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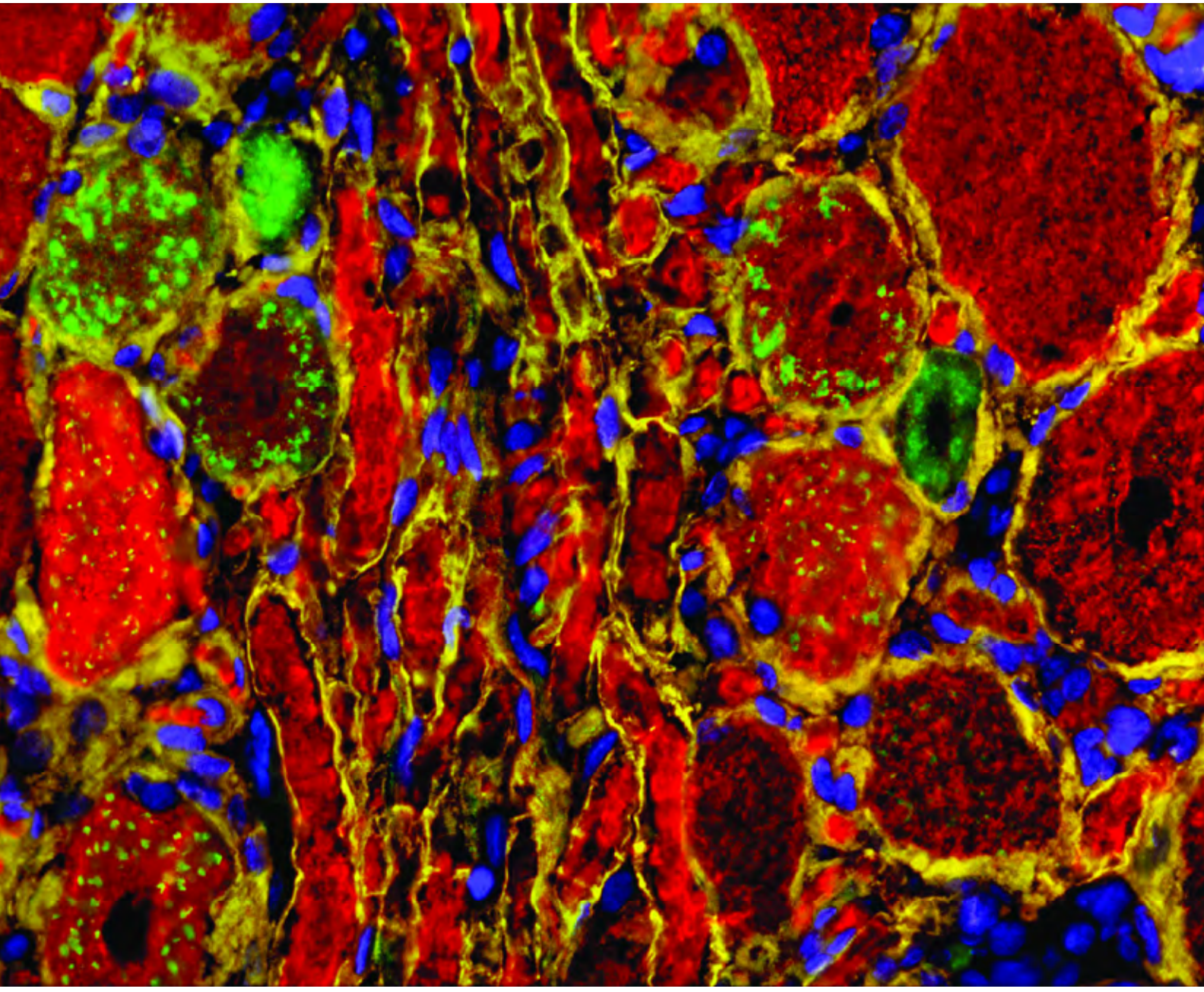

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Managing Raw Materials in a Contract Manufacturing Facility

BY TINA YOUNG and ROBIN DOUGLAS

Long-term growth of the biopharmaceutical industry is increasingly relying on outsourcing to overcome the current capacity constraints, especially for monoclonal antibody production. Companies are often reluctant to commit to building multimillion dollar manufacturing facilities for potential products with no guarantee of approval. Therefore to offset risks, companies will enter into contract manufacturing arrangements.

For both clients and contractors, there are many important details to consider when managing raw materials in contract manufacturing relationships. Technology transfer (tech transfer), the transfer of processes from one facility/ division/ unit to another, requires the transfer of process flow diagrams (PFD), assays, equipment, associated validation, and the focus of this article, the transfer of raw material information. It is important to understand that production cannot begin until the raw materials are available on-site. This includes sourcing, receipt and processing, testing, and release of the materials before they are considered available. Although the contractor: client relationship can vary depending on the contractual arrangement, the matters discussed in this article are relevant to understanding the complexities of managing raw materials in the outsourcing arrangement.

As a potential client or existing client, it is important that you:(1) Understand the contractors overall Quality Philosophy especially as it relates to handling raw materials. Companies vary in their interpretations and implementation of quality standards. (2) When possible, provide a tech transfer package including the following raw material information: a bill of materials (BOM), material specifications, sampling plans, analysis, release criteria, and preferred vendors. If this information is not available, determine what are the gaps and work with the contractor to generate the required documents to support the contractor's system. (3) If not previously defined in a quality agreement, define responsibilities of sourcing and releasing materials and levels of approval required by the client. Regardless of which entity is responsible for sourcing/ release and/or review, it is crucial that both contractors and clients fully comprehend the process, from how and when raw materials are ordered to when the final bulk product is released. Do not take it for granted that a contractor will use the same methods, or have the same standards, as the client company. It is recommended that the client walk through the contractor's processes during the quality audit. Contractors may also need to understand the client's quality processes depending on the degree of shared responsibilities.

Key Points for Managing Raw Materials

As part of the tech transfer, raw materials should be a primary focus due to the significant time required to generate the necessary material specifications and approve those specifications prior to ordering materials. Also, prior to ordering materials,a detailed material requirement plan should be generated which includes sufficient supplies to support manufacturing and sampling requirements for analytical characterization and retention quantities.

Documentation that clients should compile and review with contractors includes analytical requirements for release, in-house developed testing methods, existing outsourced testing relationships and information, sampling quantities, production quantities, and existing validation/qualification associated with test methods and stability data. Contractors should also have as much information as possible about the client's protocols for transferring processes to different sites and work with the client to satisfy internal requirements.

Documentation: The initial steps in the raw materials tech transfer process entail generating a bill of materials and the associated material specifications that define the material description, specified vendors, sampling quantities, and testing requirements for release. The details of the specification are determined jointly between the client and contractor. This process of generating specification can be a timely process if the lines of communication, with respect to quality standards and responsibilities, are not clear. It is paramount to identify who from the client side will be responsible for review and approval of all raw material related documents.

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Determine what material release documentation comes with your batch records. In many cases, a certificate of analysis or acceptance is sufficient. Verify that the documentation to support the entire process from receipt to release is available for review or audit. In the event a special request is made for associated raw data, be sure that it is clearly understood and agreed upon early in the relationship.

Ordering: Who orders the materials? Clients may have existing relationships with vendors that they want to continue. If the client company plans to provide the raw materials to the contractor, the client company must consider itself as a *supplier* instead of the internal systems accordingly with a material coordinator or planner to support your external shipping demands.

In such relationships where the client will share responsibilities relating to managing raw materials, the client should also provide the contractor a point of contact for materials coordination from the client's organization. This coordinator should develop a strong relationship with the materials planner on the contractor's site and schedule regular communications to reduce costly catastrophes that can result from changes in schedules and/or material needs.

Inventory Management: A contractor's first order of business is often developing a bill of materials from client's documentation then developing an inventory management plan. Who will be responsible for inventory management? This activity typically falls to the contractor as the manufacturing is performed on their site. If you will rely on a contractor to supply the raw materials, ensure that their system is already in place and that reorder points allow sufficient time to receive and release the shipments. Inventory management plans should also consider space/storage requirements and any special storage conditions. It is possible that if space is limited smaller shipments may be required and can result in additional testing and processing costs.

Selecting Vendors: After vendors are selected, in contract relationships where the contractor and the client have joint responsibility for sourcing materials or for outsourced testing relationships, it is imperative that you clearly define which party will be the primary conduit for communications. In some cases, three-way communication may be necessary. So early in the process, develop how you will communicate both materials and testing related issues. It is good practice to select primary and secondary vendors for all materials and if that is difficult focus on having secondary vendors for critical materials at the very least.

Testing: Determining testing requirements for raw materials will typically correlate to the phase of the project. The level of testing for developmental manufacturing will vary from that of commercial manufacturing and there are several levels in between. As part of the receipt process, materials are evaluated for expiration dates and physical conditions of the containers. As it relates to the analytical testing for release, it is important to determine whether the materials will be tested for identification (ID) only, full compendia, any other critical parameter(s) that is (are) deemed important, OR if the material will be tested against all assays on the certificate of analysis (CoA). Testing standards (USP, EP, etc.) are usually included in a quality agreement as it is the client who is ultimately responsible for quality related matters for their product. Be sure those details are included when planning the manufacturing campaign because raw materials processing, in many cases, can take several months to finalize. Giving the contractor all available information can minimize the timelines.

Standards: For contract relationships with shared responsibility, it would be a benefit to the relationship if both the contractor and the client have an opportunity to review how each organization will perform its "piece." Clients may opt to do a portion of the testing to support release of a material and the contractor will have to verify that the standard of documentation provided will satisfy internal standards. This is a small step in the process, but can result in unnecessary time to address deficiencies.

Also, as it relates to standards, be sure to notify your contractor of the regulatory bodies that you would need to satisfy. The requirements for USP, EP, JP, etc. are different and may require changes to existing systems. The matters relating to standards are typically addressed during the quality due diligence audit.

The Quality Due Diligence Audit

As part of the process for screening/selecting potential contract manufacturers, be sure to review the systems associated with the previous sections of this article. It cannot be stressed enough that one should ASK QUESTIONS during the audit rather than review documents and make independent assessments. In cases where the responsibilities are shared, ask questions relating to test results: How are out-of-specifications (OOS) results handled? When or Do we get notified of OOS results? The individual performing the audit should examine how raw materials are handled, if the area is secured, and if the materials are adequately segregated at appropriate temperatures. Evaluate the training of the raw materials staff and those that handle or test the raw materials. Be sure to review how the organization handles excursions relating to the water system, which is a critical raw material to your process.

As an auditor, it is good practice to present *realistic* scenarios to the contractor to determine how the organization would potentially handle an incident. In most cases, the contractor has systems in place to handle the typical situations of the manufacturing environment and, if necessary, may be willing to accommodate special requests.

As it relates to auditing vendors, in many cases the client will rely on the contractors to take on this activity and, if so, it is critical that the client review the procedures used to audit, qualify, or certify vendors. This will ensure that both organizations are aware of the processes used to support quality aspects of the project.

Once a contract manufacturer is selected, audits should be conducted

annually at a minimum to ensure adherence to systems and change control.

The Release Process: As part of the quality due diligence audit be sure to review the release process. The release of raw materials can be as simple as verifying information on a certificate of analysis or a compilation of testing results, which may or may not include raw data. The complexity of this process is dependent on the phase of your project and what is cited in the quality agreement. It is important to realize that the more complex the process,the more time required to complete it, therefore schedule accordingly.

Change Control Procedures: Typically raw materials vendors are required to notify their client of any changes in sourcing of critical materials. It is therefore a requirement that contract manufacturers notify the client of any changes in sourcing materials. The contractor should have a strict change control policy in place that requires a contractor's approval as it relates to any process related changes. This would include changes in materials, equipment, deviations, etc. Verify the process and ensure that you are a required signatory for critical changes.

Sampling: As part of the audit, be sure that the quality unit performs the sampling and adequate sampling information is captured appropriately. Also, verify the appropriate use of composite sampling versus non-composite sampling, which is dependent on what regulatory agencies will review your applications and the types of testing that are being performed.

Another aspect of sampling that, if addressed early, will save time is the approach to retention sample plans. As part of generating specifications, develop the plan for retention amounts and storage conditions. Allow adequate time in the project schedule for sampling of materials for testing and to store retains.

Vendor Qualification: Qualifying a vendor is important as it provides assurance of the vendors commitment to quality and consistency. As part of the audit of your contract manufacturer, evaluate the systems used by the contractor to support your project.

In the contract manufacturing relationship, know what your responsibilities are as the client and be sure to make the necessary arrangements in your organization to ensure that your obligations are fulfilled. Delays in your commitments will impact the timelines associated with the project. Having a dedicated point of contact from the client and the contract will facilitate effective communications.

Outsourcing is an excellent option for many pharmaceutical/biopharmaceutical companies and proper planning can make the process easier for everyone.