FDA INSPECTIONS

Effective Preparation for a Positive Outcome

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GRx+Biosims™
Generic + Biosimilar Medicines Conference

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Biosimilars Council
A Division of the Association for Accessible Medicines

Objective and Agenda

OBJECTIVE:

- How to prepare for a successful FDA Inspection

AGENDA:

- FDA
  - Legal Basis, Oversight, Escalation and Enforcement, Outcomes
- The Inspection
  - Preparation, Planning, the Investigators, Etiquette, Roles and Responsibilities, Interviews, Responding to Questions
- Final Recommendations

FDA – Legal Basis

WHY SHOULD YOU FOLLOW cGMPs?

It's the LAW! – Food Drug and Cosmetic Act (FD&C)

- **501(a)(2)(b):** requires conformity with cGMP
  - "A *drug*…shall be *deemed to be adulterated* if…the ***methods*** used in, or the ***facilities*** or ***controls*** used for, the ***manufacture, processing, packaging***, or ***holding*** do not conform to or are not operated or administered in conformity with *current good manufacturing practice*…"
  - "to assure that such drug meets the requirements of this Act as to *safety* and has the *identity* and *strength*, and meets the *quality* and *purity* characteristics, which it *purports* or is *represented* to possess."
- **Codified in various sections of the Code of Federal Regulations**
- **Further expectations published in Guidances**

Scope of cGMPs

- Ingredients, APIs
- Finished dosage forms (manufacturers, laboratories, packagers)
  - OTC, Rx products, device, Biologics, Veterinary drugs, Study drugs (IND, etc.)

FDA – Oversight

WHAT are the routine types of FDA inspections? (Slight differences)

- Pre-Approval and Post-Approval
- Routine Surveillance/GMP (based on risk ~2-year cycle)
- For-Cause/Directed
- Other (Follow-Up Inspection, Pharmacovigilance, BE, etc.)

While similar, they have significant differences and focuses and require different preparation.

WHY does FDA Inspect?

- To ensure Quality System conformance to law (CFR) and cGMP
- …but really to ensure ***consumer safety and product efficacy***

WHAT can FDA review, and WHERE can they go?

- Anything (except Financials, Audit Reports, HR/personnel information (except training))
- Anywhere GMP activities are performed (utility spaces? offices?)

WHAT documentation can FDA take?

- Copies of any cGMP documents - Evidence

FDA – Escalation and Enforcement

REGULATORY ESCALATION PROCESS

- Inspection – Any objectionable conditions related to current Good Manufacturing Practices as required by the CFR:
  - "Form 483" Observations (remember 15 days)
  - Management Review/Discussion Items

- Compliance Review – If the citations raise immediate concerns about marketed product or if the firm's written response does not address the concerns, then increased advisory through potential legal action can be initiated:
  - Regulatory Meeting
  - Warning Letter or Untitled Letter (remember 15 days)
  - Import Alert
  - Seizure/Injunction
  - Consent Decree
  - Criminal Prosecution
  - Significant fines
  - Debarment
  - And more…

FDA – Outcomes

INSPECTIONAL OUTCOMES

- NAI – No Actions Indicated (no 483 issued)
  - *This is where you want to be!* – typically no written response unless Management Discussion Items; but don't let it go to your head
- VAI – Voluntary Actions Indicated
  - *Manageable, but you can do better!* - indicates written response and corrective actions were accepted; expect to receive Establishment Inspection Report (EIR) and corrective actions to be reviewed during subsequent inspection
- OAI – Official Actions Indicated
  - *This is not where you want to be!* – indicates potential regulatory escalation procedures

You MUST respond to 483's and Warning Letters within 15 days (for your response to be considered in FDA further action determination)

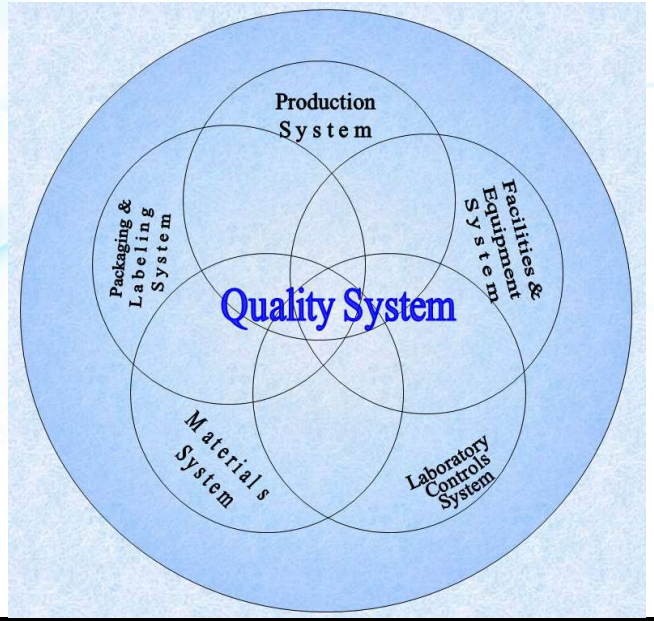
Inspection – Preparation

Successful inspections are a result of *good employees*, *STRONG SYSTEMS*, *knowledge* of regulations and what you do, *preparation*.

Working closely with Regulatory department to anticipate inspection timing and type.

6 SYSTEMS:

- Quality
- Production
- Facility & Equipment
- Laboratory
- Materials
- Packaging & Labeling



Inspection – Preparation

Highly recommend a periodic quality review/audit by an 3rd party

- Drive Quality Culture, Staff engagement, SME review
- System improvement opportunities; create a written plan (self-identified)
- Historical review and decision making, missed alerts
- Employee certifications

Inspectional focus areas that require review/preparation:

- Inadequate Investigations (always a frequent flyer)
  - Inadequate root cause (human error!); inadequate corrective action
- OOS Investigations
  - Inadequate justification for invalidation of data; stability OOS
  - No manufacturing review (Phase 2)

    https://www.fda.gov/media/71001/download
- Cross Contamination
  - Inadequate cleaning procedures; practices
  - Environmental monitoring – *objectionable microorganisms*

Inspection – Preparation

- FAR Reporting (and Recalls)
  - Failure to file; failure to file within three business days (no recall)
  - Stability failure at expiration

    https://www.fda.gov/media/114549/download
- Quality Agreements
  - Applies to API's, Finished drug products, Biological drug products
  - Comprehensive written agreement defining cGMP roles/responsibilities for all parties involved

    https://www.fda.gov/media/86193/download
- Sterile Products
  - Aseptic technique, environmental monitoring, equipment design

    https://www.fda.gov/media/71026/download
  - Inspection – particulate matter
  - See compliance program 7356.002A - Sterile Drug Process Inspections

    https://www.fda.gov/media/75174/download
  - New ISO standard on water systems (June 2019)

    https://www.iso.org/standard/73381.html

Inspection – Preparation

- Data Integrity (potential for AIP pathway)
  - ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate)
  - Trial injections (unreported product failures used as “system equilibration”)
  - Shared passwords; common log-ins, user permission levels (to make changes)
  - Audit trails (not activated; not reviewed)
  - Data Falsification - manipulation/deletion/etc.
  - Control (issuance/reconciliation) of paper records (BPRs, Forms, etc.)

    https://www.fda.gov/media/119267/download
- General GMP Topics
  - Complaints, Change Control, Annual Product Reviews, Validation (process, analytical methods, CSV, etc.), Equipment (qualification, calibration, PM), Training, Stability Program, and many more…

And never go down this road during an inspection….

- Refuse/Deny/Delay/Limit

  https://www.fda.gov/media/86328/download

Inspection – Having a Plan

Nothing replaces good judgment and preparation… *and good first impressions*! But….

- You must have a plan… investigators have one
  - Investigations Operations Manual (IOM) http://www.fda.gov/ICECI/Inspections/IOM/default.htm
  - The Quality System Inspection Technique (QSIT) https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/quality-systems
  - Compliance Program 7356.002 Drug Manufacturing Inspections https://www.fda.gov/media/75167/download
  - Inspection Guides
- The site must know what to do from initial contact through the end of the inspection, and after!
- The site must prepare and review each system of control, conduct mock inspections, train employees on interactions with FDA, and identify all SME's and inspectional roles and responsibilities.

Inspection – High Level Sequence

- FDA arrives at security desk (regular visitor sign-in procedure)
- Notification to plant leadership
- Escort Investigator(s) to inspection room
- Assemble inspection-room and back-room teams (predetermined)
- FDA presents credentials and issues 482 – Notice of Inspection
- Site should request to provide a prepared opening presentation
- "SWEEP TEAM" should run the tour route to ensure readiness (appearance, local manager availability, data boards, etc.)
- Initial documentation request list (since last inspection)
- The TOUR – first impressions
- FDA will perform detailed document, system, and process reviews
- Daily close-out meetings
- Final close-out meeting
  - Sample collection (484)
  - Affidavits
  - Did you get a 483? What to do? (corrective and preventive action + system review)

Inspection – The Investigators

- Each Investigator is different, so there is no *"absolute"* way to prepare, but you must prepare as best you can
- Investigators look for compliance to cGMP
- All Investigators have differences
  - Background – chemist, process/facility expert, microbiologist, etc.
  - Experience – trainee, seasoned Investigator, prior industry experience
  - Bias – research the Investigators when you learn their names (483's, seminars, etc.)
  - Different focus areas based on inspectional assignments (PAI, general GMP, etc.)
- During the Inspection you need to remember…
  - The Investigators may be friendly, but they are not your "friends"
  - They have a job to do. Treat them with respect, answer their questions fully, provide the requested documentation, but don't answer more or provide more than what was requested. Don't demonstrate how much you know….
  - Be **TRUTHFUL** and **HONEST** and build **TRUST**

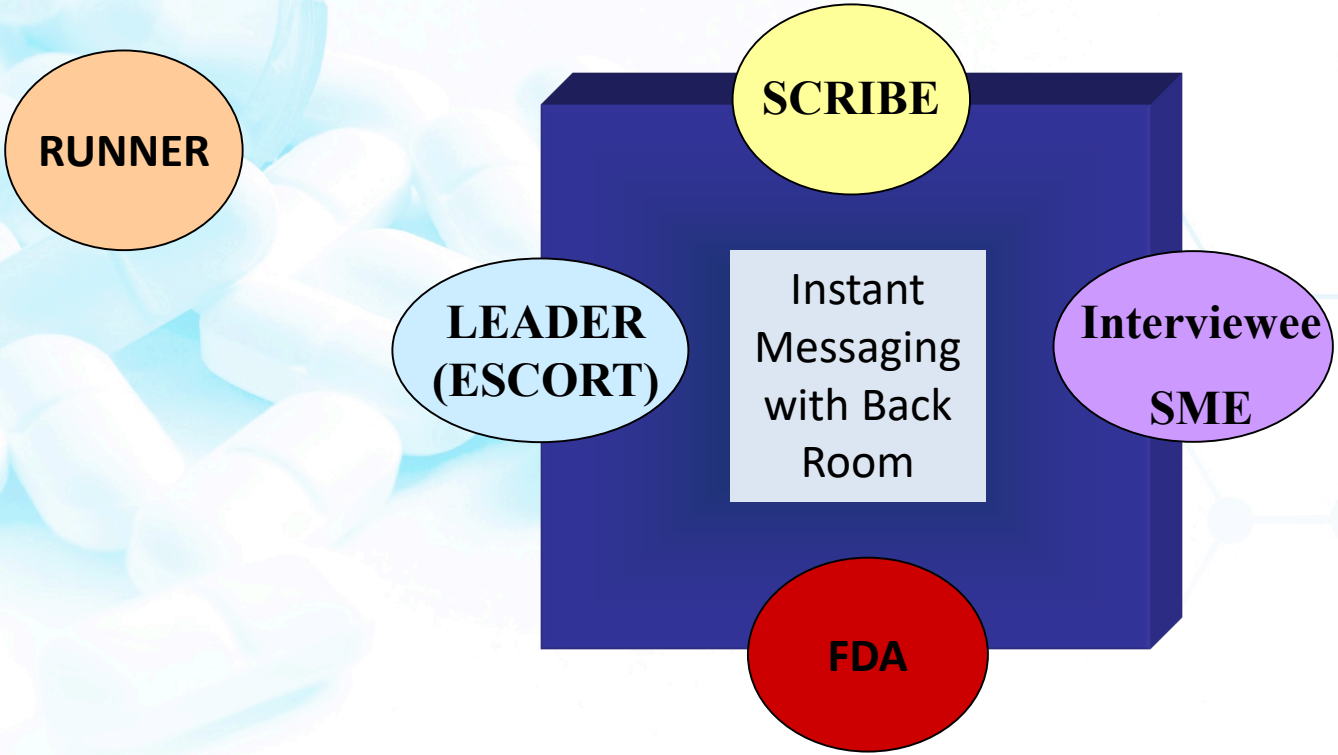
Inspection – Etiquette

- Present yourself well
  - Be genuine, natural, sincere, and be professional!
  - Proper attire, ID badge, etc.
  - FDA wants to hear from you (not from management!)
- Answer questions with confidence, speaking slowly and clearly
- Always speak in English
- Always be aware of your body language
  - Defensive posture – deceit
  - Nervous – deceit, lacking technical competence?
  - Appropriate eye contact – too much or too little?
- Keep a professional demeanor (don't argue – Investigators may be incorrect, but there is always the compliance review)
- Be attentive (no phones, computers, or other work)
- Be respectful (sit quietly if not in dialogue with Investigator)
- Do not bring food or gum into the inspection room
- Be aware of personal space (use two copies of documents)

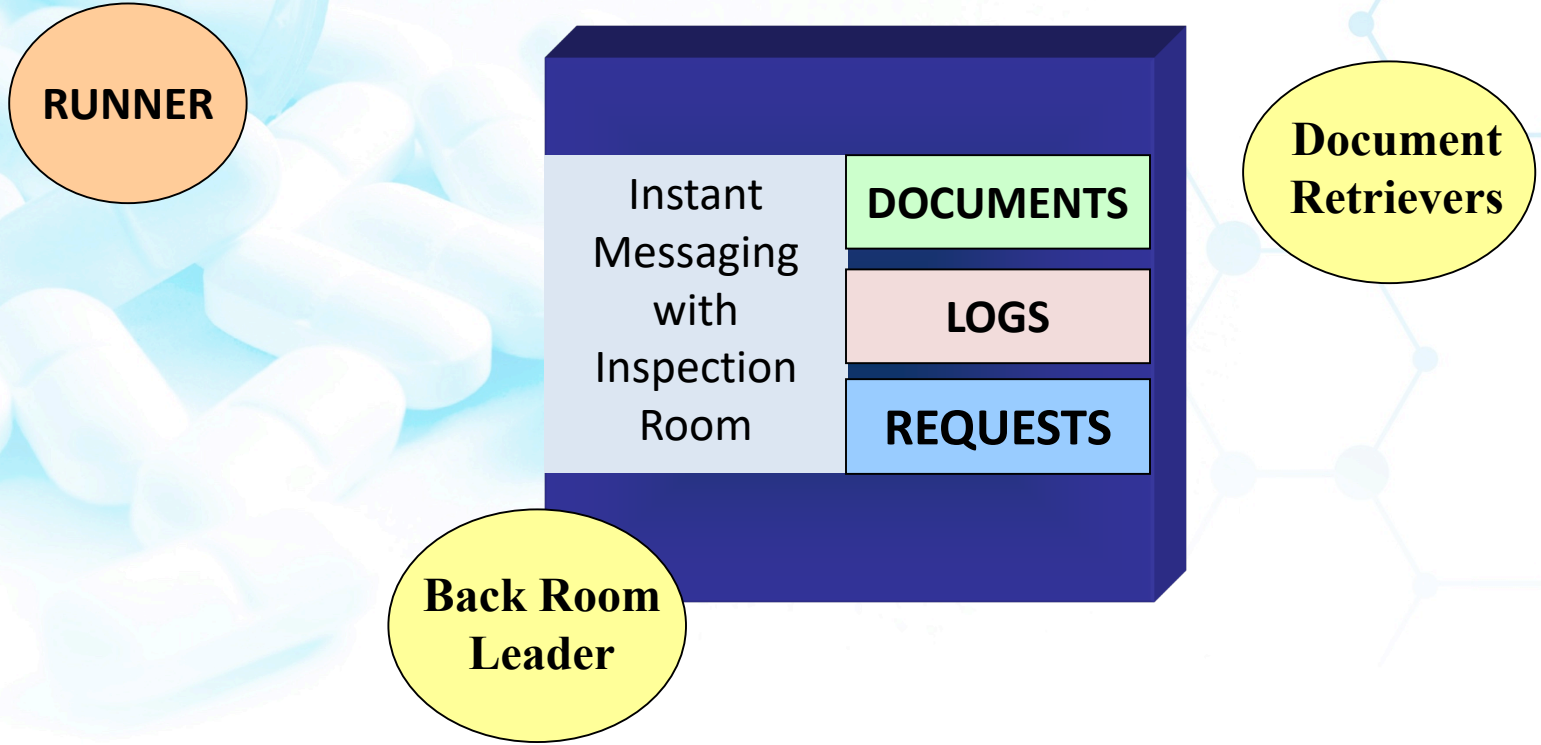
Inspection – Roles and Responsibilities

- Leader/Escort – Head of Quality or QA/Compliance Manager; responsible for overall inspection management, facilitation, anticipation of issues
- Scribe – Usually a Quality Engineer (someone with technical knowledge about plant operations); must capture all discussions elements, information/data requests, etc. during all aspects of the inspection (tour, interviews, general discussions, etc.)
- Subject Matter Expert – individual with most knowledge or responsibility for a given function (may not be a supervisor or manager)
- Runner – usually a member of the QA or Compliance team who delivers requests and reviewed documentation between the Back Room and the Front Room
- Back Room Leader – Usually Head of Compliance; responsible for review of all documents prior to delivery to the Inspection Front Room; manages documentation of overall inspection; assists in SME preparation
- Document Retrievers – usually QA; retrieves original documents from various departments or locations

Inspection – Front Room



Inspection – Back Room



Inside the Back Room

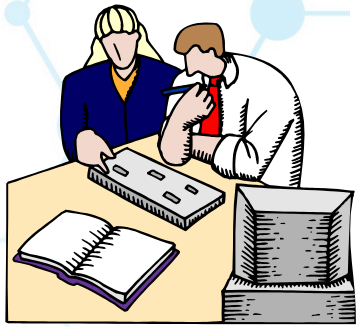
- ***ALL*** information requests are IM'ed from the Inspection Front Room to the Back Room where they are tracked
- Documents are reviewed for errors, omissions, "post-it" notes, etc.
- Understand if there are associated investigations or issues; prepare
- Inform the Inspection Front Room about reviewed document availability
- Assists with SME familiarization and preparation before SME interaction with FDA
- Only obtain documents from their official source (originals vs. copies)
- Efficient delivery of documents (delays cause concerns about control)

Inspection – Interaction Preparation

- You may interact with FDA
  - No employee is exempt from talking to an Investigator
  - You all represent your organization and GMP operations/decisions
- Interactions in *Production or Laboratories*
  - Have your SOPs, batch/cleaning records, and test methods present
  - Be able to explain what you are doing and WHY (refer to documents)
- Interactions in the *Inspection Room*
  - You should be briefed prior to entering the room
    - Why you are being questioned
    - What are appropriate responses
    - Dress rehearsal
- You should have management support
  - A Management Escort should always be present
  - They can intervene and help you with answers – to redirect and clarify if there is some confusion; but you are the SME and you should be confident
  - Never argue or contradict each other in front of FDA, defer to Quality

Inspection – The Interview

- Introduction to Investigators
  - Business card (if you have one) / but name and job title
  - Cordial / professional – it is appropriate to shake hands
- Remember your body language!
- Listen carefully and make sure you understand
  - Don't answer (assume you know) the question before it is fully asked
  - Don't guess if you are not sure of the answer
  - Don't volunteer information not requested (like a demonstration)



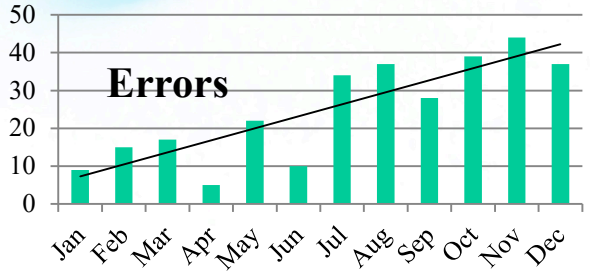
- If needed, repeat the question to the Investigator to be sure you understand or ask for clarification
- Do not argue if the Investigator disagrees; simply provide your documentation and justification
- Refer to documentation where appropriate
- Respond directly to the questions and answer truthfully; but **DO NOT** answer more than what is asked; Don't volunteer information
- Be **HONEST, CONCISE,** and **COMPLETE**

Inspection – Responding to Questions

- Remember that an appropriate answer is:
  "I'm not sure, I'll find out and get back to you."
  "Let me get that information for you."
- Note commitments and be sure to follow-up as soon as possible on things that you have committed to do
- If you are not the correct SME for the question, then say so and work with your Management Escort (in the back room) to determine who is the correct SME (don't say you are not the SME to avoid a question if it is really in your functional area)
- FDA may request a demonstration of electronic systems (JDE, LIMS, Empower, TrackWise, etc.)
  - to ensure proper controls are in place (Data Integrity – log-ins, back-ups, audit trails, review processes, privilege level, validation, etc.)
  - copies of electronic data (so they can sort and make additional risk-based requests)

Inspection – Recommendations

- Be prompt in document retrieval and providing answers to questions
  - Slow responses may raise suspicion (record modification) or indicate that something is wrong or out-of-control
  - The Investigator will follow-up to ensure receipt of information; it is best to not make them ask twice!
- Try to correct issues and present corrections to issues identified by the Investigator by opening a deviation in the Quality System (this demonstrates a sense of urgency)
- Remove questionable wall postings, charts, graphs, memos, overdue training notices, etc.



Final Recommendations

Do not:

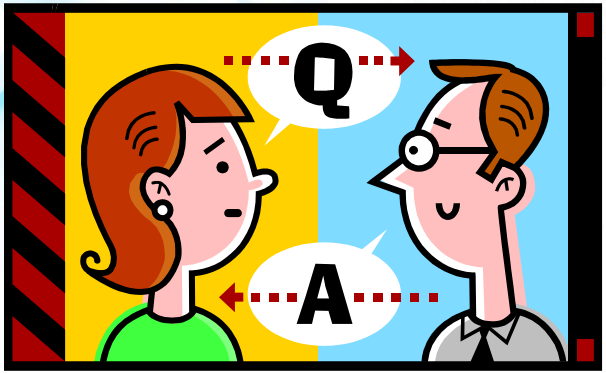
- Point out errors if you see them (but do make sure Quality knows and they get corrected)
- Comment or “apologize” for the quality of the data
- Comment on planned improvements
- Use the Investigator(s) as your “consultant”

Do:

- Anticipate – think about the commonalities of what is being reviewed and think about what questions are likely to be next
- Leave the room if you are unsure and need to discuss something; make sure you are out of earshot
- Keep your management informed!

Final Tip

Remember:
You are a cGMP professional. You know your systems and justifications.
Even though the Investigator controls the questions, you control your responses.



Thank you!

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