Contracting Organizations and the need for Written Transfer Obligations and Quality Agreements

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Outsourcing of pharmaceutical, biotechnology, and medical device clinical research and manufacturing has grown significantly in the past several years, and the trend is predicted to continue. There are several explanations for why this growth in outsourcing has occurred. The growth in clinical research, limited corporate infrastructure or in-house expertise to create new products explains some of the expansion; the mitigating of financial and compliance risk may explain the remainder. Many companies use outsourcing, in addition to internal resources, because having alternate capabilities included in the regulatory submissions provides protection in the event of supply interruptions, manufacturing problems at a given site, or unexpected increases in demand.[1] An example of an unexpected increase in demand has been the demand on vaccines manufacturers to produce the COVID-19 vaccines in addition to the seasonal influenza and other vaccines.

Increasing Government Regulatory Requirement

In 2008, approximately 45 percent of medical device manufacturers that received warning letters and 483 citations related to supplier practices were shown to be inadequate in meeting their supplier evaluation commitments per 21 CFR 820.50. This trend has continued into 2009; 40 percent of all warning letters issued are related to supplier issues.[2] Two factors contributing to this high percentage of warning letters are directly related to controlling their supplier evaluation commitments: the supplier audit process and absence of a quality agreement.

The United States Food and Drug Administration (FDA) dictates that the company submitting a product for regulatory approval is ultimately responsible for the end-to-end safety and compliance of the product. This includes all clinical trials, advertising, sourcing, manufacturing, packaging and distribution, even when these functions have been outsourced.[3] However, there is no provision in the predicate rules that allows for a marketer of a product to outsource the responsibility for ensuring compliance with good laboratory practices (GLP), or good manufacturing practices (GMP). Sections 21 CFR 312.52 outlines the requirement for written transfer obligations when a company decides to use a contract research organization (CRO) and 21 CFR 820.50 of the Quality System Regulations (QSR) identifies the need for an agreement with their suppliers, contractors, and consultants to notify the manufacturer of changes in the product or service that may affect the quality of the finished product.

ICH guidance for industry Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients recommends that companies evaluate contract facilities to ensure that contractor sites comply with CGMP for specific operations. It recommends that companies have approved written agreements with contractors that define the manufacturing responsibilities in detail, including the quality measures, of each party.

ICH guidance for industry Q9 Quality Risk Management offers a systematic approach to quality risk management as part of an effective quality system. It discusses quality risk management principles such as risk assessment, risk communication, and risk review and provides examples of tools that can be used to make effective and efficient risk-based decisions in, for example, auditing and arranging quality agreements with contract manufacturers.[4]

ICH guidance for industry Q10 Pharmaceutical Quality System states that, as part of a pharmaceutical quality system, the company is ultimately responsible for ensuring that “processes are in place to assure the control of outsourced activities and quality of purchased materials.” It indicates that these processes should incorporate quality risk management and include the following critical activities:

- Assessing the suitability and competence of potential contractors before outsourcing operations or selecting material suppliers. This could be accomplished through audits, material evaluations, or other qualification criteria.

- Defining the manufacturing responsibilities and communication processes for quality related activities of the involved parties. For outsourced activities, these should be in a written agreement.
- Monitoring and reviewing the performance of the contract facility and identifying and implementing any needed improvements.
- Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed-upon supply chain.[5]

In the U.S., supplier auditing is a regulatory requirement for all medical device, pharmaceutical and biotechnology companies; whereas, quality agreements are only required of medical device companies. In Europe, it is a regulatory requirement to have quality agreements between the company and its contracting organization and is currently regulated by European Commission Directives 2003/94/EC (1) and 91/412/EEC (2), and the International Conference on Harmonization GMP Q7 guideline (3). As early as 1991, the UK MCA published a regulatory guidance document which specified the need for a quality agreement. Today, this guidance appears as the Medical and Healthcare Products Regulatory Agency (MHRA) Rules and Guidance for Pharmaceuticals Manufactures and Distributors 2007 (4), commonly known as the Orange Guide. This guidance can be summarized as followed:

Contract Giver must:

- Assess that a contractor is competent.
- Ensure that GMPs are followed.
- Provide information necessary to produce the product.
- Provide hazards associated with the product.
- Ensure that the products received comply with the specifications and are released by the Qualified Person (QP).

Contract Acceptor must:

- Have adequate resources to carry out the work.
- Verify that all products or materials received are suitable for intended purpose.
- Not subcontract without sponsor's prior evaluation and approval.
- Refrain from activity that could adversely affect the quality of the product.

Contract must:

- Be written and specify the respective responsibilities of Contract Giver and the Contract Acceptor.
- Be written by technically competent personnel knowledgeable in pharmaceutical technology, analysis and GMPs.
- Be in accordance with the marketing authorization and agreed by both parties.
- Specify how the quality unit will release product to ensure compliance with marketing authorization.
- Define responsibility for purchasing materials, testing and releasing materials, undertaking production and quality controls.
- Define when samples are removed.
- Ensure that records, samples and retains are accessible and available to the sponsor.
- Allow for sponsor and regulatory visits to the facilities.

Contract should not:

- Cover general business terms and conditions such as confidentiality, pricing or cost issues, delivery terms, or limits on liability or damages.[6]

In September 2006, the FDA released a guidance document titled "Quality Systems Approach to Pharmaceutical CGMP Regulations." (5) Section IV.B.4 Control Outsourced Operations states that "Quality systems call for contracts (quality agreements) that clearly describe the materials or services, quality

specification responsibilities, and communication mechanisms." With the issuance of this guidance document, the FDA's current thinking aligns with that of the European regulatory bodies, in that the FDA requires a pharmaceutical or biotechnology company to have in place a quality agreement with their contract manufacturing organization. Failure to do so has resulted in warning letters being issued to those companies for not having a quality unit responsible for approving or rejecting products or services provided under a contract (21 CFR 211.22(a)).

Section 21 CFR 211.22(a) states that "there shall be a quality control unit that shall have responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products, and the authority to review production records to assure that no errors have occurred, if errors have occurred, that they have been fully investigated. The quality unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company".

On the clinical/nonclinical research side of the business, the regulations clearly states that any obligations transferred to a contract research organization (CRO) must be in writing. Section 21 CFR 312.52 outlines the responsibility when the sponsor decides to transfer obligations to a contract research organization. This section states "A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred".

With the development of complex and highly specialized technology and equipment used in the manufacturer of biological products and increase use of contracting organizations that specialized in this technology and equipment, the FDA published in November 2008 an update to the "Cooperative Manufacturing Arrangements for License Biologics" guidance document. (6) In this document the agency saw the need to put forth its current thoughts related to the relationship between biological manufacturers and the contract organizations used to manufacturer the biological products.

Responsibilities of Licensed Manufacturer and Contractor

The FDA recognized that a biological manufacturer may not have the capability or may choose not to perform all operations under its legal ownership. The agency has taken the position that all manufacturers participating in a shared (contracting) arrangement must comply with recordkeeping requirements, must have the technical knowledge and expertise needed to identify manufacturing problems and deviations, and for taking responsibility for conducting preventative and /or corrective action to ensure the safety and effectiveness of the product. Taking this one step further, the agency identified what it believes are the responsibility of both parties as it related to the relationship between both parties.

The license manufacturer is responsible for:

- The safety, purity and potency of the products as stated in 21 CFR Parts 600 through 680 and the Public Health Service Act (PHS);
- Ensuring that manufacture of the product complies with the provisions of the Biological License Agreement (BLA) and the applicable regulations, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820; and
- Compliance with both product and establishment standards.

Product and establishment standards and applicable regulations may include, but are not limited to, the following:

- Product release and in-process specifications;
- Adverse experience reports, biological product deviation reports, medical device reporting systems;

- Production and process controls;
- Reporting changes to the production process and all facilities as required by 21 CFR 601.12;
- Maintenance of master production records and control records for drug products and device master records and device history records for devices;
- Laboratory controls, including testing and release for distribution;
- Submission of protocols and samples for lot release when applicable;
- Labeling;
- Systems to ensure continued current good manufacturing practices (CGMP) functioning of equipment and facilities;
- Environmental monitoring;
- Infectious disease testing and blood components; and
- Training of personnel.

Additionally, the contract manufacturer should share with the license manufacture all important proposed changes to production and facilities including introduction of new products or at inspection.[7]

The contract manufacturer's responsibilities include:

- Compliance with applicable provisions of the Food Drug and Cosmetic Act (FDC) and applicable regulations;
- Subject to FDA inspection under section 351(c) of the PHS Act and section 704(a) of the FDC Act;
- Allowing the license manufacturer access to floor plans, equipment validation, and other production information to ensure that the contract site complies with applicable product and establishment standards;
- Fully informing the license manufacturer of the results of all tests and investigations that might have an impact on the product;
- Sharing any FDA list of inspection observations with the license manufacturer to allow evaluation of its impact on the purity, potency, and safety of the license manufacturer's product;
- The product stability and the manner of shipment to and from the contract facility;
- Providing the license manufacturer with the contract manufacturer's names, address, license number, if applicable, and registration number; and
- Providing a list of all standard operating procedures applicable to the contract arrangement.[8]

Decision to Outsource

Once a company has decided to outsource manufacturing, clinical trials, or laboratory services; the qualification process should begin. First, the sponsor company must ensure the selected contract organization has the capabilities, capacity, expertise, facilities, and systems to provide the services desired. Second, the sponsor company should assess the contract organization's willingness and capacity to modify systems, utilities, processes, or procedures to meet its requirements. Finally, the sponsor company must make sure the company is financially stable, has robust quality systems, and can conduct the services that will meet the specifications while meeting the schedules.[9] If a decision has been made to use a particular contract organization, formal agreements must be put in place after the contracting organization has passed an audit with acceptable results.

The Business Relationship

In an outsourcing relationship, the sponsor company normally owns the rights to the product or results of services, including the rights to market and sell the finally product. The contract organization agrees to provide the services and have compliant quality systems in place to deliver the product or service to agreed specifications. From the regulatory stance, however, the sponsor company is ultimately responsible for ensuring the product delivered is safe and effective and has been produced according to the regulatory requirements.

As such, the technology transfer and validation of the process/product or methods to the contract organization is a critical step in the qualification process. The same procedures used to transfer technology internally within an organization should be used to transfer process and methods externally.

From a business and quality position, the most important items are the initial supplier audit, the service contract, and the agreement. Prior to writing the agreement, a company should decide if this document will be a stand-alone document or part of the service contract (business contract). This decision may be based on whether the service contract is already in place or is being negotiated.

However, there may be various reasons why a company might implement the quality agreement as a stand-alone document versus part of the service agreement. These include that a service agreement has not been finalized; the need for revisions to either the service agreement or quality agreement; an existing approved service agreement without an existing quality agreement; or when a new product is obtained from another company that is already using a third-party contractor.[10] If a decision is made to create the quality agreement as a stand-alone document, there should be additional clauses and legal components in this document that are not necessary when the quality agreement is part of the service agreement.

Quality Agreement and Transfer Obligations

An agreement should be considered a living document that will be revised over time as the relationship changes. This document should be drafted by the quality professionals or sponsor of the study in the case of transfer obligations, who typically start the process by scrutinizing the types of services that will be performed by the contractor and the expectations of their company. The negotiation should focus only on those services that are expected to be provided by the contractor as defined in the service contract. If these services are revised at a later date, so should the agreement to address these changes.

Change control and the approval of changes are the most important parts of the agreement. Contract organizations are an extension of your operations. Changes should be submitted to the sponsor for review and approval prior to implementation. If not, changes can occur that are in conflict with regulatory filings resulting in 'adulterated' products or services. Just as important is the need to conduct periodic reviews of the agreement to ensure that the agreement complies with regulatory and business requirements. Part of this periodic review should include the resigning of the agreement, even if changes have not occurred, to document that this review has occurred. The sponsor and the contract organization are held responsible by the regulatory authorities with the sponsor having the ultimate responsible for the end-to-end safety and compliance of the product.

Format and Content

The format of the agreement is as important as the agreement itself. A company may have a standard template for these agreements that is already approved by the quality and legal departments. In absence of a pre-approved template, the agreement can be written like a legal document, written in tabular format, or a combination of both. More important than the format are the content of the agreement and the ease of identifying each party's responsibility. The agreement shall identify what documentation requirements are required to be met before product, component, etc. made under the contract can be physically shipped by the contractor or supplier.

The tabular format, as shown in table 1, is preferable, as it clearly outlines these responsibilities. This format is easier to reference, reduces confusion and it is easier for an external auditor to audit against.

GxP Category	Detail Responsibility	Responsible Parties		Comments
		Contract Giver	Contract Acceptor	
Personnel (21 CFR 211.25, 21 CFR 820.25 or 21 CFR 600.10)	Training on specific SOPs, Protocols, GMP Training, etc.	Mark with an 'X' OR with the name of the Contract Giver's Quality representative. If not used the block should indicate N/A.	Mark with an 'X' OR with the name of the Contract Acceptor's Quality representative. If not used the block should indicate N/A.	Specify any special instructions or comments that are relevant

Table 1 - Example of a Quality Agreement Tabular Format

A typical quality agreement is composed of the following major sections:

- Scope and Purpose
- Abbreviations and Definitions
- Communication and Dispute Resolution
- Responsibilities (including communication mechanisms & contacts)
- How Changes will be Handled
- Manufacturing Activities
- Documentation
- Deviations
- Visits, Audits and Regulatory Agency Inspections
- Subcontracting
- Sampling and Testing
- Complaints and Recalls
- Nonconformance
- Corrective Action and Preventive Actions (CAPA)
- Annual Product Reviews
- Final Approval
- Change Control, Revision Process, and History

The agreement should clearly outline how quality matters are communicated between the parties. Primary quality contacts should be identified with contact information such as telephone and fax numbers, email addresses, and business mailing address. It is recommended that backup or secondary contact information be provided for time-sensitive issues when the primary contact is unavailable. If multiple products and services are covered by the agreements, it may make sense to identify the quality lead for each product or service and the backup or secondary contact.

Deciding what products or services are outsourced to a contract organization should be part of the strategic planning process. While anything can be outsourced, outsourcing can result in less than optimal circumstances if the contract manufacturer has conflicting priorities with other sponsors. This can result in a failure to take advantage of market upswings because the contract organization is fully utilized or has given scheduling/capacity priority to other sponsors. In addition, there may be a higher chance for the loss of intellectual property or trade secrets with outsourcing.

Just as important of what an agreement should contain, is what it shouldn't. Examples of some standard items that should be excluded are:

- Pricing and Escalator Clauses
- General Business Terms and Conditions

- Forecasting
- Delivery Terms
- Confidential Information and Obligations
- Liability Limitations

Legal Review

Upon completion of the negotiated agreement between the two parties, the agreement must be reviewed by legal counsel. The legal counsel should clearly understand their role and function in the review process. This lack of clear understanding could cause delays in the review process. The purpose of this review is to avoid any potential litigation by reviewing the content of the document for any potential legal issues. The legal counsel should not interpret regulations nor change the content, unless there is clear indication that language contained in the agreement could prevent the company from meeting its responsibilities. Any changes should be brought to the attention of both parties involved in drafting the document. After all the reviews have been completed, the document should be approved by both parties and any changes should be handled following the change control process outlined in the agreement.

Monitoring Adherence to the Agreement

The approved agreement sets the stage not only for monitoring the quality and compliance of the services provided by the contractor but allows for monitoring the performance of the contractor and the relationship between both parties. Both parties should identify and monitor key performance indices (KPI) regarding compliance, product quality, adherence to the agreement, and overall performance. The following are a few KPIs that could be tracked:

- Product failure rates
- Out of specification rates
- Testing failures rates
- Sampling error rates
- Major product or protocol deviation rates
- Product or process nonconformance and CAPAs
- Product complaints
- Agreement deviation rates
- Notification and response times

Focus should be limited to those KPIs that provide the most useful information to both parties. Too many indices may dilute the attention from key issues and take away focus from more pressing matters.

Conclusion

In conclusion, outsourcing may be the only way for a company to bring a product to market and keep up with the demand for the product. An agreement made with contracting organization makes good regulatory sense in ensuring GxP compliance and good business sense by potentially saving the company money and time and avoiding legal issues. Agreements also need to be backed up with an active contract manufacturing management program. The agreements need to be enforced and maintained. Too many times contract organizations are treated as out of sight, out of mind. This is a recipe for disaster. Contract organizations can be a valuable part of a company's assets, but they can also be huge risks if they are not managed properly. As life science companies continue to strive for low-cost sourcing, high quality product, speed to market and lower initial costs, the use of contracting organizations will continue to grow and so will the use of these agreements.

About the Author

Kevin Bogert is currently a Managing Member of Azimuth Compliance Consulting, LLC.

He has more than 35 years of business experience, 30 of them in the life science industry, where he has been involved in global implementations of quality and regulatory systems. His background includes statistics, quality and regulatory systems, computer and process validation, and automation of manufacturing processes. You can reach Kevin by e-mail at kbogert@azimuthcc.com or by phone at (215) 990-9123.

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