combinations of the above

- Temperature, %RH, and Light specs
  - Define rounding rules: e.g. +/- 2.0°C Vs. +/- 2.5°C

- Calibration of monitoring devices
  - Frequency
    - start with manufacturer recommendation
    - reduce or increase frequency based on data
MORE

- Alarm ranges
  - Determine degree and duration of excursion before alarms activate
    - Hi and Low
      - typically +/- 2°C; +/- 5%RH for ambient condition and above
      - typically +/- 3°C for refrigerated and +/- 5°C for frozen
  - Alarm delays between 10 and 60 minutes for computerized systems are typical
  - Up to 24 hours or more for circle chart recorders?
  - Hi-Hi and Low-Low
    - consider zero tolerance for phase changes i.e. frozen or thawed
    - consider >10°C over setpoint triggers immediate alarms

- Action procedures
  - Responsiveness (“who knows what when and when does who do what?”)
  - To move or not to move samples, that is the question
  - Data gaps in monitoring system (what is your tolerance?)

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DATA INTEGRITY ISSUES

- Not recording activities contemporaneously
- Fabricating acceptable test results
- Discarding data
- Running non-documented samples
- Data too good to be true
- Stability failures not reported
- No raw data (sample weights, standards preps, sample solution preps, etc.)
INSPECTION DO’S AND DON’TS

- Be prepared
- Be honest
- Answer the question, but don’t volunteer
- Never say “never”
- Don’t argue
- Be positive and confident
- Don’t guess or speculate
- Communicate clearly
- Take corrective actions
MORE

- Avoid extraneous conversations and discussions regarding issues.

- Escort the auditors at all times.

- Provide a neutral workplace for the conduct of interviews and a place to review documents. If possible, this should be away from operations and should not require access through operational areas.
MORE

- If you do not know the answer to a question, **DO NOT SPECULATE!** Tell the auditor you do not know the answer, note the question and tell the auditor you will provide a timely answer to the question.

- If you do not understand the question, ask for clarification before answering it. It may be helpful to repeat the question as you understand it and have it acknowledged by the auditor before answering.
Either have on site or know where to quickly acquire the following:

- Current organizational charts
- Development reports
- Method validation records
- Process validation records
- Computer validation records
- Equipment qualification records
- Laboratory raw data
- SOPs
- Employee training records
- Complaint, investigation and failure files
- IND, NDA, ANDA and other regulatory filing documents
DEVELOP AN INSPECTION PROCEDURE

- One of the main keys to success of surviving an FDA inspection is PREPARATION.

- Have an SOP that addresses basic assignments, locations, Company policies, etc.

- Train upon, practice and audit against this SOP.
A PROCEDURE SHOULD CONTAIN

- Receptionist responsibilities
- Conference room locations
- General conduct for employees
- How you would like to handle the inspection
- List of key contacts
- Safety and other rules for auditors
- Procedures for tours
AND

- Attendance at daily debriefings
- Procedures for providing documents
- Accessibility of auditors
- Use of cameras
- Address 2nd and 3rd shifts and weekends
- Use of computers
- Procedures for affidavits (FDA Form 463a)
DOCUMENTS

- Have them available
- Have them organized
- Originals vs copies, electronic vs paper
- Confidentiality
- Make duplicates of any record photocopied for the Investigator
INTERVIEWS

- Have the “right” person
- Always be clear
- You don’t need to volunteer information
- If approached outside of work, no obligation to speak with an Investigator
AFFIDAVITS

- An affidavit is a “statement of purported facts,” aka, a “confession”
- If an FDA Investigator presents you with an affidavit:
  - DON’T SIGN IT
  - DON’T INITIAL IT
  - DON’T READ IT
  - DON’T LISTEN TO THE INSPECTOR READ IT TO YOU
  - THERE IS **NO LEGAL REQUIREMENT** FOR ANYONE HAVING TO SIGN AN AFFIDAVIT
SAMPLES

- Should FDA want to collect samples, they will issue a receipt (FDA form 484)
- You can charge
- You should sample too
- You should ask for results if tested
RECORDING DEVICES

- Generally, the use of recording devices should be discouraged.

- However, in a spirit of cooperation, the Company should determine its policies regarding the use of recording devices and include the policies in the inspection SOP.
PHOTOGRAPHS

- FDA considers photography to be an allowed practice during inspections.
- Pictures should not have extraneous information in the background.
- Limit the scene to the information requested; similar to the logic for limiting the answering of questions.
- Photographs of the same scene from the same angle as the Investigator should be taken by the company audit team as well.
WRAP-UP MEETINGS

- Confirm the Company’s commitment to compliance.

- Have appropriate management from the organization and all individuals who directly participated in the inspection attend the meeting.

- Take detailed notes of the comments made by all parties at the meeting.

- Ask questions about any observations or findings which are not clear. Don’t be afraid to discuss the observations for clarity and accuracy.
WRAP-UP MEETINGS

- To the degree you can, take corrective actions immediately and provide documentation of the correction to the Investigator.

- You do not need to admit that any observations or findings are a violation of law.

- Remain calm, attentive and responsive. Remember, that the FDA auditor will write a report which will draw conclusions about the tone and attitude of your communication.
THE DREADED 483

- FDA may issue a Form 483
- Think about who you want at the close-out meeting
- Know to whom the 483 should be issued
- Seek corrections of any mistakes on it
- Seek notations of observations addressed
- Note confidential information
- Make sure you are clear about each observation
- You do not have to make commitments at the close out meeting
- Always respond in writing – in NMT 15 days!
RESPONDING TO A 483

- A response can mitigate FDA’s next action (e.g., a Warning Letter)
- Be very specific with facts
- Include documentation
- Demonstrate management awareness, support (including financial) and commitment
- Can disagree and/or supply new information to overcome the observation
- Look bigger picture (on “systems,” impact on things not covered during inspection)
RESPONDING TO A 483

- Develop action plans, CAPA
- Address each observation separately
- Note whether you agree or disagree
- Be realistic, don’t promise what you cannot deliver
- Provide timelines
- Consider getting outside assistance
THE EIR

- After the inspection, the Investigator prepares an Establishment Inspection Report -- This can take some time and be a team effort
  - Investigator makes a recommendation
  - Report reviewed by management and Compliance
  - NAI - No action indicated
  - VAI - Voluntary action indicated
  - OAI - Official action indicated
COMPLIANCE REVIEW

- CDER Compliance will review the EIR, the 483, the recommendations and the 483 responses and consider next steps
- Remember that many eyes may see these documents, but these people were not at the inspection and have never been in your facility
- Your responses are your opportunity to articulate your side of the story
OFFICIAL ACTION

- Untitled letter
- Warning letter
- Consent Decree
- Seizure, injunction, prosecution
IS IT TOO LATE?

- 483 in March/April
- Responses in April/May/July
- Warning Letter in August
- Response in September
- Untitled Letter in November
- Response in February
- Meeting with in FDA March
- FDA re-inspection in September

THAT’S 18 MONTHS
COMMUNICATE WITH FDA

- Respond to the FDA communications in a timely manner (even if partial)
- Recognize the bigger picture
- Present a plan with goals, objectives, timeframes
- Be specific
- Take significant actions (products, facilities, personnel)
- Recognize it’s NOT business as usual
“TAKE HOMES” FROM THE FDA

- You cannot remediate while business as usual ... something has to give
- Shut down is a good move
- Product reduction is a good move
- 100% review of batches, investigations, etc. is a good move
- Have rationale behind decisions (e.g. avoiding drug shortages)
- Keep FDA updated, but not overwhelmed
MORE “TAKE HOMES”

- Photos are helpful
- Culture is very difficult to change
- Avoid creation of a fearful environment
- The best Q Systems recognize mistakes do happen, but implements a safe environment in which to deal with them
- Third party oversight/assessment can be helpful
- FDA expects “significant and positive change”
THE FDA RE-INSPECTION

- FDA will be back!
- Work with FDA on timing
- Remember: “The proof (of the pudding) is in the eating”
- Have evidence of significant and positive change
- Demonstrate management support, involvement, commitment
- Establish the role of the consultant(s)
IMPACT OF NEGATIVE INSPECTIONS

- Recalls
- Export restrictions
- No new approvals
- Negative press
- Merger and acquisition problems
- Actions by other regulatory agencies
- Further legal actions
- Lots of time delays
WHAT'S THE ANSWER?

Successful FDA inspections are certainly part of the answer.
TODAY

- The focus today has been FDA pharmaceutical GMPs with some particular emphasis on stability
- FDA is a law enforcement agency
- One tool is inspections
- We’ve discussed types of inspections, Quality Systems, FDA resources, and some do’s and don’ts
- I’ve shared thoughts on implementing operational excellence in stability
- Now some closing thoughts
HOW DID WE GET TO “QUALITY SYSTEMS”?

- ICH Q10 is all about Quality Systems
- The US 1906 Pure Food and Drug Act was the “birth” of today’s FD&C Act and much of today’s global pharma regulations
- But what about GMPs specifically?
- How did we get to Quality Systems?
DRUG GMPS ARE NOT NEW!

- FDA published the first pharmaceutical GMP regulations codifying what the law required in 1963
- The last MAJOR “rewrite” of the GMPs was 1978 and the 1978 GMPs are still those of today
THERE HAVE BEEN SOME UPDATES

- 1986 – added definition of gang printed labeling
- 1995 – minor tweaks regarding contamination prevention
- 2008 – some tweaks throughout the GMPs including clarification re GMPs in Phase I, but not a “rewrite”
AND MORE “GXPS” HAVE COME ALONG

- 1975 - Part 226, Type A Medicated Articles

- 1975 - Part 606, Blood and Blood Components

- 1976 - Part 225, Medicated Feeds

- 1979 - Part 58, Good Lab Practices
AND ...

- 1986 - Part 110, Human Foods
- 1996 - Part 820, Device Quality Systems
- 1999 - Part 216, Pharmacy Compounding
- 2001 - Part 1271, Good Tissue Practice
- 2007 - Part 111, Dietary Supplements
SO NOW WE REFER TO “QUALITY SYSTEMS” - WHY?

- In 1990, Congress passed the Safe Medical Devices Act which said FDA may “prescribe GMPs for devices”
- And in 1996, FDA published 21 CFR Part 820 - the device GMPs - the “Quality System Regulations”
  - A recognition that the quality of the finished product depended on design controls, verification and validation
  - A recognition that risk must be managed
PHARMA PLAYS CATCH UP

- 2001 - FDA adopts ICH Q7 - GMPs for APIs
- 2002 - FDA publishes “Pharmaceutical GMPs for the 21st Century” with a “goal to bring the Quality Systems approach to pharmaceuticals”
  - Introduces “design controls,” Quality by Design and risk consideration to pharmaceutical development
2006 - A SIGNIFICANT YEAR

- ICH Q8: Pharmaceutical Development
  - Quality Target Profiles
  - Critical Quality Attributes
  - Design Space Concepts
- ICH Q9: Quality Risk Management
  - A driving principle of the GMP initiative
- And FDA’s Guide re: Quality Systems Approach to Pharmaceutical CGMP Regulations
  - Encourages continuous improvement
  - A bridge between 1978 GMP regulations and today’s “Quality Systems” expectations
AND IT CONTINUED ...

- 2009 - ICH Q10: Pharmaceutical Quality System

- 2011 - FDA publishes Q8, Q9 and Q10 Q&As

Let’s look at a couple ........
COMPLIANCE WITH Q10

Q: How does a company demonstrate implementation of a PQS in accordance with ICH Q10?

A: When implemented, a company will demonstrate the use of an effective PQS through its documentation, its processes, its training/qualification, its management, its continual improvement efforts, and its performance against pre-defined key performance indicators.
Q: How should implementation of the design space be evaluated during inspection of the manufacturing site?

A: Inspection should verify/assess that manufacturing operations are appropriately carried out within the design space ... and within the company’s change management system.
COMPLIANCE WITH Q10

Q: How will systems-related inspections differ in an ICH Q8, Q9 and Q10 environment?

A: The inspection will process will remain similar... ... inspections will have greater focus on how the PQS facilitates the use of quality risk management ... design space ... change management
GMPS ARE NOT NEW

- For the US FDA, the importance of adherence to good manufacturing practices and their direct impact on the quality of the finished drug product was recognized in 1938. That’s 77 years ago!
In a July 2012 letter responding to a Congressional inquiry regarding drug shortages, FDA wrote:

- “There have been no recent changes to the cGMP standards or inspection processes that would substantially impact compliance for (drug) product manufacturing.”

- The number of WLs to firms for manufacturing quality deficiencies remains essentially the same year after year.
WHAT’S THE SOLUTION?

- ISO certification?
- Baldridge awards?
- Lean Six Sigma?
- Green and black belts?
- Fit for Purpose?
- Plan, Do, Check, Act?
- Right First Time?
- Poka-Yoke (mistakeproofing)
- Total Quality Management?
HOW ABOUT - FOLLOW GMPS!

- WLs are still being issued for basic GMP violations
- ICH Q10 says:
  - “Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements.”
  - “ICH Q10 is not intended to create any new expectations beyond current regulatory requirements.”
FDA’S TOP 10 DRUG CITES FOR 2014

- Deficient QC Unit
- Inadequate lab controls
- Failure to investigate problems
- Not following procedures
- Inadequate procedures
- Inadequate process validation
FDA’S TOP 10 DRUG CITATIONS FOR 2014

- Inadequate testing before release
- Poor equipment cleaning and maintenance
- Employee training issues
- Incomplete batch records

These are the same issues every year!
SOME NEWER INITIATIVES

- New laws and authority
- New inspectional approaches
- Quality metrics reporting
- Increased focus on data integrity
- More risk-based decision making
- More foreign inspections and expected parity with domestic firms
- More controls over imports
NEW INSPECTION APPROACHES

- Cite the negatives and the positives
- More question-based inspections to collect data and standardize
- More flexibility regarding when to inspect and what to inspect
- More use of “scoring” inspectional findings
- More coordination between HQ and Field, reviewers and inspections
AMENDMENTS TO THE LAW

The FDA Safety and Innovation Act (FDASIA) of 2012 added to the law:

..... GMPs includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of establishing the safety of raw materials used in the manufacture of drugs .....
Also added that “FDA may require the submission of any records or other information that FDA may inspect under the FD&C Act in advance or in lieu of an inspection by requesting the records or information from a person who owns or operates an establishment engaged in the manufacture of a drug.”
VERY CLEAR:

- Inspection can include data to FDA in advance or in lieu of an inspection.
- The drug is adulterated if it has been manufactured, processed, packed or held in a facility the owner of which delays, denies or limits an inspection or refuses to permit entry or inspection.
QUALITY METRICS

- New reporting by the Q Unit
  - Lot acceptance rate
  - Product quality complaints
  - Invalidated OOS investigations
  - Timeliness of APRs
A recognition by FDA that quality metrics are used throughout our industry to monitor quality control systems and processes and drive continuous improvement.
FDA GOALS

These metrics can also be used by FDA:

- To help develop compliance and inspection policies and practices
- To allow risk-based inspection scheduling of drug manufacturers
- To improve FDA’s ability to predict and possibly mitigate future drug shortages
- To encourage the industry to implement state-of-the-art, innovative quality management systems
QUALITY METRICS

- 2002 - Pharmaceutical GMPs for the 21st Century: A Risk Based Approach
- Encourages the implementation of a modern, risk based pharma quality assessment system.
- To allow the production of high quality drugs WITHOUT extensive regulatory oversight.
FDA’S CRITERIA FOR METRICS

- Objective
- Subject to inspection
- Valuable in assessing the overall state of and commitment to quality
- Avoid undue reporting burden
- Not all inclusive
- Demonstrate senior management’s commitment to a culture of quality
QUALITY METRICS

- Program to allow risk based scheduling
- Risk based scheduling to help FDA focus resources on facilities that present the greatest risk to consumers
- Factors:
  - Compliance history
  - Record, history and nature of recalls
  - The inherent risk of the drug
  - Whether inspected by a foreign government
FDA’S INTENT

- To further develop risk based inspection scheduling
- To identify risk for drug supply disruption
- To improve efficiency and effectiveness of inspections
- To improve evaluation of drug manufacturing and control operations
- To allow DECREASED surveillance inspections
- To provide a basis for using risk principles with respect to post-approval manufacturing changes
CONFIDENTIALITY

- FDA does not intend to publicly disclose quality metric data submissions
ESTABLISHMENTS COVERED

- Those required to register
- API and finished dosage form
- Approved under FD&C 505 (NDA/ANDA) or PHS Act 351 (Biologic)
- Marketed per OTC monograph
- Marketed unapproved
- Includes contract labs, sterilizers, packagers, and others
Quality Control Unit will be best positioned to compile the reports for submission.
METRICS

- Lot acceptance rate: rejected lots divided by lots attempted
- Quality compliance rate: quality complaints divided by number of lots
- Invalidated OOS rate: OOS invalidated divided by total OOS divided by total tests performed
- APR on time rate: completed within 30 days of due date
OPTIONAL METRICS

- Quality culture: senior management engagement support, facility improvements, resources, authority to implement

- CAPA effectiveness: training CAPA vs process re-design and re-development CAPA

- Process capability/performance: application of statistics to data collected over time
WHEN?

- First reporting period 1 October 2016 through 30 September 2017
- FDA intends to request data on a quarterly basis
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