Rapid Deployment Tips to Prepare for an Inspection Quickly

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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 production 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 eGMPs 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 subcomponents 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**

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 to be 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 Guidelines

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 pharmaceu-
tical 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 effective-
  ness 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 se-
lection prior to vendor selection, and if
management trained on risk management
prior to execution of a quality agreement.
After-the-fact training will spark ques-
tions as to how the firm made informed
decisions if management was unaware of
its current obligations, company process-
es and the potential impacts of supplier
problems. Further document scrutiny
might reveal that although a risk evalua-
tion 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 meet-
ing should be cross-functional, including
senior representatives from the quality de-
partment, 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. Close out 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 21st 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**

John Avellanet is the author of Get to Market Now! Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicine. He has gained tremendous acclaim for his speeches, corporate workshops and business-savvy compliance consulting work with clients and conference venues around the world. John can be directly reached through his independent advisory firm, Cerulean Associates LLC, on the web at www.Ceruleanllc.com or through his award-winning blog at www.ComplianceZen.com.

**References**

1. **Bulletproof Yourself against FDA Enforcement**, John Avellanet recorded webinar, January 11, 2010

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

Lorraine Murphy has over 20 years experience in the biotech industry, having held leadership positions in R&D and quality at several organizations.

**References**