被國外官方單位稽查之經驗分享

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Outline

- Statutory requirements and regulations
- Preparing for a cGMP inspection
- During the inspection
- After the inspection
- Case study
- Examples of Observations of EDA/FMA Inspection
- Top Ten Pharmaceutical Observations
- Secrets for Success

FDA/EMA Inspectors are Knocking at Your Door

Are You Ready? It is much more than an audit!

FDA Pre-Approval Inspection

- Statutory Requirements and Regulations

Federal Food, Drug, and Cosmetic Act, Section 505(d)(3)

- Grounds for refusing application;.....the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity;

21 CFR Part 210 and 211

- Good manufacturing practice for finished pharmaceuticals

FDA Pre-Approval Inspection –
Applicable Guides

ICH Q7

- Good manufacturing practice guide for active pharmaceutical ingredients

CPGM 7346.832,

- 2.1 scope – A pre-approval inspection (PAI) is performed to contribute to FDA's assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data are accurate and complete.

FDA Pre-Approval Inspection –
Human (CPGM 7346.832)

- New Drug Applications (NDA)
- Abbreviated New Drug Applications (ANDA)
- Investigational New Drugs (IND)
- Abbreviated Antibiotic New Drug Applications (AADA)
- Supplements (i.e. PAS, CBE-0, CBE-30, etc.)
- Active Pharmaceutical Ingredients (API)

FDA Pre-Approval Inspection –

What to Expect and Plan for

- **Send a team of individuals to conduct a PAI approximately 1-3 months following submission.**
  - Lead inspector
  - Analyst
    - Microbiologist
    - Chemist
  - Computer specialist
  - Reviewer from headquarters
- **Determine if :**
  - The site is ready for commercial manufacturing
  - The information submitted is consistent with site records
  - The information submitted is complete and accurate

EMA GMP inspection – Principles and Guidelines

Directive 2003/94/EC

- for medicines and investigational medicines for human use

Directive 91/412/EEC

- for medicines for veterinary use

Inspectors designation

- National procedure
- Mutual recognition procedure (MRP)
- Decentralized procedure
- Centralized procedure

Table 1 Marketing Authorisation procedures in the European Union

Centralized Procedure	Application to EMA
	1 scientific evaluation by EMA
	MA issued by the European Commission valid in the entire EU territory
	Mandatory for biotech products, for certain therapeutic classes and for orphan products
Decentralized Procedure	Parallel submission in n Member States
	Reference Member State (RMS) performs assessment
	Concerned Member State(s) (CMSs) have the possibility to object
	Member States (RMS + CMSs) grant national MAs
Mutual Recognition Procedure	When there is at least 1 existing National Authorization (RMS)
	Other Member States (CMSs) mutually recognize the existing national MA in the RMS
	RMS updates previous assessment
	CMSs have the possibility to object in case of serious public health concerns
	Member States (CMSs) grant national MAs
National Procedure	Application to 1 Member State only
	National MA in 1 Member State
	Not allowed if the product is already authorized in another Member State

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Preparing for a GMP Inspection–
Before the Inspection

- Inspection is likely
  - Initial inspection: ask regulatory authority
  - Follow-up inspection: anticipate when
- Determine scope of inspection
  - Ask for inspection plan
  - Ensure appropriate staff are on-site

Preparing for a GMP Inspection--
Establish a GMP Inspection SOP

Roles and responsibilities of all personnel

- Security and reception—the first impressions count!
- Hosts
- Scribes (note takers)
- Subject matter experts (SME)
- Runners

Company policy

- Electronic data, entry into controlled areas, hygiene, sample collection, the use of cameras, videos and sound recording.

Preparing for a GMP Inspection—
Function of Host

- Ensure a pleasant inspection atmosphere and co-ordinates the general inspection procedure (duty to supply information!)
- Makes sure that the inspectee responds (correctly) to a question
- Negotiates GMP interpretations (where appropriate)
- Arrange organizational matters with other host(s)
- Summons meetings at short notice if required (“crisis meeting”)

Preparing for a GMP Inspection—Function of Scribe

- Makes a note of the items inspected and covered
- Stamps the documents handed out with a “confidential” stamp
- Records which documents have been looked at/handed out

Preparing for a GMP Inspection—Function of Scribe (Cont'd)

- Informs a fixed person sub-group*, if required, and at least once a day, writes a concise report about how the inspection is proceeding (scribe's report):
  - Area inspected and items discussed
  - Observations and other distinctive aspects

*sub-group of relevant persons for the scribe's report: environment and persons (in)directly affected who will be covered on the next days' agenda, management

Preparing for a GMP Inspection—
Function of runner

- Provides necessary documents
- Makes sure that the correct documents are handed out
- If necessary, looks at the documents with the inspectee before handing them out

Preparing for a GMP Inspection--

Establish an Inspection management team

Inspection preparation is a team effort!

- Individual accountabilities defined
- inspection procedures defined and implemented
  - Training on inspection procedures and policies
  - Training on managing inspectors
- Ensure all supporting systems and data are in place
- Agree and rehearse “inspection logistics”

Preparing for a GMP Inspection–
Selecting SMEs

- Competency in answering an inspector's questions
- Performance under stress -- Will they keep calm or will they panic?
- Demeanor and attitude – Does he/she appear professional, appropriately dressed and confident?
- Adaptability – Can he/she handle unexpected requests and changes in the mood or direction of the inspection?
- New personnel – Need some extra coaching, require additional time to practice face-to-face, learn how to work with an inspector.

Preparing for a GMP Inspection–
Training SMEs (Interview Dos)

- Answer all questions honestly;
- Say “I don’t know” or I’ll get the answer for you;”
- Avoid such phrases as “I think,” “Sometimes/often/usually,” ”never” and “next time;”
- Stop speaking once the question is answered;
- Ask for explanations or interpretations of what you do not understand;
- Maintain a friendly and cooperative attitude;
- Control your temper; remain courteous and professional;
- Maintain eye contact.

Preparing for a GMP Inspection–
Training SMEs (Interview Don'ts)

- Volunteer information or answer a question that hasn't been asked;
- Be sarcastic;
- Guess answers;
- Attempt to answer "what if ?" or hypothetical questions;
- Argue with an inspector;
- Philosophize, ramble or editorialize;

Preparing for a GMP Inspection–
Training SMEs (Interview Don'ts) (Cont'd)

- Point out deficiencies or errors;
- Apologize for problems or comments made by an inspector;
- Feel the need to respond to every comment made;
- Become defensive or evasive;
- Look away, fidget or look nervous;
- Make statements about your personal opinion of the FDA/EMA.

Preparing for a GMP Inspection –

Kinds of Questions Typically Asked by Inspectors

- Close-ended questions are narrowly focused and require only very brief answers, often a simple “yes” or “no”.
- Open-ended questions are designed to encourage the SME to talk and provide as much information as he/she wishes.
- Leading questions are phrased to suggest what kind of answer the inspector is seeking, such as “You don’t believe that process is effective, do you?”

Preparing for a GMP Inspection –
Kinds of Questions Typically Asked by Inspectors (cont'd)

- Nondirective or neutral questions, such as "How do you like your job?"
- Assumptive questions, for example "So your CAPA system does not require an investigation for all non-conformances?"
- Restatement of questions – The inspector may ask the same question multiple times of the same SME or different SMEs.

Preparing for a GMP Inspection –
Document Management Plan

Components and Subcategories

1. Product description
   - Technology transfer
   - Development
2. Process
   - Manufacturing instructions
   - Historical batch performance
   - Process development
   - Support validations
   - Process equipment

Preparing for a GMP Inspection – Document Management Plan (Cont'd)

3. Analytical
   - Lab practices
   - Analytical equipment
   - Lab investigations and method issues
   - Method validation and qualification
4. Facility
   - Systems and utilities
   - Preventive maintenance / calibration
   - Change over / cleaning
   - Support equipment (i.e. freezers, stopper and glass washers etc)
   - Environmental monitoring

Preparing for a GMP Inspection – Document Management Plan (cont'd)

5. Quality and compliance
   - Quality systems and SOP's
   - Quality Agreements
   - Investigations / deviations
   - CAPA closeouts
   - Batch history and quality trends
   - Change control
   - Training
   - Raw material and components
   - Storage and warehousing
6. Storage and distribution
   - Shipping procedures
   - Shipping validation
7. Stability

Preparing for a GMP Inspection –
Key Documents Will be Reviewed

- Procedure for handling deviations,
- OOS,
- OOT,
- Data integrity,
- CAPA,
- Change control,
- supplier qualification program,
- Release of product,
- APR

Preparing for a GMP Inspection –

Do Some Research for an Inspection

- Review previous inspection reports—your own and other companies!
- Ensure that all deficiencies are closed out and documented.
- Gain some “intelligence” on the inspectors to find out their areas of expertise and focus.

Preparing for a GMP Inspection – Inspectors Review the Documents Before Arriving on Your Site

- Site Master File—if the inspector is new to your site!
- Validation Master Plan
- Previous inspection findings and your responses
- Complaints and adverse events

Preparing for a GMP Inspection – Define Tour Routes

- Define routes through the facility for the “inspection tour”.
- Designate “hosts” at each area who are capable of answering inspectors’ questions.
- Prepare your hosts—practice some mock questions and answers.

Preparing for a GMP Inspection – Prepare the site

- **Ensure site is clean and tidy**
  - Outside
  - Inside - remember toilets!
  - Empty rubbish
  - Do repairs
- **Clear out drawers and desks in production areas**
  - Remove everything that shouldn't be there
  - Remove unofficial notices etc

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- Top ten Pharmaceutical Observations
- Sources for Success

During the Inspection

- Make a good impression as the inspectors arrive on-site.
- Security personnel check individual inspector's ID, register them in the visitor's book and provide them with appropriate ID badges.
- Have available a room where the inspection team can be located

During the Inspection

Opening meeting

- Introduction of the inspection team and the group of inspectees
- Reconfirmation of the inspection scope and objectives
- Presentation and brief discussion of the inspection plan
- Establishing a tentative time and date for the closing meeting
- If not offered, request summary session at the end of each day.

During the Inspection (Cont'd)

Opening meeting

Advise the inspectors about the:

- Company policy on health, hygiene and safety
- Company policy on photographs, video and sound recording
- Normal operating hours [e.g. 8am to 5pm]
- Times for lunch, breaks, coffee, end of day etc.

During the Inspection

Have your own "back room"

- Provide an area to hold documents requested by the inspectors
- Line up the experts
- Action inspector requests for information
- Follow-up questions that can't be answered immediately
- Provide an area to review documents before they are given to the inspectors

During the Inspection

- Mark all photocopies provided to the inspectors as “uncontrolled” or “commercial in confidence” and “copyright of XXX”
- Make sure that current and correct version of copy is given
- Documents provided to the inspectors must be compliant to GMP standards-no sticky notes, incomplete fields or unchecked data.

During the Inspection

- Attempt to correct deficiencies immediately or provide evidence while the inspectors are still on site.
- Request that such corrective actions are acknowledged in the final inspection report
- Prepare internal summary of inspection each day and meet to discuss if any action is necessary

During the Inspection

- When a document is required, provide this and no more.
- Do not volunteer information that has not been requested unless it is to your advantage to do so.
- Do not guess an answer.
- Do not hide information.
- Do not lie to the inspector.

During the Inspection (Cont'd)

- Do not argue or display anger towards the inspector, even if you are frustrated.
- Do not cause a deliberate delay. If for some reason you cannot deliver a copy of a document quickly, explain the reason for delay.
- Allow inspectors to question any staff member (i.e. do not steer the inspector away).
- Always deliver something you have promised.
- Look confident and smile.

Closing Meeting

- All personnel involved should attend the final wrap-up meeting (including management)
- Scribe should compare deficiencies presented with what the inspectors recorded.
- Question deficiencies that you do not understand; seek clarification.
- Suggest the inspectors re-visit the area or document, if a deficiency is clearly wrong.
- Discuss any deficiencies that are clearly outside the scope of the GMP guide.
- Do not be argumentative.

FDA Inspection Close-Out

- **There will be a close-out meeting**
  - No surprises
  - FDA-483 (inspectional observations)
    - May or may not be issued
- **Firms have the opportunity to respond in writing to the investigator's observations or discussion points**
  - Verbal (during the inspection) and in writing
  - 15 days to respond for consideration of further action
- **If physical samples were collected, FDA-484 (receipt for samples) will be issued.**

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After the Inspection

- FDA Inspections are generally classified into one of three categories
  - **NAI** - No Action Indicated
  - **VAI** - Voluntary Action Indicated
  - **OAI** - Official Action Indicated

After the Inspection

- Assign personnel for receiving the inspection report, answering any follow-up questions, coordinating corrective actions and compiling the written response to regulatory authority.
- Use internal CAPA system to correct and close out each deficiency.
- Conduct post inspection review to address any areas of weakness identified by the inspectors and by your personnel.
- Correct these weaknesses now rather than wait for the inspector to identify them next time around.

*Keep in mind: After the inspection is before the inspection

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Case Study Scene #1

- Inspector (I): Do you have a procedure for complaint handling?
- SME (S): Yes, we have a procedure for complaint handling. It's been recently updated because of an internal audit observation.
- I: I see. Could I see a copy of the updated procedure, the associated change record, the internal audit report and the CAPA associated with this observation?
- S: Sure, we'll get you that information.

Case Study Scene #1 (Cont'd)

- I: While we are waiting for the documents I requested, can you tell me what the observation was?
- S: Sure. The observation was that the procedure didn't require that we document the evaluation we perform to determine whether a further investigation is required.
- I: What are the actions that you have taken?
- S: One of the actions is overdue. We updated the procedure to require that the evaluation is now documented; a rationale for why we're not going to perform further investigation, if that's the case, and the signature of the individual who performed the evaluation. We're making a change to the software to accommodate this.

Case Study Scene #2

- I: When will the actions be complete?
- S: I think they may be done in about a month.
- I: How late are they?
- S: I believe a month or so.
- I: A month or so? Why is this OK? (Inspector leans forward and takes an aggressive tone.) Do you think it's OK to continue to not appropriately evaluate complaints?
- S: Well, no. (SME folds arms.) But management didn't assign somebody to the validation right away.

Case Study Scene #2 (Cont'd)

- I: How long did it take management to assign someone? Don't they think this is important?
- S: I don't know (SME sounds irritated.) You'll have to ask them.
- I: All right. Let's bring in the manager who was responsible to assign the resources and ask them.
- S: OK. (SME sighs.)

Case Study Scene #3

- I: Let's look at the CAPA and the procedure update.
- S: Here they are.
- I: What is the change that you made?
- S: We added this section here which requires the evaluation of the need for further investigation to be documented, along with a signature of the person who did it.
- I: Do you have an effectiveness check?
- S: Yes, the records are checked by another person to ensure that this has occurred.

Case Study Scene #3 (Cont'd)

- I: I do not see it here.
- S: Well, we are performing this check. I could show you the records.
- I: (Pauses.)
- S: Since this will now be a required field in the software, you can't proceed without entering this information. It's a very nice system. Would you like to see it?

Case Study Scene #4

- I: Have you looked at your historical complaint records to ensure an investigation was performed where required?
- S: No.
- I: How can you be sure that you have?
- S: Well, we evaluate all of our complaints. It just wasn't documented before.
- I: What about the corrective action to make a software change? This document shows it was due one month ago.
- S: Well, I've looked into this, and we should be done with this within a week.
- I: Is management aware of this?
- S: I'll follow-up on that question.

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Example of Observations of FDA Pharmaceutical Inspection

1. Failure to document production and analytical testing activities at the time they are performed.
2. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.
3. Failure to maintain complete data derived from all testing, and to ensure compliance with established specifications and standards.

Example of Observations of EMA Pharmaceutical Inspection

1. A critical deficiency was cited with regards system failures to ensure that the manufacture of medicinal products were fit for their intended use, complied with the requirements of the Marketing Authorisation and did not place patients at risk due to inadequate safety, quality or efficacy.
2. No action was taken to assess the risk of remaining products in the markets.
3. Adverse trends in stability-indicating attributes were observed but no investigated.

Example of Observations of EMA Pharmaceutical Inspection (Cont'd)

4. Product impact assessments failed to ensure that the defective product was not potentially supplied to the user.
5. Failure to notify competent authorities on the discovery of defective products.
6. Failure to address the root cause due to ineffective CAPA. Also delay in CAPA implementation.
7. Failure to escalate the incident and conduct effective investigations in a timely manner.

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Top Ten Pharmaceutical Observations

1. The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed].
2. There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed.
3. There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Top Ten Pharmaceutical Observations (Cont'd)

4. Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity.
5. Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release.

Top Ten Pharmaceutical Observations (Cont'd)

6. Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.
7. Equipment and utensils are not [cleaned] [maintained][sanitized] at appropriate intervals to prevent [malfunctions] [contamination]that would alter the safety, identity, strength, quality or purity of the drug product.

Top Ten Pharmaceutical Observations (Cont'd)

8. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established][written] [followed].
9. Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of inprocess material and the drug product.
10. There is no written testing program designed to assess the stability characteristics of drug products.

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Secrets for Success

- Being well prepared
- Providing a good first impression
- Having good inspection management
- Ensuring that personnel who front the inspectors have the require technical knowledge and expertise, confidence and presentation skills
- Establishing an SOP and training personnel

Thank you for your attention


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