

Manufacturing Arrangements: Industry Compliance

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My presentation focuses on some ideas and issues to consider for enhancing your contracts and auditing activities with your manufacturing partners to ensure they are in compliance with FDA requirements. I will provide you with information on how the 21 CFR 1271 requirement applies to you, applicable industry standards that have been developed as well as examples of how to address the requirement that focus on auditing tools.

Slide 2:

1271.150(c) This Requirement Applies to:

- Establishments that perform a manufacture step for you
- Manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor (1271.3(e))



FDA regulations for Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/Ps) under 21 CFR Part 1271 have been in effect since May 25, 2005. The 1271.150(c) requirement entitled Compliance with Applicable Requirements—Manufacturing Arrangements specifies that if another establishment performs a manufacturing step for you under a contract, agreement, or other arrangement that you must ensure that the establishment complies with requirements applicable to that manufacturing step. In addition if you become aware of information that suggests the establishment is not longer in compliance with the applicable requirements you are responsible for taking steps to ensure compliance or terminate your contract, agreement, or other arrangement with the establishment. FDA defines manufacture to mean any or all steps from recovery to distribution as well as the screening or testing of the cell or tissue donor.

Slide 3:

1271.150(c) This Requirement Applies to:

- Examples of establishments that perform manufacture steps for you include:
 - Outside serology testing laboratory
 - Terminal sterilization
 - Tissue recovery
 - Microbial monitoring/testing
 - Tissue storage and distribution
- Applies to all HCT/P manufacturers including those where HCT/Ps are regulated as medical devices or biological products



Examples of establishments that might perform manufacturing steps for you include the laboratory that performs infectious disease tests on donor specimens, terminal sterilization of your product such as gamma or e-beam irradiation, tissue recovery, pre and post processing microbial testing, and tissue storage and

distribution. For ocular establishments, another example might be an establishment that performs any processing steps for you utilizing microkeratomes or lasers. Because there is no comparable requirement for HCT/Ps regulated as medical devices or biological products, this requirement applies.

Slide 4:

Why is FDA Concerned?



- 2006 Order to Cease Manufacturing: Biomedical Tissue Services (BTS), a recovery establishment
 - Inadequate screening
 - Falsified documentation
 - Resulted in a large recall of tissue
 - Resulted in FDA inspectional focus for all recovery establishment
- This and other cases of non-compliance by recovery partners resulted in major FDA scrutiny and poor public recognition of the tissue donation process
- Also resulted in
 - Enhanced standards from AATB for recovery partners
 - 2006 FDA Guidance



The FDA 1271 regulations are focused on preventing the introduction, transmission or spread of communicable disease from HCT/Ps. FDA included this provision in rulemaking as it was recognized that compliance is evaluated during an FDA investigation, but establishments can also help identify and prevent problems that may provide risks to product quality and patient safety by evaluating their contracting manufacturing partners. Such monitoring may have prevented a situation uncovered in 2006 where a recovery establishment utilized by some of the major tissue processors, was found to be performing inadequate screening and falsifying donor identification and testing documentation. FDA shut down the activities of this establishment and added additional inspections for other recovery establishments. The unwanted publicity from this episode also resulted in enhanced industry standards that support the FDA requirement. FDA also published a guidance for immediate implementation (Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements) to provide more detailed information on how an establishment can perform the due diligence activities necessary to be compliance with this requirement.

Slide 5:

Industry Standards: AATB

- B1.500 Multi-Facility Tissue banking
 - Relationships and responsibilities delineated in writing and documentation maintained
 - Records to demonstrate compliance are readily accessible to distributing tissue bank
 - Inspection/audits of other facilities required
- B1.600 Contracted and Non-Contracted Laboratory Services
 - Documented assurance that tissue microbiological and donor infectious disease testing is performed per FDA requirements
 - Paper audit or on-site audit
 - Requires archived samples from donors be stored

American Association of Tissue Banks standards required for their accredited establishments and applicable to manufacturing arrangements include ensuring that all relationships and responsibilities are documented and maintained as well as inspection/audits of partner facilities. Another standard focuses on laboratory services and the need to document that tissue microbial and donor infectious disease testing are performed per FDA requirements. This standard provides the option of performing paper audits or on-site audits of these outside laboratories and also requires donor samples to be archived.

Slide 6:

Industry Standards: EBAA

C3.510 Eye Bank Functions Performed by Another Establishment
Any EBAA accredited organization engaging with another establishment that performs eye banking functions prior to distribution must either:

- Document that the establishment is currently EBAA accredited for the eye bank functions performed; or
- Document that the establishment is in compliance with EBAA medical standards, state and federal regulations appropriate to the eye bank functions performed
 - This option requires a written agreement and the EBAA accredited organization is responsible for performing compliance audits
 - Policies and procedures shall describe the audit plan, scope and frequency

Similarly the Eye Bank Association of America Medical standards require facilities to document in writing the responsibilities of a manufacturing partner and also require EBAA accreditation for another establishment that performs eye banking functions. EBAA accredited facilities must have policies and procedures in place that describe audit plans, scope and frequency.

Slide 7:

Industry Standards: AABB (Advancing Transfusion and Cellular Therapies Worldwide)

4.0 Agreements

The facility shall establish, implement, and maintain policies, processes, and procedures for developing, approving, and reviewing agreements. Include:

- Review to ensure requirements are adequately defined
- Determining the facility has the capability to meet the agreement requirements
- Review at defined intervals to ensure that the terms continue to meet requirements

AABB standards for cellular therapies similarly spell out the details needed in agreements with other establishments. The emphasis of this standard is documentation of responsibilities and determining that the partner facility has the capability to meet the agreement requirements and they be reviewed at defined intervals to ensure the terms continue to meet requirements.

Slide 8:

Industry Standards: AABB

4.8 Obtaining Materials, Services and Cellular Therapy Products

The facility shall establish and maintain policies, processes, and procedures to ensure that purchased, donated, or otherwise acquired materials, services, or cellular therapy products conform to specified requirements. Includes:

- Accreditation by AABB or other accrediting body
- Review of package inserts for all infectious disease testing reagents and kits to verify acceptability of use
- Monitoring performance and taking corrective action

In addition AABB further details specific documentation needed to be established by their manufacturing partners such as procedures and accreditation by AABB or other accrediting bodies. Specific for infectious disease testing laboratories is a review of the package inserts for the tests performed on donor samples. This standard does not specify how often a partner should be monitored but notes that such monitoring be performed and corrective action taken when deemed necessary.

Slide 9:

Manufacturing Arrangements

- Qualifying and managing your manufacturing partners is not only good business, but a regulatory requirement
- Assessments are instruments to evaluate and document the state of the partners quality system and controls in place to ensure that all of your organization’s requirements are consistently being met
- There are a number of ways to meet this requirement
- This is an ongoing requirement not just one time evaluation



Now that we have discussed what the FDA requirements and industry expectations are, I will focus on how you can implement them for your facility. Here I note that qualifying and managing your manufacturing partners is not only a regulatory requirement but good business. The emphasis is that these activities should result in better and more consistent service. Though there are a number of ways to evaluate your manufacturing partners, assessments or audits are an important component of such evaluations. Utilizing good audit practices to evaluate and document the state of your partners quality system and controls in place provides value to this exercise. I would emphasize that such evaluations are not a one time exercise but should be ongoing.

Slide10:

Initial Assessment Activities

- Internal
 - Develop and implement SOPs for how you will address and document 1271.150(c) requirements
 - Develop criteria for inclusion in a contract – a formal contract is recommended rather than an agreement or other arrangement
- External
 - Ask around for recommendations for possible partners
 - Initial contacts with possible manufacturing partners should address significant issues related to 1271 compliance
 - Develop and negotiate a contract
- FDA
 - Explore websites for evidence of compliance actions and documentation of active registration and listing



I now want to focus on some recommendations for moving forward. If you are just beginning to address this issue, which I hope is not the case given the regulations have been in effect over 10 years now, I describe here some of the activities you might pursue to ensure that your arrangements are comprehensive and you pick a partner who is going to be compliant. Internal activities include

development and implementation of SOPs and determine what criteria is significant to include in a contract. I recommend that a formal contract is developed rather than an agreement or other arrangement. I also recommend asking some of your colleagues for recommendations for facilities that they have successfully worked with. The next step is to contact possible manufacturing partners to begin to develop a relationship and negotiate a contract. In addition, it’s a good practice to explore the FDA websites for evidence of compliance actions and documentation of active registration and listing. Keep in mind that registration does not necessarily mean a facility is FDA compliant.

Slide 11:

Example: Contract with Testing Laboratory Should Include:

- Information concerning the specific testing panel you require
 - Check FDA’s website for current test kit list
- A statement that these tests must be performed in accordance with the manufacturer’s instructions
- Assurance that the laboratory is and will remain registered with the FDA
- A clause that they must notify you of any regulatory action initiated by FDA against the laboratory



Here is an example of the type of issues you should include in a contract with your infectious disease testing laboratory. This is probably the most significant manufacturing partner as this testing is utilized to determine if your donors are eligible and products can be released for utilization. Contract should include a statement that the laboratory is testing using the appropriate test kits and these are being performed according to the manufacturers instructions (package insert). Also a statement that the laboratory is and will remain registered with FDA and that they must notify you of any regulatory action initiated by FDA against them especially if it involves the accuracy of the testing they perform for you.

Slide 12:

Example: Contract with Testing Laboratory Should Include:



- Assurance that they are and will remain certified to perform such testing on human specimens either under CLIA or equivalent
- A clause detailing your right to continue to audit them by whatever means your SOP details
- A clause that specifies roles and responsibilities for various activities

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In addition, there should be a clause in your contract that they are and will remain certified to perform such testing on human specimens either under CLIA or an equivalent. This is a FDA requirement. As I mentioned earlier this is not a one time exercise so language should be included to ensure the laboratory understands you will continue to audit them. As for all contracts, specific clauses should be included that spell out roles and responsibilities for you and your partner.

Slide 13:

Audits/Assessments



- Types
 - Initial
 - Periodic
 - For cause
- Direct on-site audits
 - Audit by your staff
 - Audit by 3rd party organization
 - Is the best option if the audit is for cause

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Depending on the situation audits would be considered an initial evaluation of your manufacturing partner, periodic or for cause if you become aware of information suggesting the facility is not FDA compliant. You could perform on site audits either by your staff or by a 3rd party organization that has expertise in auditing the type of facility you work with. Would recommend a direct on site audit if the situation is for cause.

Slide 14:

Audits/Assessments



- Mail-in audits – self assessment survey
 - Used for initial and periodic audits
 - Development of a self-assessment checklist is a useful tool for evaluation
- Off-site document reviews – SOPs
 - Minimal audit
 - Not as comprehensive as above
 - Would probably not assure 1271.150(c) compliance

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Other types of audit include a mail in self assessment survey questionnaire. These are often used for initial and periodic audits. It is important to develop a self assessment checklist that will provide you with the information you need to determine the facility has for instance a robust quality program and staff that are competent. Another method to assess your manufacturing partner is to review their SOPs. This can also be performed off-site but is considered a minimal audit that probably would not provide sufficient information that could document that the procedures have actually been implemented. Which ever method of audit you decide works well for you, it should be documented in your SOP.

Slide 15:

Audit Checklist Recommendations



- Develop a checklist – it can be utilized for
 - Direct on-site audits
 - Mail-in self assessment survey audits
- Include a request for copies of:
 - All federal, state and local registration certificates
 - Certificates indicating certifications/approvals such as CLIA
 - Master list of procedures
 - Organization chart including roles and responsibilities

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A checklist can be utilized for on-site and mail-in audits. It is a valuable tool if it captures the information you need to assess that your manufacturing partner is in compliance with the regulations and standards that are applicable for the manufacturing step that the facility performs for you. Recommend that the first matter to address is to request copies of federal, state and local registration certificates as well as certifications such as CLIA. Obtaining a master list of procedures is helpful to evaluate the scope of the operations performed at the facility as is an organization chart.

Slide 16:

Audit Checklist: Quality Program Effectiveness



- Is a Quality Program maintained?
- What functions are the Quality Program currently performing?
- Is an individual not directly responsible for the performance of operations responsible for the Quality Program?
- Are internal audits performed?



Now I will focus on important elements of an audit checklist to consider to assist you with evaluating compliance with Part 1271. The first is the facility's quality program. Determining how robust the quality program is and the functions such as internal audits it performs at the facility. Having individuals not directly responsible for audit oversight is an important concept, but sometimes difficult for small facilities to maintain.

Slide 18:

Audit Checklist: Procedures



- Are procedures available on-site?
- Does a quality program establish, maintain, review and approve the procedures for steps used in manufacture of HCT/Ps?
- How are revisions to procedures distributed?
- What measures are in place to assure that old revisions are not assessable?



The regulations state that there must be procedures for steps used in manufacture of HCT/Ps. Determine if the quality staff have the responsibility to establish, maintain, review and approve these procedures. Are procedures available to staff and how are revisions and archived procedures handled.

Slide 17:

Audit Checklist: Quality Program Effectiveness



- How are complaints documented and routed?
- How are deviations to procedures handled?
- Is there a procedure in place for document control ?
- Is there a procedure for handling corrective and preventative actions?



These are basic functions a facility regulated under 127 should have in place. These include a review of documentation of oversight of complaints, HCT/P deviations, document control and corrective and preventative actions.

Slide 19:

Audit Checklist: Records



- Is there a records management system in place?
- Are records kept on site?
- Are records maintained electronically?
- Can electronic records be printed out as hard copies?
- What records are kept and for how long?



FDA expectation is that manufacturing records must be maintained concurrently with the performance of each manufacturing step. All records must be accurate indelible, legible and maintained in a records management system. In addition records must be retained for 10 years after their creation or longer depending on then the HCT/P is distributed, disposed of or expired. Audit issues to address include assessment of the facilities record keeping management system and record storage.

Slide 20:

Audit Checklist: Facilities



- Is the size of the facility adequate for the operations?
- Is routine cleaning performed and if so, how often?
- Are there security measures in place such as
 - Locks on entries
 - Limited access to key areas, and
 - Electronic records security?



In regards to facilities, it is important to determine if the size of the facility is adequate for its operation. Requesting a floor plan may be helpful. Is it routinely cleaned and are security measures in place. The focus is on assessment there are controls in place to minimize any contamination or cross contamination.

Slide 21:

Audit Checklist: Supplies and Reagents



- Is there a procedure for receiving supplies and reagents including specifications?
- Are sterile supplies and reagents used as necessary?
- Are supplies and reagents quarantined by inspection status?
- How are expired supplies or reagents disposed of?



Depending on the functions performed for you by your manufacturing partners, utilization of supplies and reagents to ensure they are appropriate is a significant function. Verification that supplies and reagents meet certain specifications especially sterility where needed will decrease the circumstances that increase the risk of introduction, transmission, or spread of communicable disease. Regard this as an especially significant issue for recovery operations.

Slide 22:

Audit Checklist: Equipment Maintenance



Determine that there are procedures for assuring:

- Calibration of equipment
- Preventative maintenance of equipment
- Lockout/tagout of equipment not in working order
- Cleaning of equipment



Ensuring that equipment is well maintained and calibrated and there is documentation of this is important. This is especially an issue for infectious disease testing facilities given the sensitivity of the equipment they utilize for donor testing.

Slide 23:

Summary

- Due diligence assessment of your manufacturing partners is not a one time exercise
- Define parameters of how you will assess in your procedures
- Develop audit checklists that work for you
- Method for audits should be based on the risk associated with the service provided
- Define in your contracts
- Ongoing communication with partners essential!!



In conclusion, the important concepts I have focused on here that could enhance your manufacturing arrangements include assessment of your manufacturing partners compliance is an ongoing exercise. Defining how you make these assessments is critical to success and includes development of procedures, contracts and audit checklists. The method you use for these ongoing audits should be based on the risk associated with the service that your manufacturing partner provides.