

Getting Ready for an FDA Inspection

(Adapted from *XytexXtra*, Summer 2004)

Facilities processing human reproductive tissues (sperm, ova, embryos, gonadal tissues) became subject to regulatory requirements of the US-FDA in May, 2005. Compliance with these requirements is confirmed by inspection by FDA employees called “investigators.” These investigators conduct unannounced inspections in accordance with FDA manual at www.fda.gov/ora/inspectref/ion/ (see subchapter 560). The regulations derive from the FDA Center for Biologics Evaluation and Research (CBER).

Inspections are predicated primarily on documentation. You will be expected to have the documents (specimen records, personnel records of laboratory workers) required by 1271 and by your own SOPs. Your SOPs must be thorough, completely describing your processes, generally going far beyond 1271. For example, you would have a SOP for selecting reference laboratories and even one for managing a FDA inspection! All processes in reality must conform to requirements of both 1271 and to SOPs. Investigators are alert to discrepancies between actual behavior (processes) and specified behavior (SOP). So it is essential to accurately document processes long before any inspection occurs.

Before an inspection occurs, your facility should designate an “Inspection Team,” which will play host to the inspection. The Team will enable the inspection to occur efficiently while protecting the interests of your facility. For this to occur, the Team needs to be carefully selected, trained and kept in practice. The Team may be small, more than one person but perhaps no more than two or three. All members must be cross-trained. Each one should have thorough knowledge of your procedures (operations) that the FDA will want to examine in detail as well as the permissible scope of FDA inspections. (Yes, some investigators will try to get stuff they are not entitled to!) Members of the Team should have authority to cut through “red tape” in order to respond to investigators’ legitimate requests. They should have the authority to make immediate “corrective” decisions. Team members must possess good judgment and good communication skills, having the ability to respond to detailed questions without becoming defensive or threatened. Inspections are stressful, yet team members must remain composed.

Team members should be trained in GTPs and communications skills. They should conduct internal audits on a regular basis. They should have the authority to use outside consultants including attorneys when necessary to critique systems and to recommend improvements. Clearly, when an inspection actually occurs, they should be able to anticipate the inspector’s needs and have the necessary information available. (Required information that cannot be located is very serious.) Your principal objective is to satisfy FDA that your program is in control of the processes and procedures required under 1271 and is in compliance with all other applicable provisions of the Food and Drug Act and regulations.

As a general rule, expect to be routinely inspected at least once every two years. Earlier inspections may occur for a variety of reasons: a re-inspection after a Warning letter; a recall effectiveness check; a directed inspection in response to an informant (a “tipster” or “whistleblower”). Since inspections are unannounced, always be prepared.

All employees should know and be reminded that government investigators are expected at any time and upon arrival investigators should be immediately introduced to the Inspection Team: only Team members are authorized to provide program information to investigators, including tours of work areas.

Upon arrival of investigators, the Team will review the investigators' credentials and the FDA "notice" of the inspection. Escort the investigators to a meeting room suitable for interviews where they can also review documents and do required paperwork. The first 30 minutes of an inspection sends an investigator signals that formulate his/her opinion of the program. Let the investigator know through your attitude and actions that the inspection is taken seriously. A pleasant and cooperative approach is usually met with reciprocal courtesy. However, do not give away the "store." Inform the investigator about your (written) inspection policies: all inquiries must be directed to Team members; no cameras or video recorders; materials not available for inspection [e.g., financial data, sales data (other than shipment data), personnel data (other than qualifications of technical personnel), research data (other than that required by 1271)]; a Team member should take duplicate samples of any samples collected by an investigator and retain the duplicates under appropriate custody and control; do not initial or sign government documents; do not permit investigators to mark your original records and make copies of all records provided to the FDA. It is imperative that confidential records should be marked as such and that senior management be informed that an inspection is under way. It is a good idea to also inform your legal counsel.

Understand all questions and their context before responding to investigators. Be certain of your answers. Questions and requests need not be answered immediately; ask for clarification. See the big picture – read between the lines. Respond to specific observations, but know they are only examples. Be receptive to valid criticisms, but avoid being apologetic or defensive. Avoid admissions against your interests. Give yourself credit for your accomplishments (e.g., training, documentation), but do not brag. Get a written request if you are asked to provide something the FDA is not entitled to obtain.

During the course of the inspection, the Team should take detailed notes and, in some situations, prepare a daily summary about the progress of the inspection and any special or unusual comments of the investigator. It is appropriate to take corrective actions during the inspection; these should be included in your notes and ask the inspector to include them in his/hers. The investigator may insist on paying for copies and even for courtesies such as coffee; this is to avoid the appearance of "taking inducements" or conflict of interest.

Request an exit interview. Both the Team and senior management should be there. Listen and, when appropriate, tell FDA what has been done or will be done to correct deficiencies. Again, the Team must take good notes of the interview.

The investigator will make written notes of observations that, in his or her opinion could be violations. Commonly, such observations are about SOPs, record-keeping and validation. Such observations are recorded on FD-483, usually listed in order of significance. Ask the investigator(s) to include your corrective actions taken during the inspection. A copy of the 483 will be given to you, and you should also keep in mind that it is available to your competitors

under the Freedom of Information Act (FOIA). You are not required to respond to FD-483, but it is in your best interest to do so in writing.

The investigator will also prepare an “Establishment Inspection Report” (EIR) that is not routinely provided to the inspected program. Ask the District Office for it and/or file a FOIA request if necessary. (Matters “under investigation” are exempt from FOIA; refusal to provide an EIR is an ominous sign.)

Enforcement action beyond the issuance of an FD-483 is taken based on the significance of the violation, the public health risk, and the likelihood of voluntary corrective action. The FDA focuses on the pattern of violative actions. Enforcement actions range from a Warning Letter (made public every Thursday); an Order for Detention, Recall and Destruction; Seizure; Injunction; Consent Decree (including a fine); Criminal Investigation; and even individual criminal liability of senior executives with no direct involvement in the allegedly unlawful behavior. A satisfactory response to an FD-483 usually is sufficient to avoid enforcement action.

In responding to an FD-483, address the real issues; remember that problems cited in the FD-483 are not necessarily inclusive of everything perceived to be in violation. Fulfill all promises in a timely manner; do not promise anything you cannot deliver. (Failure to keep promises will be remembered and you will be goaded about them.) Establish open communication with the District Office; frequent written updates and personal visits are both beneficial; a contentious attitude is not.

Center for Biologics Evaluation and Research as a major component of FDA is a work in progress, evolving. The inspection process is evolving. Change must be expected; establishments must remain ever vigilant as to current expectations of FDA.