Handling the Inspection and Closeout Meeting

cerulean associates LLC
lean compliance + FDA consulting

FDANEWS

Agenda

annual activities
pre-inspection activities
handling activities
closeout activities

Site inspection response team
Site inspection proof binder
Sample inspection handling SOP walkthrough
More policies and SOPs to consider
Regulatory training (a practical approach)
If you're going more virtual….

ANNUAL ACTIVITIES

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Five Elements to Keep Current

- Site Inspection Response Team
- Site Inspection Proof Binder
- Inspection Handling SOP
- More SOPs/Policies
- Regulatory Training

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Site Inspection Response Team

Role	Name	Office Phone	Cell Phone	Email
Quality Assurance				
Back-up				
Regulatory Affairs				
Back-up				
IT				
Back-up				
RIM				
Back-up				
Senior Mng Rep				
Back-up				

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Site Inspection Proof Binder

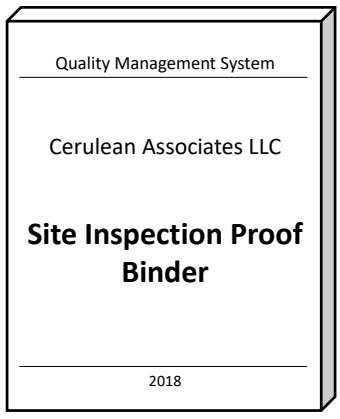
Two sections

- Basic site info and records (e.g., proof)
- Specific/supplemental records

Update Section One annually after QSMR or APR

Reuse internally for:

- your inspection prep
- training personnel on inspection handling
- conducting internal quality audits
- review as a template with critical suppliers



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Site Inspection Proof Binder

WHO *Guidelines for Drafting a Site Master File (SMF)*
www.who.int/publications/en/

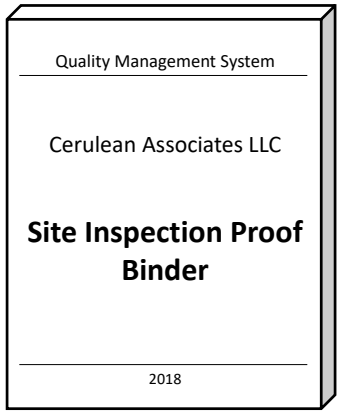
PIC/S *Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File*
www.picscheme.org/publication.php

Checklist: Binder Contents

In reference materials

Section 1: Basic Site Info

- Site address, phone #'s, business hours
- Top-level organization chart for site
- Overall site diagram with workflows
  - If sterile lock-down areas are important, make sure to clarify location on diagram and air handling
- List of products made/assembled at site (include reference to any specific NDA/BLA/510K)
- List of products distributed from/stored at site
- List of critical vendors and tier 1 distributors
- Overall quality policy
- Index of SOPs and policies
- List of recent (within past 5 years) inspections and 3rd party audits (and results)
- List of current company certifications and/or awards
- For any nearby sites, add a map showing sites



Case Study: Section 1 Excerpt

List of Inspections and 3rd Party Audits over past 5 years			
Type/Scope of Inspection	**Inspection Body**	**Date Performed**	**Results/Findings**
Routine cGCP	ANM – Romania	July 2006	No findings
Routine cGCP	MHRA – UK	January 2007	1 minor finding
Study specific	FDA – US	July-August 2008	4 FDA Form-483 findings, no WL
Routine cGMP	MHRA – UK	October 2010	No findings
GMP for controlled substances	IGZ – Netherlands	May 2011	No findings
ISO 9001 renewal	Cerulean	October 2011	ISO certificate re-issued

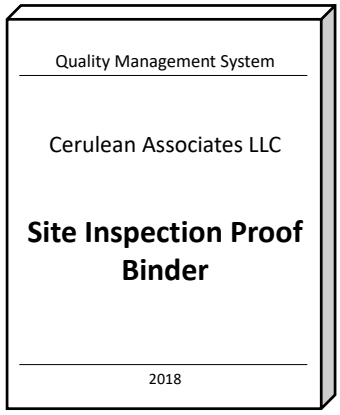
Section 2: Specific Information

Section Two: **Specific/Supplemental Info**

- Specific SOPs
- Relevant CAPAs or OOS's
- Clinical trial protocols
- Site data integrity compliance plan
- etc.

Very specific to inspection cause

If routine inspection, consider compiling remaining records from Frequently Requested Records list



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Case Study: Section Two

Specifics from a Recall Closeout Inspection:

- List of all consignees (as close to patient as possible, so minimum 1st tier – preferably through 3rd tier)
- Summary *Memo to File* of the various steps taken with clear timeline of events, from initial realization/complaint to today
- CAPA(s) and investigations associated with (including recreation of event)
- Associated product and QC SOPs (before and after fixes/changes to resolve)
- Any copies of investigations conducted by suppliers who caused/were relevant to recall
- Copies of all press releases, including web and social media announcements (FDA will google beforehand, so you better have copies of all of them … including from contract sales force)
- Correspondence from any customers certifying they destroyed/disposed of product if they didn't return it
- Spreadsheet of consignee contacts – calls, emails, letter attempts, dates, etc.
- Copies of typical letter/email to consignees
- DMR – before and after (if changed)
- Photos or video of actual destruction process (FDA will take photos when they observe as evidence)

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Inspection Handling SOP

- greeting investigators
- establishing proper logistics
- tracking inspection progress
- using an observation-closure matrix
- note-taking and duplicate photo taking
- coordinating employees and contractors interviewed
- answering questions – best practices
- logging documents shown to v. requested by the investigator
- providing samples
- handling affidavits
- correcting observations during an inspection
- managing the closeout meeting

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Sample SOP: Inspection Handling

In reference materials


Handling Regulatory Agency Inspections

1. PURPOSE

2. PERSONNEL AFFECTED

3. SPECIFIC RESPONSIBILITIES

Practical Tip
Try to keep any "welcome to our firm" presentation to 15 slides or less

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More Polices/SOPs to Consider

Policy: Site Visitor Access
- sign-in logs, visitor badges, web v. LAN access
- escort of guests
- providing access to general v. secured areas, documents, systems
- allowances for photography or videotaping
- requirement for 15-minute safety orientation for guest workers

SOP: Responding to Regulatory Agency Inspectional Findings
- correspondence drafting and reviews
- provision of proof

SOP: Tracking Regulatory Agency Communications & Commitments
- log or tracking spreadsheet as record
- reviewing progress and communications with management

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Regulatory Training

FDA likes to see everyone be aware of the regulations a firm, its products and processes are under

Timing	Activity
Year 1 (including new hires AND new contractors)	In person training that relates regulations to day-to-day job tasks (SOPS/policies) and a safe/efficacious product
Year 2	Read n' review or CBT training
Year 3	Lunch and learn session on new or recent, relevant guidance OR Warning Letter to competitor Read n' review or CBT training
Year 4	In person training (as per Year 1)
For new or revised regulation	In person training (cycle starts anew)

Considerations If Your Firm is Going More Virtual….

- Where will FDA be situated?
- How will you provide FDA records requested?
- Who will take notes and log records?
- Who will lead the closeout meeting (and push back as necessary/make oral commitments)? Only make commitments you (not your suppliers) have physical control over….
- Who will be responsible for spearheading any response?
- How will you show FDA which supplier is responsible for what regulated activity and records?
- Do your quality agreements clearly document:
  - your accountability
  - suppliers' responsibilities

FAQ: "Should we show our supplier audit reports to FDA investigators?"

Caution! You are **currently** ONLY required to give FDA supplier audit reports under six limited circumstances

see www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073841.htm

That said...

- You are required to turn over to EMA, Health Canada, TGA, MHRA, etc.
- It may be in your best interest – if you are going more virtual – to provide the supplier audit report
- **Be aware** that with the inspectional program and policy changes with NIPP and MDSAP, this self-imposed FDA policy limit may change

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Upon notification
Tasks just prior to the investigator's arrival
And if you're surprised…

PRE-INSPECTION ACTIVITIES

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Upon Notification

- Letter or phone call
  - international inspections ***used to be*** only by 4-6 week "heads-up"…
- Determine:
  - any leeway on start date
  - can you send anything ahead of time (Site Inspection Proof Binder)
- Verify:
  - type of inspection (routine/risk-based, for cause, PAI, etc.)
  - scope and primary focus (closeout previous inspection, clinical trial, specific product, recall closeout, etc.)
  - investigators who will attend **(google them!)**
  - anticipated length (days, weeks)

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Upon Notification

Notify **Senior Management** and the **Site Inspection Response Team (SIRT)**

- consider inviting senior management to your *rapid review and prep session*
- depending on context, suggest notifying:
  - critical suppliers (CMOs, CROs, etc.)
  - other (subsidiary) sites
- give a draft site notification to be sent out to all site employees by the facility head (CEO, etc.)
  - scope of the inspection
  - dates of inspection
  - reminder of Site Inspection Response Team members (direct questions to)
  - reminder link to Regulatory Inspection Handling SOP
  - reminder link to corporate ethics policy

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Upon Notification

Conduct a rapid review and inspection prep session with the Inspection Response Team (and backups)

- expectations for how inspection will unfold
- quickly refresh everyone about any previous inspection and results
- schedule daily debriefing and review meetings
- remind about rules surrounding special/restricted access areas (clean rooms, loud rooms, labs, etc.)
- quick review of your Regulatory Inspection Handling SOP
- quick review of your Site Inspection Proof Binder (update as necessary)
- remind everyone of best practices for answering questions
- clarify any current known open issues and status (e.g., recalls, etc.)
- identify note-takers (make sure they also have a camera)

Helpful Checklist

In reference materials

Divided into 2 sections:

- upon initial notification
- prior to investigator arrival

And If You're Surprised….

- In "Bonus" section of reference materials
- 7-steps designed to carryout in less than 10 hours (although typically in less than 5-10 days if you're really thorough)


Rapid Deployment Tips to Prepare for an Inspection Quickly

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Interactive Exercise


Exercise #3 - Initial FDA Inspection Handling

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This is ALL viewed from the perspective of your inevitable response to inspection

Greeting the investigators professionally
Turning the site tour to your advantage
Providing access
Responding to questions
Inspection observation-closure matrix
Some record do's and don'ts
Logging items requested v. provided

HANDLING ACTIVITIES

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Inspection Flow

Opening Mtg
- Verify credentials
- Provide Site Inspection Proof Binder

Site Tour
- Showcase specific, visible controls
- Take notes

Record Review
- List records provided v. requested
- Include in debrief

Closeout Mtg
- Identify gaps
- Discuss for clarity
- Known next steps

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Checklist: Handling Inspection

In reference materials

Greeting the FDA Investigators

1. If you have a logbook, make sure to have *each* investigator sign-in
2. If your site utilizes guest/visitor badges, provide to *each* investigator
3. Verify the investigator's credentials
    - do NOT try to photocopy his/her credentials (18 USC § 701)
4. Escort the investigators to a meeting room (or your prepared inspection/audit room)
    - offer/provide professional refreshments (non-alcoholic drinks)
5. Notify each member (or backup) of the Site Inspection Response Team
6. Obtain a copy of the Form FDA 482, Notice of Inspection (US only)
    - this should include investigator(s) name, purpose of inspection
    - verify the form has the right company name and address
7. Provide a copy of the Site Inspection Proof Binder
    - if current and you've not already provided

Turning a Tour to Your Advantage

Reminder: this NOT a typical show-and-tell

Remember
Investigators visually assessing if you are operating in a "consistent state-of-control"

Goal: Showcase physical controls

- locked and secured areas
- calibration labeling
- labeling of storage areas, cabinets, etc.
- cleanliness and orderliness ("everything in its place and a place for everything")
- controls over special areas (clean rooms, labs, etc.)
- workflow "gates"
- any alarmed doors, security video cameras, etc.
- humidity and temp sensors

!CAUTION!
Any cameras used in production or CAPAs are open to inspection

Providing Access

- Escort the investigators at all times
  - a known tactic is to try to "escape" the escort
  - make sure the investigators gown up, etc. for special controlled areas!
- Log records requested v. given
  - consider making duplicate copies of any copy provided
- Have a dedicated note-taker document
  - significant items
  - questions and answers
  - areas visited within site
  - photographs taken (consider taking your own)

Responding to Questions

- Be honest and cooperative
- HOWEVER…

"If you don't need to say, it's best to stay silent"

- Preface answers with **"**To the best of my knowledge…."
- Refer to SOPs, policies or widely recognized industry standards (such as ISO, GAMP, ICH, IMDRF, etc.)
- Be **careful** referring to FDA guidance documents
- Whenever unsure – refer to the company expert or a member of the Site Inspection Response Team
- Avoid arguing with the investigators

Responding to Affidavits

- Do NOT sign
- Do NOT listen (yes, you can walk away)
- Do NOT handle, review, skim through, etc.
- Do NOT initial or correct any errors

Contact your legal counsel immediately

Tracking Progress

With **Investigators** and **Site Inspection Response Team**

- daily debriefs or inspection summaries with FDA
- use this time to ask questions/clarifications and show any fixes

Follow with a private **Site Inspection Response Team** review

- share impressions
- discuss potential corrective actions
  - quick fixes (and proof to provide the investigators)
  - longer term fixes (and proof to provide)
- update senior management

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Observation-Closure Matrix

- Keep simple to allow easy tracking and rapid review
- Use in debriefing meetings
- Use in closeout meeting
- Use to help formulate responses (and proof)
- Don't forget to open a nonconformance or CAPA

This is the PROOF you will send with your response to any FDA-483 so do NOT skip this

Inspectional Observation	Owner / Accountable	Status	Proof (documents)

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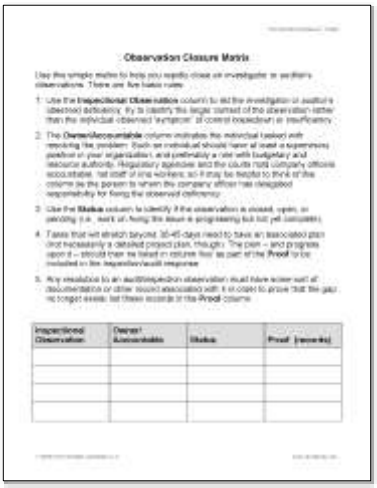
Template: Observation-Closure

In reference materials

- use during inspections
- use during follow-up
- use during internal quality audits



Observation Closure Matrix

Inspectional Observation	Owner/ Accountable	Status	Proof (records)

During a regulatory inspection, the investigator asks for a specific record. After 24 hours, you cannot find it. Which response is best?

a) Give us another 24 hours to locate the record

b) The record is at another site

c) We noted a discrepancy and opened a CAPA

Reasonable Record Turn-Around

For paper records onsite: **less than 1 hour**

For records offsite: **4-24 hours**

For e-records on archived media: **4-24 hours**

For records at a supplier: **3-12 hours**

- Can your suppliers provide record review via webinar?

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Some Record Do's and Don'ts

- Do **NOT** provide investigator with original documents to take with him/her
  - make sure to follow your SOP on making copies of controlled documents!
  - strongly consider stamping *COPY* on it and using different colored paper….
  - call District Office immediately if investigators insist on taking originals
- Do **NOT** provide any confidential/trade secret documents without clear demarcation on the documents
- Do **NOT** inhibit investigators from taking photographs
- Do **NOT** hide records from investigators (or redact items within a document)

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Some Record Do's and Don'ts

- Do **NOT** create false records (including completing any blanks in already filed forms) to fill in gaps in record trail
- **DO** explain if you cannot find or produce a record (printer or copier is broken or jammed, the record is in transit to an outsourced provider, USB drives are locked, etc.)
- **DO** verify investigator's request in your lingo (does a request for a "quality manual" mean "all your SOPs and policies" or your Site Master File or …?)

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Logging Requests v. Provided

Item #	Item Requested	Description/Intent	Date Requested	Date Provided	Provided by

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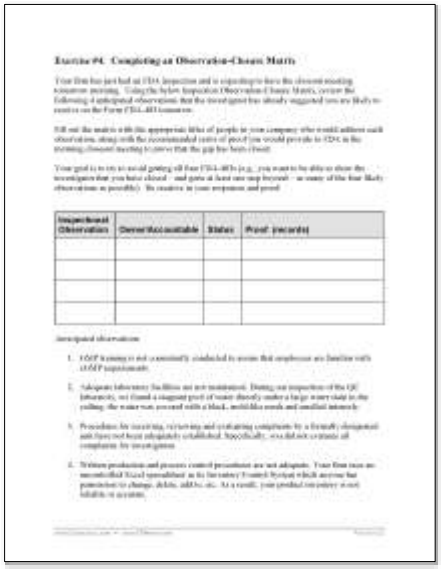
Interactive Exercise



Exercise #4. Completing an Observation-Closure Matrix

Your firm has just had an FDA inspection and is expecting to have the closeout meeting tomorrow morning. Using the below Inspection Observation-Closure Matrix, review the following 4 anticipated observations that the investigator has already suggested you are likely to receive on the Form FDA-483 tomorrow.

Fill out the matrix with the appropriate titles of people in your company who would address each observation, along with the recommended notice of proof you would provide to FDA in the morning closeout meeting to show that the gap has been closed.

Your goal is to try to avoid getting all four FDA-483s (e.g., you want to be able to show the investigators that you have closed – and gotten at least one step beyond – as many of the four likely observations as possible). Be creative in your responses and proof.

Inspectional Observation	Owner/Accountable	Status	Proof (records)

Anticipated observations:

1. GMP training is not consistently conducted to ensure that employees are familiar with cGMP requirements.
2. Adequate laboratory facilities are not maintained. During our inspection of the QC laboratory, we found a stagnant pool of water directly under a large water stain in the ceiling; the water was covered with a black, mold-like weed and smelled intensely.
3. Procedures for receiving, reviewing and evaluating complaints by a formally designated unit have not been adequately established. Specifically, you did not evaluate all complaints for investigation.
4. Written production and process control procedures are not adequate. Your firm uses an uncontrolled Excel spreadsheet as its laboratory Control System which anyone has permission to change, delete, add to, etc. As a result, your product laboratory record reliability is in question.

Again, this is ALL from the perspective of writing your response

Managing the closeout meeting
Immediately after the closeout

CLOSEOUT ACTIVITIES

Managing the Closeout Meeting

- **Senior management must attend** (preferably in person)
- All primary members of the Site Inspections Response Team should also attend
- Treat the investigators like the professionals they are
- Listen for opportunities where you can go beyond the observation to demonstrate "good faith"
- Remember that the Center and ORA now make the final determination on deficiencies
- **Only pushback with supporting, objective evidence** like guidance documents, industry consensus standards, and company records

Understanding Each Observation

- Discuss deviations and other observations – get clarity on expectations v. concerns
  - ask questions around obtaining clarity (avoid asking to release any non-conforming products, continue with unsafe trials, etc.…)
- Understand the basis for each observation
  - what are the underlying facts supporting the observation
  - what records/samples/photos support the observation
  - what are your regulatory v. guidance obligations
- If you are confused by an observation, ask, ask, and ask again
  - avoid stating in any written response that the company is confused....
- Try to get investigator's viewpoint and resolution suggestions/opinion ("If we did … / Would that …?")
- Discuss and make sure you grasp the larger, systemic issues that these "snapshot in time" observations represent

Closeout Meeting Do's

- **DO** remember that just because it's not on the Form FDA-483 doesn't mean it won't end up in a Warning Letter
- **DO** treat the inspection work products as professional products
- **DO** display a willingness to understand and make the expected corrections
- **DO** find opportunities where you can go beyond gap closure to demonstrate you "get it"
- **DO** pushback when you have clear supporting evidence such as guidance documents and specific company records as objective evidence

Closeout Meeting Do's

- **DO** write down any next steps/timeframes, investigator comments or suggestions, etc.
- **DO** only commit orally to those actions and resolutions you have control over (e.g., be careful about committing on behalf of suppliers)
- **DO** be conservative in any corrective action timeframes

Closeout Meeting Don'ts

- Do **NOT** pull out your iPhone/smartphone and start texting, or calling, or Face Timing…and no Twitting….
- Do **NOT** make commitments without knowing resources/time required
- Do **NOT** tell the investigator you need a "stiff one" and ask if he/she will join you
- Do **NOT** beg for forgiveness, complain like it's a death sentence, etc.
- Do **NOT** pull out resume and ask if the FDA has any open positions

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Closeout Meeting Don'ts

- Do **NOT** scoff or take a "yeah, right" attitude
- Do **NOT** take notes for calling the *Wall Street Journal* to give them your side of the story
- Do **NOT** casually place on the table a draft press release, blog post or letter to your Congressman supporting FDA budget cuts
- Do **NOT** ask if you can delay your response while you go on vacation (especially to an upscale location)
- Do **NOT** threaten or otherwise try to intimidate the investigators

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Closeout Meeting Don'ts

- Do **NOT** ask what might…you know… "influence your decision…?"
- Do **NOT** claim that inspection findings will "put us out of business"
- Do **NOT** complain that "no one else does this" (or vice versa)
- Do **NOT** point out that no one "actually died"
- Do **NOT** grumble that all this "paperwork won't make our product better"
- Do **NOT** suggest that the investigator doesn't understand your industry

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Closeout Meeting Don'ts

- Do **NOT** blame all observations on poor training or "stupid employees"
- Do **NOT** remind the investigator that previous inspections didn't write up a particular FDA-483 observation
- Do **NOT** intimate that the investigator is ignorant/naïve because "we hired ex-FDA guys and they didn't find anything wrong"

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Immediately Afterward

- Hold a post-inspection Site Inspection Response Team meeting
  - treat as private daily debrief meeting
  - review Inspection Observation-Closure Matrix
    - what needs to be updated?
    - what did the investigators believe was effectively closed?
    - do you have the right people assigned to open items?
    - are the timeframes and resources required appropriate?
    - can you also "go above and beyond" during the corrections within those timeframe and resources?
  - identify next steps for drafting the response

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