Preparing for Regulatory &/or Customer Compliance audits.

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The aim of any audit

Assess compliance of a facility, its processes and procedures.

Ensure they are under adequate control.

Auditing is 90% preparation

The same can be said about being audited!

Preparation should be a constant state!

Before closing any report, investigation etc, ask - would I be comfortable handing this to an auditor?

Be honest with yourself.

Any doubts – it's incomplete.

Primary objective of an auditee:

Demonstrate compliance and control.

Initial Contact – First Steps

- Initial notification: Typically ~ 1-2 months beforehand.
  - unannounced inspections can be performed where required.
- Block out schedules – ensure key personnel are available.
- Does your company have a procedure for GMP audits?
  - Useful for unannounced audits – details key contacts, phone numbers etc
- Identify personnel likely to be involved in the audit
  - Presenters – Primary Contact, Area-specific presenters,
  - Reception,
  - People to be in the audit room (this should be limited),
  - Note takers,
  - Runners,
  - People for the 'war room' (prep area).

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Typically requested ahead of time

- Current Site Master File.
- Procedures for deviation, OOS management & Change Control.
- List of significant changes since the last inspection.
- Validation Master Plan.
- Validation schedules for equipment, facilities, processes, methods and utilities.
- List of sponsors for whom testing of medicines is performed (testing lab requirement).
- List of test methods relating to the licence.

Do Your Research!

- Check if there is any information available on the auditor
  - FDA warning letters (for US inspectors)
    - Can indicate what an auditor likes to focus on.
    - Can indicate their background/training.
      - People naturally gravitate towards their comfort zone.
    - Where other companies fell down.
  - Other contacts within the industry/Seminars
    - Is there a particular (current) focus from a regulatory body?
- Regulatory updates
  - These shouldn't be a surprise!
  - Ensure you have fully implemented any new regulations.
  - Ensure you are prepared for any upcoming regulatory changes.
    - Auditors will like to see early implementation of changes.
- Review the last audit report
  - Ensure all actions have been closed.

The FDA has publicly available guides for investigators and other FDA personnel:

http://www.fda.gov/ICECI/Inspections/InspectionGuides/default.htm

These can be useful for preparation, investigations and risk assessments.

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Drugs

- High Purity Water System (7/93)
- Lyophilization of Parenteral (7/93)
- Microbiological Pharmaceutical Quality Control Labs (7/93)
- Pharmaceutical Quality Control Labs (7/93)
- Validation of Cleaning Processes (7/93)
- Dosage Form Drug Manufacturers cGMPs (10/93)
- Oral Solid Dosage Forms Pre/Post Approval Issues (1/94)
- Sterile Drug Substance Manufacturers (7/94)
- Topical Drug Products (7/94)
- Oral Solutions and Suspensions (8/94)

Foods & Cosmetics

- Allergy Inspection Guide (4/01)
- Aseptic Processing and Packaging for the Food Industry
- Nutritional Labeling and Education Act (NLEA) Requirements (8/94 - 2/95)
- Computerized Systems in the Food Processing Industry
- Grain Product Manufacturers

A Risk-Based approach is used by the TGA for scheduling re-audits.

Inspection frequency matrix – medicines and blood, tissue and cellular therapies

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Risk category	Re-inspection period in months			
	Compliance Rating			
	Acceptable			Unacceptable
	A1	A2	A3	
High	24	18	12	Determined by Review Panel
Medium	30	20	12	Determined by Review Panel
Low	36	24	12	Determined by Review Panel

There is also a schedule for medical devices.

https://www.tga.gov.au/manufacturer-inspections-risk-based-approach-frequency

Level A1 = Good

No ‘major’ deficiencies or non-conformities were found, which are of a relatively minor nature.

Level A2 = Satisfactory

1 to 5 major deficiencies and/or a larger number of minor deficiencies or non-conformities were found.

No critical deficiencies were found.

Level A3 = Basic

6 to 10 major deficiencies and/or a large number of minor deficiencies/non-conformities were found.

No critical deficiencies were found.

Not rated = Unacceptable

1 or more critical deficiencies and/or > 10 major deficiencies were found.

Preparation

- Review key procedures
  - Investigations, CAPAs, Complaints, Change Control, Product Release …..

- Review critical/major investigations
  - Ensure these have been adequately addressed.

- Review new equipment validations.

- Review critical/major complaints.

Auditors often ask for a list of these investigations etc.

- Can and should be prepared ahead of time.

Don’t forget about the previous audit response – ensure all actions were completed.

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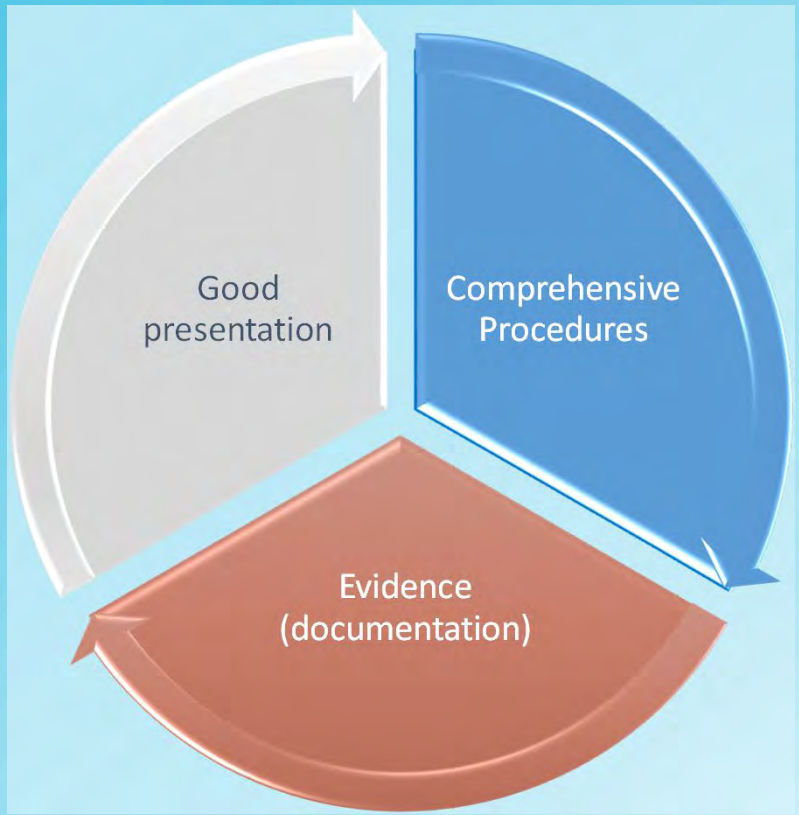
Preparation

- One of the first items:
  - A review of the major changes since the last audit
    - Validation protocols/reports.
    - Risk Assessments.
    - Change Control Forms.
    - Ensure they are reviewed and available in the war room!

- Identify key exposures within each area
  - List exposures (team brainstorming sessions).
    - Include a review of completed investigations, new product introductions,..
  - Prioritize major/critical exposures.
  - Agree actions.
  - Assign responsibility & timelines for each action.
  - Periodic review & progress updates
    - Move resources if needed
  - Assess the need for ‘Position Statements’.
    - Typically prepared where gaps cannot be addressed.

Success in any audit requires 3 things



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- The importance of good presentation
  - You can’t make a bad system look good.
  - You CAN make a typically good system look bad.

  Examples:
  - Notice boards with operational details present
    - Trend data may lead an auditor to issues.
    - Remove all unnecessary information.
  - Poor housekeeping.
  - Obvious non-compliances on the tour.
    - An inspection is not the time to find these.
  - Unprepared or poor/non-versatile presenters.

Selecting Your Presenters

- Identify subject matter experts in each area
  - Important: identify back-up presenters
    - Auditors may split up or primary presenter unavailable.
  - They should be involved in pre-reviewing procedures for currency.
  - Should be comfortable answering questions.
    - Don’t select a quivering mass of indecision!

  - Typically presenters are managers or team leaders
    - General employees may also be questioned.

Who makes the best presenter?

- The spin doctor
- The defence lawyer
- The mute

The ideal presenter must be all three! - Versatility

Spin-doctor:	Pleasant, confident & promotes all that is good in the system.
Defence lawyer:	Must reassure the inspector of the systems capability e.g. redirecting to other procedures if necessary.
Mute:	You must know when to stop talking.

Training – Responding to Questions

- Train the presenters:
  - to understand the audit process,
    - to ‘not panic’ when it changes suddenly.
  - to cope with difficult & unexpected questions,
  - remind them that they can refer to procedures,
    - Do not guess.

- How to effectively answer questions:
  - Answers should be
    - Complete.
    - Truthful.
    - Concise – with no additional information.

Training – Responding to Questions

Do you have the time?

Typical answer – “It’s 11:45”

Volunteers more information than was asked for!

This also applies to providing documentation!

Training – Auditing Techniques

- The different techniques used by inspectors.
  - Open ended requests ..
    "Describe the procedure to me."
  - The silent treatment.
    Don't feel the need to speak first!

- Different starting points/audit types
  - Finished Product (backwards/top-down)
  - Raw materials (forwards/bottom-up)
  - Major investigations
  - Major changes
  - Complaints
  - CAPAs

Training - Audit Etiquette

- Be polite and helpful.
  - Don’t be obstructive.

- Accept citations.
  - Don’t argue.
  - You can present your case to a point.
  - Know when to stop!

- Let the ‘Presenters’ present.
  - Don’t offer answers for areas where your knowledge is limited.

Conduct Mock Audits

- Can help to identify compliance issues.
- Familiarize employees with the process.
- Enable employees to practice how best to answer questions.
- External auditors – less familiar but may be useful.
  - If internal staff are not experienced.
  - Preparation for an initial license application.

Note: more than one should be planned if possible.

Preparations for Audit Day

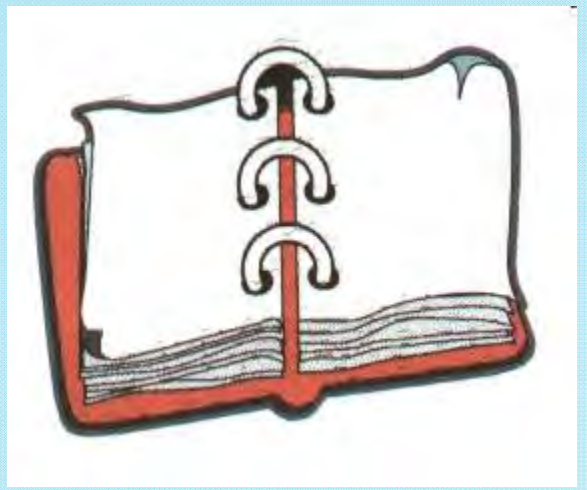
- Key things to address:
  - Who to notify when the auditor arrives on site.
  - The location of the audit room.
  - Who will be present at the opening meeting.
  - The tour route.
  - Any site specific H&S issues which the auditor needs to know about.
    - Suitably sized coats etc available.
  - Assembling any information requested by the auditor (if not already communicated to them).

War Room

Primary function - support for presenters.

- Ensure it is adequately resourced
  - Getting requested documents.
  - Tracking location of the auditor.
  - Holding documents likely to be requested.
  - Documenting requested information & if it has been presented.
  - Reviewing documents prior to their presentation.
  - Area for presenters to wait.

- Establish communication channels for key personnel.



A log should be set up for

- All documents requested by the inspectors,
- removed and/or requested from archives, QA etc..

You need to make sure they go back after.
The log can help to prepare for future audits.

Thank You

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Useful Links & References

TGA Inspection Process:
https://www.tga.gov.au/book/inspection-process

TGA examples of medicine inspection deficiencies:
https://www.tga.gov.au/book/appendix-2-examples-medicine-inspection-deficiencies

TGA Re-Inspection Timetables:
https://www.tga.gov.au/manufacturer-inspections-risk-based-approach-frequency

FDA Warning Letters:
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

FDA Inspection Guides:
http://www.fda.gov/ICECI/Inspections/InspectionGuides/default.htm

Inspection Readiness: A Guide to Preparing Subject Matter Experts to Face the FDA

http://www.fdanews.com/ext/resources/files/The_Food_And_Drug_Letter/2013/Inspection-Readiness-ExecSeries.pdf

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Useful Links & References

US FDA - Investigations Operations Manual, Chapter 5 – Establishment Inspections:

http://www.fda.gov/ICECI/Inspections/IOM/default.htm

Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Part 2: Regulatory Auditing Strategy:

http://www.fda.gov/ohrms/dockets/dockets/06d0011/06d-0011-gdl0001-Tab-11.pdf

International Regulatory Audits for Pharma:

http://www.pharmacompliancemonitor.com/international-regulatory-audits-for-pharma/1704/

Preparing your analytical lab for a regulatory audit:

https://www.chem.agilent.com/Library/eseminars/Public/Preparing_Your_Analytical_Lab_For_A_Regulatory_Audit.pdf

How to plan for a GMP audit in Pharmaceuticals:

http://www.pharmaguideline.com/2013/10/how-to-plan-for-gmp-audit.html

Planning and procedure followed during regulatory audits:

http://www.pharmaguideline.com/2014/08/planning-and-procedure-for-regulatory-audits.html#

White Paper – Preparing for GMP audits:

http://www.pharmout.net/downloads/index.php#whitepapers

Auditing as a Component of a Pharmaceutical Quality System:

http://www.ivtnetwork.com/sites/default/files/AuditingComponent_01.pdf