

# Rapid Deployment Tips to Prepare for an Inspection Quickly

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On the desk sits the letter with blue and black letterhead from the U.S. Food and Drug Administration informing you that Agency inspectors will arrive at your facility the Thursday after next.

Now what?

## Drafting an Action Plan

Most regulatory and quality professionals would agree that a best practice is to have a pre-defined inspection preparation action plan at the ready, rather than assembling and executing one in an ad hoc manner under a tight timeline in an environment suddenly fraught with the tension and anxiety inevitably accompanying the announcement of an impending inspection.

And yet, day-to-day activities, projects, interruptions, distractions and business, as usual, gobble up good intentions. Defining a comprehensive action plan is often postponed. Tasks that might have been planned and executed ahead of time are left undone. Now, given the arrival of a U.S. FDA inspector in ten days or less, time is short and the firm must get the biggest impact for its preparation efforts. In this light, there are seven rapid impactful activities:

1. Review the notification letter
2. Review previous inspection records
3. Review the FDA quality system inspection technique (QSIT) manual
4. Review the relevant FDA inspection manuals
5. Review relevant harmonization guidelines
6. Prioritize likely areas of scrutiny
7. Hold an inspection expectation overview meeting

These are all in addition to those activities typically covered in a regulatory inspection and third-party audit handling standard operating procedure (SOP) such as setting aside two rooms, one for the inspector and one for company use only. (1)

The key to proper inspection preparation is divining where the inspector may go and having knowledgeable personnel and records ready to meet him or her. While these seven steps may seem like they will take significant time, experience has shown that they are accomplishable in ten days or less with two caveats: 1) Upon notification of an impending inspection, preparing for that inspection is the number one priority for the next 80 hours or less, and, 2) Reviewing the regulatory documents discussed below is vital for making educated guesses as to what is most likely to be asked by the inspector.

## *Review the documentation for specific areas of concern on the part of previous inspectors*

### 1. Review the Notification Letter

With luck, the letter will spell out the type of inspection the Agency intends to conduct, including the records the inspector expects to review. This may be a preapproval inspection (PAI), “statutory” inspection, a “for cause” inspection or a “follow-up” inspection. In such cases, the inspection is largely confined to those areas identified in the letter; although, the inspector can, and sometimes does, ask about and review supporting documentation for other areas of relevance. For example, one notification letter, sent by the FDA, informed a recipient that the Agency intended to conduct an inspection related to a whistleblower complaint around data integrity associated with clinical trial production or finished product contamination. In that case, the inspection led to a review of risk evaluations for pilot plant production and process parameters, the risk evaluation, qualification and oversight of the active pharmaceutical ingredient manufacturer and so on, not just pilot plant batch records, electronic record integrity and clinical trial produc-

tion quality control data.

In any “for cause,” PAI or “follow-up” inspection, the Agency will likely provide some level of insight into the areas of the compliance program and the records the FDA intend to review. And while no inspection is good news per se, this will at least help focus preparation far more than a general inspection based on calendar year timing.

### 2. Review Previous Inspections

Assuming the firm has been inspected by the Agency before, previous establishment inspection reports (EIRs) and FDA Form 483 observations should be available for review. Companies that have not yet been inspected by the Agency can turn to their critical suppliers such as a contract manufacturer (CMO) or contract research organization (CRO). This is especially important if the company is receiving a preapproval inspection or if a “for cause” inspection cites clinical or manufacturing oversight concerns. The CMO or CRO may have been inspected by the Agency. If so, they will have EIRs and Form 483s that can be reviewed.

Review the documentation for specific areas of concern on the part of previous inspectors. For instance, if the previous report cited inconsistencies in calibration records for a specific titrator, the inspector might want to either look at more calibration records for other equipment or focus on the overall maintenance program from equipment logs, cleaning records and even personnel qualifications (or supplier qualifications if maintenance is outsourced).

Records that raised questions and led to further scrutiny of supporting activities and their documents are good candidates to be examined again. Since the last inspection, how has the company attempted to resolve questions raised by the previous inspector? And what track record of improvements does the firm have to show? From a review of previous FDA observational forms and any related correspondence, compile a list of the records reviewed. This should provide a good idea ►

of where the inspectors will at least start their review.

### 3. Review the QSIT Manual

The third step is to review the FDA's Quality System Inspection Technique (QSIT) manual. (2) Originally written to help inspectors of medical device and diagnostic firms since the publication of FDA's *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach* with its emphasis on a holistic compliance framework and quality system, the QSIT is well worth the time to review; it provides example questions to which the FDA inspector might seek answers. For instance, in order to assess the role of senior management in promoting and overseeing FDA compliance at a firm, the inspector may make sure to obtain answers to questions such as:

- Have measurable quality policy objectives been implemented?
- Are quality audits conducted?
- Does the quality unit have appropriate responsibility, authority, and resources?

This is not to say the inspector will outright ask such questions; rather, the inspector will ask questions of both senior management and other personnel while looking for records (e.g., proof) that substantiate and/or answer the above questions.

### 4. Review the FDA Inspector Manuals

At this point, it's time to start sketching out the likely path the inspection will follow. The agency has provided some help in the guise of three publications:

- Investigations Operations Manual
- Inspection Guides
- Compliance Program Guidance Manual

For the Investigations Operations Manual, review chapters four, "Sampling," and five, "Establishment Inspections." (3) If scrutiny is expected around oversight of an international supply chain, examine chapter six, "Imports." If review of product recall handling is anticipated, take a look at chapter seven, "Recall Activities."

There are a number of inspection guides, so skim the detailed listing on the FDA website to see which best apply. (4) Remember, the objective is to make a quick

list of the likely targets of scrutiny within the firm. Thus, if a preapproval inspection is expected given a recent submission, look specifically at the guide *Pharmaceutical Quality Control Labs*. (5)

Multiple chapters in the Compliance Program Manual deal with specific sub-components of regulatory expectations. (6) The inspector will try to ascertain the company's level of compliance with these expectations, so a review of his/her default inspectional objectives can be helpful. The two most useful sections for uncovering specific expectations will be 7346.843 on Post Approval Audit Inspections, (7) and 7346.832 on Preapproval Inspections/Investigations. (8)

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## *The key to proper inspection preparation is divining where the inspector may go*

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Be aware that while a review of the statutes and regulations may also be helpful, particularly if it has been some years since the statutes, regulations and their preambles have been read. Each of the publications referenced above cites specific regulatory sections for the inspector. Given the limited time available in preparing for the inspector's arrival, other inspection preparation activities may preclude a more comprehensive regulatory review. Keep in mind the goal is to rapidly identify questions most likely to be asked by the inspector. As stated earlier, this seven step preparation process assumes approximately ten days or less (e.g., 80 hours or less). Thus, use the time available before the inspector arrives as a guide as to how in-depth statutes, regulations and preambles are reviewed in order to get the greatest return on investment given the limited preparation time available.

### 5. Review Relevant Harmonization Guidances

Just as the FDA QSIT and the three FDA publications noted above can help guide rapid preparation by identifying potential questions to be prepared to answer, so too

can guidance documents from the International Conference on Harmonization (ICH) and the Global Harmonization Task Force (GHTF). In practice, however, ICH guidelines can be of limited value in time-sensitive situations such as preparing for an inspector's imminent arrival. GHTF guidelines, while ostensibly written for the device industry, are much more specific in terms of questions to be answered and the documentation to be kept around quality systems; thus, much more helpful when preparing for an inspection.

The more virtual the biopharmaceutical firm (i.e., the more the firm outsources development, manufacturing and/or distribution), the more likely the FDA inspector is to focus on supplier selection, evaluation, qualification and oversight. Given such a supplier management focus, the most relevant GHTF document to look through is the *Guidance on the Control of Products and Services Obtained from Suppliers*. (9) Pay particular attention to the end of each section entitled "Objective evidence may include" as well as any sentence ending with the phrase "...should be kept." This will help quickly identify examples of records that will support the answers to the questions the inspector may ask.

Be aware that FDA is slowly converging its regulatory compliance infrastructure expectations for device, biologic and drug firms to a common set of holistic, risk-based quality system controls (10); thus, biopharmaceutical quality and regulatory affairs personnel who ignore recent harmonization guidelines directed more at medical device firms may unwittingly be doing themselves a disservice. If a harmonization guideline addresses common quality system and other core compliance infrastructure issues, the guideline document is well worth a quick review to ascertain if it has specifically applicable advice. (11, 12)

### 6. Prioritize Areas of Scrutiny

With the list of potential questions and possible documentation to provide, it is time to prioritize likely inspection points. Identify between 5-10 likely areas that will be reviewed. For instance, if the review indicates the agency is concerned about

management involvement and support for the company's quality system, then what is it about management involvement and support that is likely to draw inspector scrutiny? For a more virtual pharmaceutical firm, one specific area might be the effectiveness of supplier oversight in the context of management involvement. In this case, expect to provide the inspector with copies of records such as:

- Quality system management review SOP
- Quality system management review summaries and action plans
- Training SOP
- Training records, including effectiveness assessments, for management
- Executive resumes
- Organizational chart
- Management job descriptions
- Supplier evaluation and selection SOP
- Documented risk evaluation of various suppliers and supporting documentation showing management

involvement

- Documented decisions and rationales on which suppliers to use and the controls to be put in place, including supporting documentation showing management involvement
- Quality or technical agreements with critical suppliers, and any supporting documentation showing management involvement
- Documentation showing management review of supplier deviations and/or investigations

It is important to be prepared to answer and provide proof as to if management trained on supplier evaluation and selection *prior to* vendor selection, and if management trained on risk management *prior to* execution of a quality agreement. After-the-fact training will spark questions as to how the firm made informed decisions if management was unaware of its current obligations, company processes and the potential impacts of supplier problems. Further document scrutiny

might reveal that although a risk evaluation clearly showed one supplier would be more problematic from a drug safety and efficacy issue, the price was much better and the supplier was chosen *with no additional controls or safeguards put into place* given the increased level of risk. It is then easy to call into question whether the firm is operating in a state of control capable of consistently producing a safe and efficacious product.

### 7. Conduct an Inspection Expectation Overview

With those 5-10 specific areas in hand, and a list of documents to be expected to turn over for each area, schedule a meeting to review the preceding analysis's results and obtain feedback. This meeting should be cross-functional, including senior representatives from the quality department, regulatory affairs, information technology (IT/ICT), manufacturing, clinical and so on. The meeting should try to update everyone on inspection expectations and identify items that may



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have been overlooked. Closeout this meeting by briefly reviewing your firm's regulatory inspection and third-party audit handling process.

### Final Thoughts

These seven steps will help a firm meet an inspection with confidence. The seven steps are accomplishable within ten days or less under two assumptions: first, preparing for the inspection becomes the top priority for those 80 hours or less, and second, reviewing the regulatory agency documents referenced above is strictly for rapidly estimating what is most likely to be asked by the inspector, and not for the purpose of training or in-depth comprehension. This lean compliance, seven-step preparation assumes that many of the requirements spelled out in statutes and regulations are already accounted for in a firm's 21<sup>st</sup> century quality system and compliance infrastructure.

Preparing for an impending FDA inspection is like preparing for a suddenly announced visit from new in-laws. Knowing what to expect can save hours of anxiety, headache, and heartburn. The seven steps outlined above can help executives excel in less than ten days.

Are you ready?

### About the Author

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### References

1. *Bulletproof Yourself against FDA Enforcement*, John Avellanet recorded webinar, January 11, 2010
2. FDA Guide to Inspections of Quality Systems, August 1999, U.S. FDA, <http://www.fda.gov/downloads/ICECI/Inspections/UCM142981.pdf>, accessed on June 10, 2010.
3. FDA Investigations Operations Manual, U.S. FDA, [www.fda.gov/ICECI/Inspections/IOM/default.htm](http://www.fda.gov/ICECI/Inspections/IOM/default.htm), accessed on June 11, 2010
4. FDA Inspection Guides, U.S. FDA, [www.fda.gov/ICECI/Inspections/InspectionGuides/default.htm](http://www.fda.gov/ICECI/Inspections/InspectionGuides/default.htm), accessed on June 11, 2010.
5. FDA Pharmaceutical Quality Control Labs, July 1993, U.S. FDA, [www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074918.htm](http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074918.htm), accessed on June 11, 2010.
6. FDA Compliance Program Manual, U.S. FDA, [www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm2005382.htm](http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm2005382.htm), accessed June 11, 2010.
7. FDA Compliance Program Guidance Manual, Program 7346.843, Chapter 46, January 29, 2003, U.S. FDA, [www.fda.gov/downloads/ICECI/Compliance](http://www.fda.gov/downloads/ICECI/ComplianceManuals/Compliance)

[ProgramManual/ucm125398.pdf](http://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/ucm125398.pdf), accessed on June 11, 2010.

8. FDA Compliance Program Guidance Manual, Program 7346.832, Chapter 46, May 12, 2010, U.S. FDA, [www.fda.gov/downloads/Drugs/DevelopmentApproval/ProcessManufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf](http://www.fda.gov/downloads/Drugs/DevelopmentApproval/ProcessManufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf), accessed on June 11, 2010.
9. GHTF Quality Management System – Medical Devices – Guidance on the Control of Products and Services Obtained from Suppliers, February 5, 2009, GHTF, [www.ghrf.org/documents/sg3/sg3final-N17.pdf](http://www.ghrf.org/documents/sg3/sg3final-N17.pdf), accessed on July 21, 2010.
10. *Get to Market Now! Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicines*, John Avellanet, Logos Press, Washington, D.C., May 2010, pp. 23-90.
11. *Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers*, Part 1: General Requirements, GHTF, [www.ghrf.org/sg4/sg4-workplan.html](http://www.ghrf.org/sg4/sg4-workplan.html)
12. *Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers*, Part 2: Regulatory Auditing Strategy, GHTF, [www.ghrf.org/sg4/sg4-final.html](http://www.ghrf.org/sg4/sg4-final.html)

### *Arm Yourself with Knowledge for Your First Inspection, continued from page 17*

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### References

1. FDA Preapproval Inspections, Compliance Program Guidance Manual 7346.832, U.S. FDA, [www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/)

2. UCM071871.pdf
2. Martin Hynes, ed., *Preparing for FDA Preapproval Inspections*, (USA: Marcel Dekker, Inc, 1999).
3. John G. Grazel and John Y. Lee, "Product Annual/Quality Review," *Pharmaceutical Technology*, March 2008 (p88-104).
4. FDA Drug Manufacturing Inspections, Compliance Program Guidance Manual 7356.002, U.S. FDA, [www.fda.gov/downloads/ICECI/](http://www.fda.gov/downloads/ICECI/)

[ComplianceManuals/ComplianceProgramManual/ucm125404.pdf](http://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/ucm125404.pdf)

5. Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice, U.S. FDA, [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070342.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070342.pdf)
6. Walter L. Pines, "How to Work with the FDA: Tips from the Experts," FDLI, 2002