Are you ready for the FDA? How to prepare for and manage your FDA inspection

Martha Wells, MPH, RAC
Clay Anselmo, BS, RAC
Rich Weiskopf, BS, ABA, RAC

Introduction

Reproductive establishments are subject to FDA inspection as a part of the regulatory framework contained in Title 21, Part 1271 of the FDA Code of Federal Regulations (21 CFR Part 1271). For many fertility clinics, these inspections can be a source of anxiety and concern. There are often misunderstandings about FDA expectations and what may occur during an inspection. In addition, FDA inspections are unannounced and have a markedly different focus from other types of accreditation audits, which can create additional worry. This article discusses the purpose of FDA inspections and addresses how to prepare for and manage them successfully.

Background

The FDA announced its plans for a more comprehensive, risk-based approach for regulation of human cells, tissues and cellular- and tissue-based products (HCT/Ps) in 1997. This approach included regulation of musculoskeletal, ocular and skin HCT/Ps, hematopoietic stem cells and reproductive tissues (sperm, oocytes and embryos). This new regulatory paradigm was implemented through rulemaking, codified in 21 CFR Part 1271 and became effective for HCT/Ps recovered on or after May 25, 2005. The focus of the new requirements is to prevent use of HCT/Ps that have the potential for transmitting infectious disease. For reproductive establishments, including fertility clinics, the requirements include the following:

- Annual registration and listing with FDA
- Adherence to FDA donor eligibility requirements
- Adherence to FDA manufacturing arrangement requirement
- Inspection by FDA investigators

The FDA formally initiated inspections in reproductive establishments with the final implementation of 21 CFR Part 1271 in 2005, though other HCT/P establishments had undergone inspections in previous years. There is currently no requirement for the FDA to conduct annual inspections of manufacturers of HCT/Ps. The FDA determines the frequency of inspections after considering available resources and risk-based priorities, such as previous violations.

Rise of HCT/P inspections

The number of HCT/P inspections has increased annually since 2005 (see Figure). According to the FDA, 208 of the 565 establishments inspected in 2010 were...
reproductive establishments. There are currently more than 600 actively registered reproductive establishments listed in the FDA database.

Since the 21 CFR Part 1271 regulations became effective in 2005, an increasing number of FDA compliance actions and activities have been noted for reproductive establishments. For example, 29 percent of inspections in 2010 resulted in inspectional observations listed on Form FDA 483. Table 1 lists the top inspectional observations for reproductive establishments in 2010.

When inspectional observations are issued for violations of regulatory significance, the FDA may also issue an untitled letter or warning letter. A warning letter is issued when there are significant, more egregious violations of the regulation that do not provide adequate protections against risks of communicable disease transmission. Such a letter may also be issued if the HCT/P is infected or contaminated because manufacturing conditions do not provide adequate protections. Warning letters are published on the FDA website. Violators are required to provide a written response to the FDA within a given time frame. Warning letters are usually the FDA’s last attempt to get a company’s attention before additional enforcement action. An untitled letter is issued to establishments when violations do not meet the threshold of regulatory significance for a warning letter but existing regulatory concerns cannot be addressed through other means (e.g., Form 483). In 2010 and 2011, the FDA issued seven untitled letters and three warning letters to reproductive establishments for significant regulatory noncompliance issues. Table 2 lists the specific regulatory actions cited in 2010 and 2011 on warning and untitled letters.

Preparing for an FDA inspection
Performing some internal assessments can help you understand your risk areas and your level of readiness for an FDA inspection. Because inspections are typically unannounced, it is important to be prepared at all times. Preparing for an inspection should include the following:

- Understanding of the scope and logistics of an FDA inspection
- Developing a plan
- Identifying personnel who will be involved
- Reviewing inspection do’s and don’ts

Understanding the FDA’s focus
Reviewing the FDA’s Compliance Program Guidance Manual for HCT/Ps is the best way to understand what the FDA is looking for during an inspection. This document outlines how the FDA expects its investigators to conduct an inspection. It also notes which issues they should look for during the process. This reference is especially important for reproductive establishments that may need clarification regarding which 21 CFR Part 1271 requirements are currently applicable to reproductive cells or tissues. These distinctions are clearly discussed in Attachment H – Reproductive Tissue.
Table 1. Inspectional observations in 2010

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Inspectional observation</th>
</tr>
</thead>
</table>
| 1271.47    | Procedures for all donor eligibility steps were not:  
• Established and maintained  
• Reviewed and approved before implementation  
• Designed to ensure compliance with the requirements |
| 1271.50    | • Donor eligibility was not determined by screening and testing.  
• Donor eligibility was not determined and documented by a responsible person. |
| 1271.55    | Records accompanying an HCT/P after completion of the donor eligibility determination were not accurate, indelible and legible. |
| 1271.75    | Donor screening was not performed by reviewing donor’s relevant medical records, including risk factors for and clinical evidence of relevant communicable disease agents and diseases. |
| 1271.90    | HCT/Ps excepted from donor eligibility requirements were not labeled with the appropriate warning statements. |

Table 2. Regulatory actions cited in 2010 and 2011

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Regulatory action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1271.85</td>
<td>Failure to test specimens from anonymous or directed reproductive donors for evidence of infection due to relevant communicable diseases.</td>
</tr>
<tr>
<td>1271.75</td>
<td>Failure to screen an anonymous or directed reproductive donor of cells or tissue by reviewing the donor’s relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases.</td>
</tr>
<tr>
<td>1271.75</td>
<td>Failure to determine whether HCT/P donor is eligible based on results of donor screening and donor testing.</td>
</tr>
<tr>
<td>1271.80</td>
<td>Failure to collect a donor specimen for testing for relevant communicable disease within 30 days prior to oocyte recovery or up to seven days before oocyte recovery or up to seven days before or after recovery of semen donors.</td>
</tr>
<tr>
<td>1271.50</td>
<td>Failure of a responsible person to determine and document the eligibility of an anonymous or directed donor of reproductive cells or tissue.</td>
</tr>
<tr>
<td>1271.47</td>
<td>Failure to establish and maintain procedures for all steps performed in testing, screening, determining donor eligibility and complying with all other requirements of Subpart C in 21 CFR Part 1271.</td>
</tr>
<tr>
<td>1271.75</td>
<td>Failure to determine as ineligible a donor who has risk factors for, or clinical evidence of, relevant communicable disease agents and diseases.</td>
</tr>
<tr>
<td>1271.80</td>
<td>Failure to determine as ineligible a donor whose specimen tests reactive on a screening test for a communicable disease agent. (Example: An anonymous oocyte donor tested positive for Chlamydia trachomatis and resulting embryos were transferred to a surrogate.)</td>
</tr>
</tbody>
</table>
| 1271.47    | Failure to follow established procedures for determining donor eligibility.  
Examples:  
• Specimen for donor testing was not collected within required time of recovery.  
• No physical examination was documented.  
• Standard operating procedure allowed the use of HCT/P recovered from an ineligible anonymous donor. |
| 1271.150   | Failure to ensure that establishments who, by contract, agreement or other arrangement, perform any manufacturing steps for you are in compliance with applicable requirements.  
(Example: No information is available concerning current test kits used for donors.) |
Specifically, FDA inspections and enforcement requirements under 21 CFR Part 1271 are focused on minimizing the risk of transmission of communicable disease from HCT/Ps. The FDA’s focus for reproductive establishment inspections is to determine that there is objective evidence of compliance with the donor eligibility requirements of Subpart C. In particular, inspectors will be looking for procedures and records that indicate you are following all relevant requirements for donor screening and testing and determining donor eligibility. They will also search for evidence that HCT/Ps are adequately labeled and stored to prevent contamination and cross-contamination.

Knowing this, it is wise to prioritize your regulatory efforts, focusing on donor eligibility from start to finish. In particular, routinely review relevant records and documentation. It may also be useful to search the FDA’s website regularly for warning letters and other compliance actions in order to learn from the mistakes of others. To receive up-to-date announcements of public meetings, FDA presentations, new guidance documents or regulations and compliance actions, subscribe to FDA’s email notification of news relevant to tissues at www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm125685.htm.

**Developing a standard operating procedure**

An inspectional standard operating procedure (SOP) is the most important tool you can develop and implement in preparation for an FDA inspection. The SOP should identify and detail the following:

- The most responsible persons, listed in priority order with descriptions of their duties during the inspection
- Who should be contacted when the investigator arrives
- Duties of the person responsible for accompanying FDA investigators and facilitating the inspection
- Directions for dedicating a conference room or other area to the inspection
- Guidelines for appropriate staff conduct during the inspection

Train staff on the SOP, then perform a mock FDA inspection or have an external firm conduct one to confirm that staff and documentation are adequately prepared. It is also advisable to perform an internal audit or have an external firm perform a gap assessment of all operations regulated under 21 CFR Part 1271.

**Role of the most responsible person**

The most responsible person (MRP) should be the person with the highest rank or most authority in the area of inspection. The MRP does not have to be the CEO or medical director. Ranking of alternate MRPs should be done in advance and noted in the SOP so a suitable MRP is always available at the time of inspection. The MRP may be responsible for conducting an introductory briefing with the FDA investigator to discuss ground rules and review logistics, such as hours of business. The MRP should also be available for a close-out meeting. In addition, the MRP can request daily debriefings with the investigator to discuss any findings, note if additional information is needed and discuss a plan for the next day to ensure that appropriate staff and documents are available.

**Role of the FDA escort**

Certain staff should be trained in advance on the responsibilities of being the FDA escort. A properly trained escort should be able to readily identify documents for review and keep track of which documents are reviewed or copied. This person should also be able to field questions and obtain responses to expedite the process and demonstrate to the investigator that staff members understand the FDA-regulated operations and are well trained in the inspection process.
**Inspection process and your responsibilities**

Upon arriving, the investigator will provide identification and ask for the MRP. A receptionist who greets an investigator should ask the investigator to wait until the MRP arrives. At the beginning of each inspection, the investigator will present credentials, which may include an FDA badge, and state the purpose of the visit. The investigator will issue Form FDA 482, Notice of Inspection, to the MRP. If possible, a conference room should be made available as a focal point for the inspection.

The FDA investigator will usually ask to tour the facility first and may ask to question certain key personnel as necessary. The investigator will also ask for copies of certain documents and is under strict rules in regard to confidentiality of donor and patient identification. It is important to answer an investigator’s questions truthfully and clarify any misunderstandings. Keep notes of what is discussed and which documents are reviewed or copied.

The investigator may inspect any operational function that falls under the regulations. These significant functions required in Part 1271 are listed in Table 3, though other records and practices may also be inspected.

**Close-out meetings**

The investigator will ask for a meeting to close the inspection and, if applicable, will provide a list of significant observations on Form FDA 483. The investigator may also verbally describe less significant observations during the meeting. This meeting is important and should be attended by the MRP, the FDA escort and other key staff responsible for making any corrections. A member of your staff should also be assigned to take careful notes.

---

**Table 3. Areas for inspection under 21 CFR Part 1271**

<table>
<thead>
<tr>
<th>Subpart B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration</td>
</tr>
<tr>
<td>Listing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subpart C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Records of screening, testing and eligibility determination</td>
</tr>
<tr>
<td>Records of departures from procedures</td>
</tr>
<tr>
<td>Record retention practices and procedures</td>
</tr>
<tr>
<td>Quarantine practices</td>
</tr>
<tr>
<td>Procedure for and records of quarantine</td>
</tr>
<tr>
<td>Storage practices, including storage of HCT/P from ineligible donors</td>
</tr>
<tr>
<td>Procedures for and records of storage</td>
</tr>
<tr>
<td>Labeling for HCT/P, including accompanying records</td>
</tr>
<tr>
<td>Procedure and records for labeling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subpart D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcontracting practices (manufacturing arrangements)</td>
</tr>
<tr>
<td>Procedure for and records of subcontracting (e.g., with infectious disease testing laboratory)</td>
</tr>
<tr>
<td>Practices/donors that have been granted exemptions and their records</td>
</tr>
</tbody>
</table>
Be sure to understand any written observations and indicate whether you agree or disagree. The investigator will ask if you intend to correct any objectionable conditions and will take notes on what is said and who says it. If a correction has been determined, explain what will be done and when and what evidence of correction will be provided. Otherwise, indicate that you need additional time to determine an appropriate correction.

Responding to observations

Though not required, it is highly recommended that you provide a written response to any Form 483 observations within 15 business days of the inspection. The response should include a short cover letter emphasizing your intent to comply with the law and regulations. This should be followed by a reiteration of each observation and your response. If you agree with an observation, explain how and when you will correct the problem. Provide a specific response to the identified issue as well as a systemic response that reflects how you will ensure that the problem does not recur. If you have corrected the problem, supply evidence that you have done so. If you disagree with an observation, explain why and provide any documentation that will support your position. Providing a timely written response is especially important if the observations are egregious. A timely and effective response may help you avoid other compliance actions, such as a warning letter.

Summary

While the thought of an FDA inspection may cause some anxiety, it is possible to successfully prepare for and manage such a visit. Remember these recommendations:

• Understand the FDA’s focus.
• Prioritize your regulatory efforts and create a comprehensive regulatory training program.
• Use FDA’s website to learn about recent compliance actions and subscribe to notifications about HCT/P regulations.
• Develop a standard operating procedure for an FDA inspection.
• Audit your program for the FDA-related functions at least annually.

Investing time and resources to prepare for a possible FDA inspection can be highly valuable. At a time when HCT/P inspections are on the rise, it is essential to be prepared at all times.
About the authors:

Martha A. Wells, MPH, RAC, is the vice president of regulatory affairs for tissue and biologics at Reglera LLC, a regulatory compliance and quality assurance consulting and process outsourcing company. She oversees development and implementation of strategic regulatory approaches for complex human tissue and cellular therapies. Wells is the former chief of the Human Tissue and Reproduction Branch of the Division of Human Tissues, in the Office of Cellular, Tissue, and Gene Therapies, CBER, FDA. She holds a master’s degree in public health in health policy and management from Johns Hopkins University.

Clay Anselmo, BS, RAC, is president, CEO and cofounder of Reglera. He has more than 20 years of experience in operations and management in the medical devices and tissue bank industries. Anselmo previously held management positions in several large medical devices corporations. He has expertise in developing and implementing strategic regulatory approaches for medical technology products that include medical devices, device/tissue combination products, human tissue products and in vitro diagnostics. Anselmo holds a bachelor of science degree in mechanical engineering from the University of Washington.

Rich Weiskopf, BS, ABA, RAC, is senior director of quality at Reglera. He has nearly 25 years of experience in the medical devices, tissue banking and biologics and pharmaceutical industries. Weiskopf is the former director of one of the largest providers of bone and soft tissue allografts in the United States. He holds a bachelor of science degree in microbiology from Colorado State University and is an American Bar Association-accredited paralegal.

References


3. Malarkey M. Compliance update. Presented at: 7th Annual FDA and the Changing Paradigm for HCT/P Regulation; February 2011; San Antonio, TX.


7. Cervantes E. Inspection update: common problems found in HCT/P inspections. Presented at: 7th Annual FDA and the Changing Paradigm for HCT/P Regulation; February 2011; San Antonio, TX.
This publication should be used for general educational purposes only and is not intended to be a substitute for professional medical advice. Although it is intended to be accurate, neither Walgreen Co., its subsidiaries or affiliates, nor any other party assumes liability for loss or damage due to reliance on this material. This information is not intended to create any warranty, and ALL SUCH WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF FITNESS FOR A PARTICULAR PURPOSE, ARE HEREBY DISCLAIMED. This information does not replace professional judgment.