Centre for Biopharmaceutical Excellence

Managing Successful Regulatory Audits

(Preparing for Regulatory Inspections and Investigations)

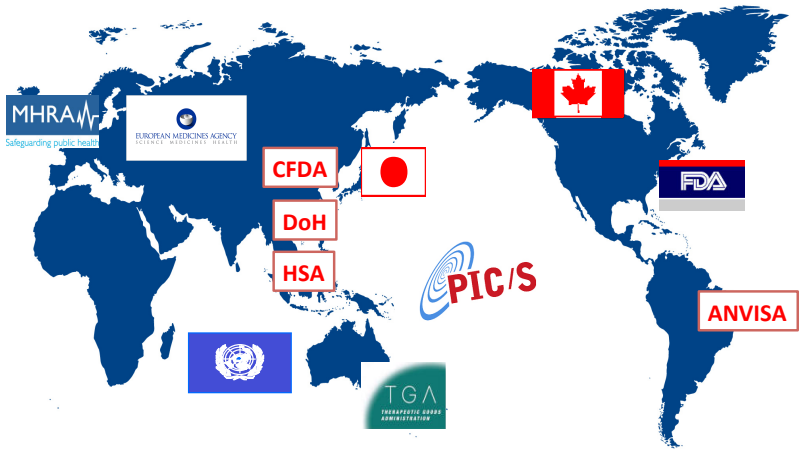
Module Outcomes

On the completion of the module, participants should be able to define the differences and similarities between regulatory agencies, prepare for an audit and successfully navigate regulatory inspections from international regulatory agencies such as WHO, FDA, TGA and PICs.

Module Topics

- CBE Different Agencies and their Approaches
- CBE Preparation for an FDA "PAI"
- CBE Preparation for a General GMP Audit
- CBE Managing the Audit Itself
- CBE What to Do / What Not to Do
- CBE Closing Meeting and Responses

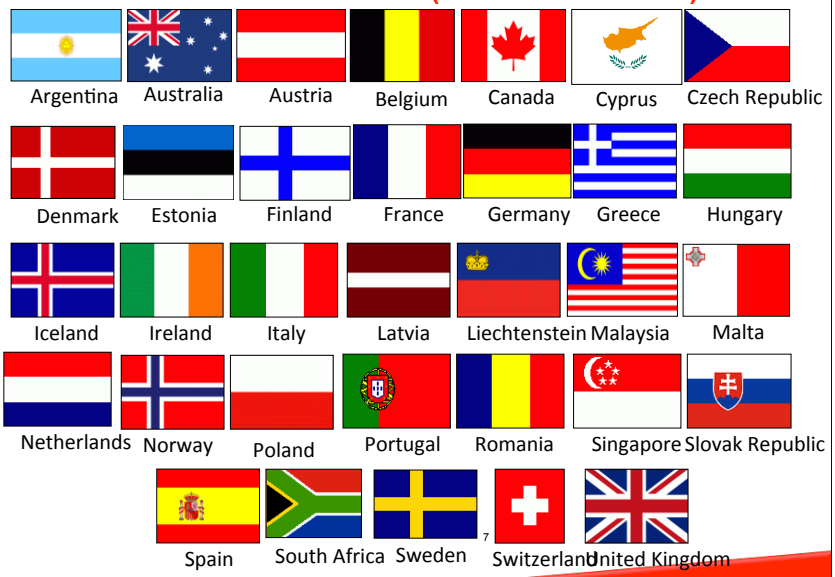
Key Regulatory Agencies



Major International Codes of GMP

- **PIC/S Guide to Good Manufacturing Practices - PE 009 - 2014**
- **EU Guide to Good Manufacturing Practices (Eudralex Ch 4)**
- **United States - FDA CFRs Part 21**
  - 210/211 for Drugs and Biologics - current GMPs
  - 820 Quality Systems for Medical Devices - current GMPs
- ICH Q7 GMP for Active Pharmaceutical Ingredients
- Canadian cGMP (aligned with PICs)
- **World Health Organisation (WHO) – TRS986**
- ISO 13485 : 2003 - Medical Devices
- ICH Guidance Documents – Technical Standards

PIC/S Members (Now 41 Countries)



Pharmaceutical Inspection Co-operation Scheme (PIC/S)

- PIC/S' mission is "to lead the international development, implementation and maintenance of harmonized Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products".
- Membership means mutual recognition of members GMP licensing schemes and GMP standards.
- Facilitates trade since, individual GMP clearance for each country is avoided.

PICs and EU Guide To GMP (International Rules)
Part I (Basic Requirements for Medicinal Products)

CHAPTER 1 - QUALITY MANAGEMENT	CHAPTER 2 - PERSONNEL	CHAPTER 3 - PREMISES AND EQUIPMENT
CHAPTER 4 - DOCUMENTATION	CHAPTER 5 - PRODUCTION	CHAPTER 6 - QUALITY CONTROL
CHAPTER 7 - CONTRACT MANUFACTURE AND ANALYSIS	CHAPTER 8 - COMPLAINTS AND PRODUCT RECALL	CHAPTER 9 - SELF INSPECTION

PIC/S Guidance Documents

#	Title
E 005-3	PIC/S GMP GUIDE FOR BLOOD ESTABLISHMENTS
PE 010-3	GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS
PI 005-3	GUIDANCE ON PARAMETRIC RELEASE
PI 006-3	VALIDATION MASTER PLAN INSTALLATION AND OPERATIONAL QUALIFICATION NON-STERILE PROCESS VALIDATION CLEANING VALIDATION
PI 007-5	VALIDATION OF ASEPTIC PROCESSES
PI 008-3	PIC/S GUIDE TO INSPECTIONS OF SOURCE PLASMA ESTABLISHMENTS AND PLASMA WAREHOUSES
PI 011	GOOD PRACTICES FOR COMPUTERISED SYSTEMS IN REGULATED GXP ENVIRONMENTS
PI 012-3	RECOMMENDATION ON STERILITY TESTING
PI 014	ISOLATORS USED FOR ASEPTIC PROCESSING AND STERILITY TESTING

Important ICH Quality Guidance

- Q1 : Stability (topics: A – F)
- Q2 : Analytical Method Validation
- Q3 : Impurities (topics: A – C)
- Q4 : Pharmacopoeias (topics: A & B; 10 annexes)
- Q5 : Quality of Biotechnological Products
- Q6 : Specifications (topics: A & B)
- Q7 : GMPs for Active Pharmaceutical Ingredients
- Q8 : Pharmaceutical Development
- Q9 : Quality Risk Management
- Q10 : Quality Management System

Quality and Risk Management
(PIC/S requirements)

- PIC/S emphasizes QMS principles – seen as critical to GMPs
- Require a full working QMS (CAPA, Deviations, Change, etc.)
- ICH Q10 – Pharmaceutical Quality System will be introduced
- Annex 20 Risk Management included into the QMS
- Extensive annual product review required

WHO Pre-Qualification (Reasons for Site Audits)

- Part of the initial evaluation
- As follow-up to corrective actions taken by the manufacturer following WHO recommendations, and
- For reassessment purposes.

- They may also be deemed necessary as a result of
- complaints or reports of serious adverse events following immunization (AEFIs) if a quality problem is suspected.

- WHO may reference the NRA report(s) to determine the type and size of the audit.

WHO Pre - Qualification Audit Team

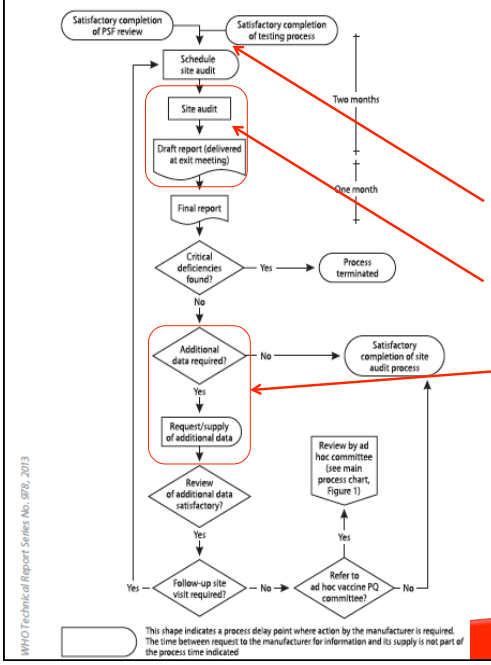
- Team members must have expertise in the areas of production, quality control, quality assurance, quality system and GMP;
- Generally add a technical expert on the vaccine;
- NRA auditors are invited to join as observers;
- WHO appointed consultants/experts may make up the team;

WHO Pre-Qualification Site Audit Objectives

- whether the company has an adequate quality system in place
- whether the vaccine is produced in compliance with WHO-recommended GMP.

- Other important aspects of the assessment include, but are not limited to, labelling, packaging, whether a post-marketing surveillance system is in place, vaccine vial monitor (VVM) implementation when required, and a stability programme.

Figure 4
Site audit



Audit Process

Three Critical Points

1. Period leading up to the audit – Preparation;
2. Audit Management;
3. Follow up responses and requests for Information;

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Audit Findings and Responses

- The findings and recommendations of the team will be discussed with the company on a daily basis, as required during the site audit;
- Opportunity for discussion, questions and clarifications at the closing meeting
- The draft report, which includes the main findings, recommendations and closing remarks, is prepared by the WHO team and left with the manufacturer;
- Final report within 30 days;
- NRA follow-up assessment, if needed on specific areas, within 6 months. These NRA assessments will be used to assist in making a decision.

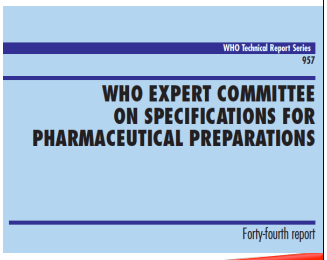
CAPA

Manufacturer can prepare a corrective action plan to address critical recommendations and establish deadlines for receiving responses, WHO will postpone final recommendations until CAPA is resolved;

CAPAs are verified by WHO - If the company does not comply with the agreed deadlines, the prequalification process may be terminated.

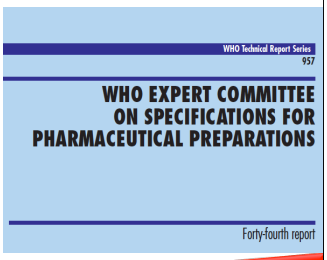
WHIO cGMP – Main Code

1. Pharmaceutical quality system
2. Good manufacturing practices for pharmaceutical products
3. Sanitation and hygiene
4. Qualification and validation
5. Complaints
6. Product recalls
7. Contract production, analysis and other activities
8. Self-inspection, quality audits and suppliers' audits and approval
9. Personnel
10. Training
11. Personal hygiene
12. Premises
13. Equipment
14. Materials
15. Documentation
16. Good practices in production
17. Good practices in quality control



WHO cGMPs – Important Annexes

- Annex 1 - GMPs for pharmaceutical quality control laboratories
- Annex 2 – GMPs for active pharmaceutical ingredients
- Annex 3 - GMPs for pharmaceutical products containing hazardous substances
- Annex 4 GMPs for sterile pharmaceutical products
- Annex 5 – GDPs for pharmaceutical products



MHRA Inspections - Top 10 Issues 2012

Rank	Issue
1	Investigation of Anomalies
2	Quality Management – Change Control
3	Investigation of Anomalies – CAPA
4	Complaints and Product Recall
5	Quality Management
6	Supplier and Contractor Audit
7	Contamination, Chemical/Physical – Potential For
8	Documentation – PSF/Procedures/Technical Agreements
9	Documentation –Manufacturing
10	Process Validation

Some emerging industry challenges globally

- Counterfeiting & economically motivated contamination
  - Heparin, Glycerin and Melamine in Milk contamination raise risk perception for big pharma and regulators
- Global supply chain – inherent risks in GDP - Poor control over distribution chains
  - In the biotech industry it's not uncommon to have 3 - 8 different manufacturing centres around the world
  - How to manage remote Contract Manufacturing Organisations ?
- Costs of bringing a new product to market rising
- Biosimilars debate
- Falsifying GxP Records and Clinical Trial Data – Data Integrity

U.S. Food and Drug Administration

Department of Health and Human Services

FDA Inspections and Investigations

Office Regulatory Affairs (ORA)

- CDER – Drugs Proteins
- CBER – Vaccines Blood
- CDRH – Devices & IVDs
- Office Combination Products

14 District Offices + Offices in China and India

FDA - some numbers

- FDA regulates more than $1 trillion (25% of all trade)
- FDA monitoring a third of all imported goods
- Domestic drug inspections are unannounced and more intense - mandated every 2 years
- Foreign inspections are pre-announced and usually set timeframes – follow up is difficult - not mandated every 2 years
- FDA conducts far fewer foreign inspections than domestic

FDA Drug Manufacturing Inspections Program 7356.002 - Identified Control Systems

1. **Quality System**.
   - Change control, reprocessing, batch release,
   - Annual product review
   - Validation protocols,
   - Product defect evaluations
   - Evaluation of returned products.

2 . **Facilities and Equipment System**.
   - Buildings and facilities along with maintenance
   - Equipment qualifications (IQ/OQ);
   - Equipment calibration and preventative maintenance;
   - Cleaning and validation of cleaning processes.
   - Utilities - HVAC, gases, steam and water.

3. **Materials System**.
   - Control of finished products, components, water, gases,
   - Containers and closures.
   - Validation of computerized inventory control
   - Drug storage, distribution controls, and records.

4. Production System.
   - Batch compounding, dosage form production,
   - In-process sampling and testing,
   - Process validation.
   - Master batch records and manufacturing procedures.

5. Packaging and Labeling System.
   - Packaging and labeling operations & controls
   - Label examination and usage,
   - Label storage and issuance,
   - Validation of these operations.

6. Laboratory Control System.
   - laboratory procedures,
   - testing, analytical methods development
   - Method validation or verification,
   - Stability program.

FDA Pre-Approval Inspections (PAIs) (what are they ?)

- FDA regulate by Product not Manufacturing Facility
- Specific to FDA – generally for specific Rx Drugs and Biologics
- Triggered by a US Marketing Application:
  - NDA, ANDA or BLA etc.
- Audit target is clearly defined:
  - The API supplier
  - The facility and services in which the product will be made
  - The equipment used for manufacture
  - The processes used for manufacture and “validated state”
  - The laboratory testing for the RMs and Finished Product
  - Development data provided in application eg. stability
  - The quality system supporting the product and processes
  - Any 3rd party laboratories

Preparation for a General GMP Audit

The "Challenge" with cGMPs

Accurate Interpretation by Auditor and Company

14.14 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. ✔

14.12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release. ✔

15.5 Documents should be regularly reviewed and kept up to date. ?

12.5 Premises used for the manufacture of finished products should be suitably
designed and constructed to facilitate good sanitation. ?

14.6 Water used in the manufacture of pharmaceutical products should be suitable for its intended use. ?

What are Inspectors likely to be interested in ? (1st Tier)

- Annual or Periodic Product Reviews
- Key Quality Metrics or Signals of Problems
  - **Events:** Deviations, Investigations and resulting CAPAs
  - **Marketplace**: Recalls and Complaints and their Resolution
  - **Failures:** Rework and Reprocessing Oversight
  - **QC Failures:** Laboratory Out of Specification Results (OOS)
- Change Control
- CAPA close out rate and effectiveness
- Manufacturing in compliance with registered details, or not.
- Data Integrity
- Close out of Previous Deficiencies

FDA View on GMP Metrics

Indicator	Metric
Lot Acceptance Rate	Number of lots rejected in a year / number of lots produced
Right First Time Rate	Number of deviations / lot
Complaint Rate	Number valid complaints/number of lots released per year
Invalidated (OOS) Rate	Number of OOS test results invalidated /tests performed
Annual Product Review (APR) on Time Rate	Number of APRs generated within 30 days of annual due date
Management Engagement	Most senior manager that signed each annual product review
Process capability or performance index	Whether performed for each critical quality attribute as part of that product's APR.
Corrective and Preventative Action (CAPA) Rate	Number of CAPAs that were initiated due to an APR, divided by the total number of APRs generated.

What else are Inspectors interested in ? (2nd Tier - GMPs)

- Lists of SOPs - their currency and coverage/training
- Content of selected Batch and Testing Records
- Integrity of Risk Assessments
- "Validated State" – process, equipment, HVAC, Water
- Potential for Cross Contamination and Hygiene
- Outcome of the audit programs
- Traceability and Tracking of Materials and Products
- Counterfeit Detection Capability
- 3rd Party Agreements and Oversight of API Quality
- Release for Supply

Careful Preparation = Success

- **Must prepare well in advance ! (3 – 6 months)**
- List your Business' vulnerable issues - meet weekly
- Form an inspection readiness team and run this from a senior management level
  - QA
  - QC
  - Production
  - Validation
- Check closure of previous inspection findings
- Go over deviations and failures and their CAPA close out
- Review APRs
- Check that SOPs are current and traceable to training

Regular "Walk Through" Plant Audits

- Commence walk through audits by QA
- Ask Area Managers to conduct self inspections
- Focus on housekeeping issues
  - Piping and tanks – leakage and signage adherence
  - Tidiness and adherence to dress code
  - Completion of paperwork
  - Locations of written procedures
- Are materials stored in their place and labeled
- Potential for contamination risk in the plant
- Security and separation in warehouses
- Make sure all visual cues are OK – gauges, labels etc.

Preparation of Staff

- Assume that inspectors/auditors will talk to staff at any levels
  - Not restricted: IT, Customer Service, Warehouse etc…
- Hold sessions on how to respond to audit questions
- Practice responding in internal audits
- Manager should be present when operators are interviewed
- Require that managers and supervisors are very familiar with SOPs and Records for their area – check this in internal audits.

Anticipate "Packages"

- Collect and prepare "packages" of information anticipated in advance – makes for a smooth audit
- Review content and integrity well in advance of audit
- **Packages**
  - Significant deviation reports and associated CAPAs
  - Customer complaints
  - PQRs
  - OOS events
  - Equipment Qualifications and Reports
  - Process Validations and Reports
  - SOP lists and their currency – especially QMS Procedures
  - Evidence of past NCs close outs
  - EM and Water Profiles

Just before and on the first day

Prior to the Audit

- Entitled to ask for a general agenda and timeframe
- Need to know number of inspectors coming – any special dietary needs
- Ask for number of inspection days
- Any specialist inspectors attending ?
- Any 3rd party visits involved

Opening Meeting - Executive management should be present

- Presentation of company and products (slides) < 30 minutes
- Ask for first day(s) agenda – to organize managers availability
- Identify initial walk through expectations
- Will inspectors split up ?
- Hygiene: Specific dress codes, lunch, rooms set aside, finishing times
- Planned Debriefs each day

The Initial Walkthrough (Visual Inspection)

- Alert area managers of an inspection walkthrough
- Expect walkthrough will commence at inwards goods and progress following product flows
- Small team with walk through (QA, Production Manager)
- Ensure ALL gowning requirements are adhered to
- Avoid entry to rooms where processing is occurring
- Keep moving but the inspector will set the pace
- Take notes of any points raised by the inspector
- Take notes of any RMs or Products inspected – Lot #
- No contractors or maintenance activity on the day

Managing the Audit Itself (Front Room Management)

- Only experienced managers in front room
- Need 1 manager per auditor – accompanied at ALL times
- Need a note taker or "runner"
- Record requests on "Audit Request Form" and time of request by which auditor
- SME should present the information requested
- Take notes during interview:
  - SOPs, Protocols, Reports or Batch Records inspected
  - Any concerns identified ?
  - Note any requests for copies
- At end of the interview ask if there were any concerns
- Never ask if the inspector "would you like to see….."

Managing the Audit Itself (Back Room Support)

- Need someone to find information requested in Audit Request Form
- Allow no more than 30 - 45 minutes to find the information. If a delay in finding information let the inspector know.
- Check the information for integrity before sending to audit room.
- The SME / presenter should familiarize themselves with the request and the information being submitted before they enter the interview room
- Do NOT take additional, non requested, information to the audit room eg. if a specific protocol was asked for do not take the folder of all protocols.

The Inspection Basic Rules when Answering Questions

- Listen very carefully to the question/request
- **You are not required to fill in silence in the interview**
- If you don't understand the question ask for it to be rephrased or repeated – clarify
- **Always refer to the current SOP or record if one is available**
- Don't expand on the point or offer opinions beyond the question
- If you don't know the answer just say so – "would you like me to refer it to someone"
- Never make up an answer you think the inspector may be looking for. Always answer honestly (to the best of your knowledge)
- You can politely disagree with inspectors impression but never be aggressive – it's not about you.

What Not to Do

- Argue with the inspector/auditor – their job is stressful enough
- Be disrespectful to the auditor
- Blame someone in front of the auditor – team first
- Admit to a problem on the spot, unless its clear
- Never embellish answers or be untruthful
- Deliberately delay providing information
- Deliberately omit information requested
- Update or change information being requested
- Backdate signatures
- Present superseded procedures
- Insist on audio recording

Good Inspection Management Practice

- Have two people in interview room
- Where possible correct a problem during the inspection and provide the evidence to the inspector. E.g. updated SOP
- Take notes as you go
- Stick to the facts and refer to documents to guide answers
- Take time in presenting and explaining information
- Follow up on requests, even the next day – have information ready if asked for.
- **Debriefs:**
  - With inspectors at end of the day – request feedback on progress
  - **Internally after inspector has left** – actions for next day, any significant issues that arose, any information needed, get organized.

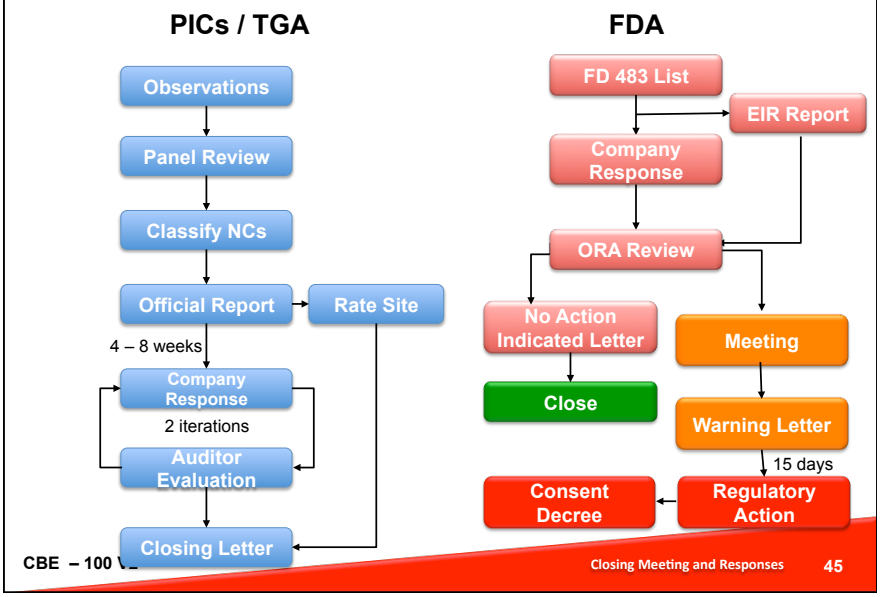
Closing Meeting and Responses (Set Up)

- Inspector(s) will prepare list of interim observations (PICs/ WHO) or list of FD483s (FDA)
- Request to see the list in advance of the closing meeting
- Review the list and decide
  - Who will respond to the item – generally heads of QA and Production
  - Whether any "correction" of misconceptions/errors are needed
  - Whether any of the NCs will be challenged at the meeting;
- General/Executive Manager should attend the meeting
- Ask line managers to attend to listen to issues
- Take copies of the inspector's draft report – control copies

Closing Meeting and Responses (Exit Interview)

- During the closing presentation do not be reactive to the observations. Respect the Inspector's position;
- Listen very carefully – the inspector cannot consult;
- Not a place to offer more objective evidence – too late;
- If you disagree with NC politely highlight the concern or error; Ask the inspector to note that you disagree;
- Make sure there is a note-taker. Audio recording is usually not advised;
- Consultants are allowed to attend but should not interject;
- May clarify which observations are likely to be Major;
- Ask senior people to respond at the end – generally with re-assurances the issues will be addressed in full.

Regulatory Processes Post Audit



Immediately After the Exit Interview
(getting organized)

- Internal review of findings – identify which items are likely to be significant issues;
- Note: PIC/s will send the final report weeks later – do not wait for this to come before getting started on big items;
- Assign responsibility for CAPA to individuals (not only QA!)
- Assign one person to co-ordinate responses (should be QA!)
- Prepare a tracking sheet for responses (against # of the NC)
- Ideally continue the daily or regular meetings to keep the momentum going.

Post the Audit – Company Response (PICs Expectations)

- 4 – 6 only weeks to respond
- Major findings require **objective evidence (OE)** of CAPA
- Be specific on actions, dates and evidence – no generalizations
- Can submit plans where the timeframe is inadequate – must be detailed; actions, timeframes etc.
- Must respond with:
  - Investigation findings and most probable root cause for issue
  - Immediate **Corrective Action/Correction** taken
  - **Preventive Action** to be implemented or taken
- Review responses and OE before submitting – consultants can be helpful
- QA should sign off the response letter and package

Submitting Objective Evidence (OE)

PICs/ TGA	FDA
Must submit OE packages for all Majors and Critical NCs.	Must submit OE packages for all FD 483s.
Have 2nd opportunity to supplement.	Packages will be evaluated.
Must confirm OE is available for Minors/ Others – will be reviewed at the next inspection.	Little opportunity to supplement.

Re-inspection Timeframe (Risk Based)

PICs / TGA

Site ➔ Compliance Product Risk ↓	High (A1)	Acceptable (A2)	Minimal (A3)	Unacceptable
High	**24 Months**	**18**	**12**	Review Panel Determines
Medium	**30**	**20**	**12**	Review Panel Determines
Low	**36**	**24**	**12**	Review Panel Determines

Re-inspection Timeframe (Risk Based)

FDA

Domestic: mandatory 2 year maximum

Internationally: Target every 2 years but insufficient resources at present:

- For cause (recall, safety reports etc.)
- 2 – 7 years depending on risk of site compliance and product risk
- Triggered by PAI application
- Triggered by other regulatory agency information

In Summary

- **Inspection success or failure is a team thing, not just QA**
- **Planning and Preparation** is the critical success factor
- GMP Inspections are driven by **Objective Evidence** from both parties
- Inspectors should not speculate beyond reasonable interpretation of the cGMP – their interpretation should be fair and not based on their own opinion or experience
- The cGMP are basic requirements, minimum standards
- Inspections are business critical and should be planned for and managed proactively by the whole business
- Ideally should be inspection ready at any time an inspector arrives

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