Quality Agreements and Managing Contract Supplier Quality

American Society for Quality

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Abstract

Contract manufacturing and research service providers are increasingly being utilized to supplement 'in-house' capabilities. Formal Quality Agreements with these service providers are key to effectively managing regulatory compliance and satisfying product and service quality needs. In addition, they are useful in establishing successful service partner relationships, ensuring proper management of mutual quality system needs, and maximizing the value of the outsourcing opportunity.

This presentation will describe what Quality Agreements encompass, their value, and the regulatory and practical basis for them. It will also describe typical content, the relationship with the business agreement, and the process for establishing, negotiating, and properly maintaining an effective Quality Agreement. Suggestions will also be provided to establish a framework for a collaborative partnership that creates value and facilitates project and product success.
The Dow Chemical Company

• A global leader in science and technology
• Annual sales $40 billion
• 43,000 employees
• Serving customers in 175 countries

Our Mission

To constantly improve what is essential to human progress by mastering science and technology
Dowpharma History

Marion Merrell Dow

Dowpharma / Dow Ventures includes BioAqueous SM Biological Services

BCMS 2001

Aventis

CMS 1995

ChiroTech 2001

ChiroScience

Celltech

Dowpharma
Dow and the Drug Life Cycle

Drug Delivery Technology
- BioAqueous SM
- Pegylation
- ChelaMed SM

Delivery Strategy
- Process Development
  - Phase I
- Formulation Development
  - Phase II
- Clinical Supply
  - Phase III
- Launch & Commercial Manufacture

Lead Optimize
- Process Development
  - Phase I
- Clinical Supply
  - Phase II
- Clinical Supply
  - Phase III

Collaborative Research
- Synthesis Route Selection
- Product Characterization / Specification Development
- Process Optimization
- Engineering Scale-Up

Clinical Supply Manufacture
- Commercial Mfg.

Fermentation/Isolation Process Development

Product Characterization / Specification Development

Clinical Supply Manufacture
- Commercial Mfg.

Filing / Validation Strategy
- Validation & Facility Approval
Technology Platforms

- BioAqueous<sup>SM</sup> Solubilization Services
- Biopharmaceuticals
- ChelaMed<sup>SM</sup> Radiopharmaceutical Services
- Nucleic Acid Medicines
- PEGylation
- Plant Biopharmaceuticals
- Small Molecules
Quality Agreements

What is a Quality Agreement
Value and regulatory basis
Content and structure
Key areas
Negotiating process
On-going Maintenance
Summary key points
What is a Quality Agreement?

Formal document that defines the ‘rules of engagement’ between the sponsor and client for proper management of mutual quality and quality regulatory needs in an outsourcing arrangement.

Establishes mutual understanding of the quality management system to be applied and who is responsible (sponsor or client) for the execution of the various aspects of that quality management system.

It’s a ‘get to know you’ exercise. Key early step in developing an effective, trusting, inter-dependant relationship.

Ideally it is separate from the Commercial agreement, though linked.
Shared Quality and Regulatory Accountability

The sponsor is ultimately responsible for the finished product
--responsibility for quality and compliance can’t be totally
abdicated to contracting firm

Sponsor and contract supplier both have regulatory obligations
to satisfy

Sponsor and contract supplier both have reputation and
credibility at stake

Success truly becomes a shared responsibility

A good Quality Agreement defines these shared
responsibilities
Drugs

Pharmaceutical CGMP’s (Part 211)

4. **Control Outsourced Operations**

When outsourcing, a second party is hired under a contract to perform the operational processes that are part of a manufacturer’s inherent responsibilities. For example, a manufacturer may hire another firm to package and label or perform CGMP regulation training. **Quality systems call for contracts (quality agreements) that clearly describe the materials or service, quality specifications responsibilities, and communication mechanisms.**

Under a quality system, the manufacturer ensures that the contract firm is qualified. The firm’s personnel should be adequately trained and monitored for performance according to their quality system, and the contract firm's and contracting manufacturer’s quality standards should not conflict. It is critical in a quality system to ensure that the contracting manufacturer’s officers are familiar with the specifics requirements of the contract. However, under the CGMP requirements, the QCU is responsible for approving or rejecting products or services provided under contract (see § 211.22(a)).
Drug Actives

From ‘Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients’:

XVI. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) (16)
All contract manufacturers (including laboratories) should comply with the GMP defined in this guidance. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

Companies should evaluate any contractors (including laboratories) to ensure GMP compliance of the specific operations occurring at the contractor sites.

There should be a written and approved contract or formal agreement between a company and its contractors that defines in detail the GMP responsibilities, including the quality measures, of each party.

A contract should permit a company to audit its contractor's facilities for compliance with GMP. Where subcontracting is allowed, a contractor should not pass to a third party any of the work entrusted to it under the contract without the company's prior evaluation and approval of the arrangements.

Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.
Biologics

Cooperative Manufacturing Arrangements for Licensed Biologicals, August 1999
http://www.fda.gov/cber/gdIns/coopmfr.pdf

- Divided Manufacturing Arrangements
  - More then one party owns the Product License and produce jointly
- Shared Manufacturing Arrangements
  - License for parts of the entire process
- Contract Manufacturing Arrangements
  - License holder is responsible to assure compliance with product and establishment standards
Medical Devices

Good Manufacturing Practices (GMP) / Quality System (QS) Regulation (Devices)

Contract Manufacturers
A person(s) that manufactures a finished device under the terms of a contract with another manufacturer is a contract manufacturer. The agreement between the manufacturers should be documented in a written contract. Contract manufacturers of finished devices shall comply with applicable requirements of the quality system and shall register their establishment with FDA. Depending on the circumstances, both the contractor and manufacturer may be held jointly responsible by FDA for the activities performed.

from http://www.fda.gov/cdrh/devadvice/32.html
Regulatory Basis

Broadly required, can be considered a general requirement for any outsourcing arrangement

Inspectors are asking for them -- defines scope of work, who’s accountable for what, and therefore helps define scope of inspection

Even where not strictly required, it’s still good practice!
Linking Expectations with Delivery

CMO Capability  

Sponsor Requirements

Quality Agreement defines how CMO will satisfy Sponsor Requirements
Maximizing Value in the Relationship

How work gets done – the shared Quality Management System

Efficiency is greatest in the overlapping area -- expand it through the Quality Agreement

- worth spending time to find a CMO with a similar culture
- work to understand differences – are they real, meaningful?
- be flexible, open – opportunity to learn from one another
- create a meaningful partnership through the dialogue
## Relationship between Commercial and Quality Agreement

<table>
<thead>
<tr>
<th>Quality Agreement</th>
<th>Commercial Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>- product/service quality focused</td>
<td>- pricing, delivery, indemnification</td>
</tr>
<tr>
<td>- agency reviewable</td>
<td>- normally not a concern for the agency</td>
</tr>
<tr>
<td>- more easily updated, ‘living’ doc</td>
<td>- relatively static</td>
</tr>
<tr>
<td>- establishes communication mechanisms</td>
<td>- typically more signatories</td>
</tr>
<tr>
<td>- ‘relationship’ expectations</td>
<td>- legal requirements</td>
</tr>
<tr>
<td>- typically fewer signatories</td>
<td></td>
</tr>
</tbody>
</table>

Can be one document, but quality agreement sections should be extractable for practical distribution and use.
## Typical Content

<table>
<thead>
<tr>
<th>Subject and Purpose of this Agreement</th>
<th>Quality Assurance and Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of cGMP Expectation</td>
<td>Change Control</td>
</tr>
<tr>
<td>Definitions</td>
<td>Notice and Approval of Deviations</td>
</tr>
<tr>
<td>Raw Materials</td>
<td>Sampling/Retained Samples</td>
</tr>
<tr>
<td>Specifications</td>
<td>Testing</td>
</tr>
<tr>
<td>Procurement of Raw Materials</td>
<td>General Inspection and Testing</td>
</tr>
<tr>
<td>Inspection, Testing and Labeling</td>
<td>Laboratories/third party testing</td>
</tr>
<tr>
<td>Storage and Handling of RM’s</td>
<td>SPONSOR managed testing</td>
</tr>
<tr>
<td>BSE and TSE Compliance</td>
<td>Dispute Resolution</td>
</tr>
<tr>
<td>Qualified Supplier(s)</td>
<td>Release and Shipment of Product</td>
</tr>
<tr>
<td>MSDS Information</td>
<td>Certificates of Compliance</td>
</tr>
<tr>
<td>Manufacturing and Packaging</td>
<td>Certificates of Analysis</td>
</tr>
<tr>
<td>Specifications</td>
<td>Stability testing, reporting</td>
</tr>
<tr>
<td>Site of Manufacture/Subcontracting</td>
<td>Documentation</td>
</tr>
<tr>
<td>Production and Facility Procedures</td>
<td>Document Retention, location</td>
</tr>
<tr>
<td>Manufacturing Batch Documentation</td>
<td>Requests for documentation</td>
</tr>
<tr>
<td>Lot Numbering, Date of Manufacture</td>
<td>First Three Lots Product</td>
</tr>
<tr>
<td>Labeling and Packaging</td>
<td>Subsequent Lots of Product</td>
</tr>
</tbody>
</table>

**SM**

23-Dec-08  
DOW CONFIDENTIAL - Do not share without permission
Most firms have established their own quality agreement templates.

Breadth and level of detail will vary with nature of activity.

Keep quality agreements focused on expected scope of work, but challenge yourself to consider ‘what ifs’.

The form is much less important than the up-front dialog!
Key Areas

Change Management
Deviations, investigations
Product Release
GMP Audits
Regulatory inspections
Management of Change (planned changes)

Changes run the gamut in complexity and potential impact
Varying levels of Sponsor involvement
Need to define what is a change, and what should be done as a function of type of change
Example changes are useful here to help characterize subjective terms (like “major” or “minor” etc)
How and when to communicate – can have an big impact on timing (are sponsor reps available?)
How/who approves ... and when?
Deviation management (unplanned changes)

Every event is unique -- can have a big impact on $, schedules
Expectations of what to do in response to deviations of varying severity vary widely
Most important to build communication framework into quality agreement (and then communicate!)
Investigation process can be involved – who participates and how are decisions made and communicated?
How/who approves?
Product Release

Regulatory requirements for who is responsible is not clear
 Widely varying interest in direct Sponsor involvement
 Can have a significant impact on $, schedules
 Typically Sponsor has final responsibility, but who (and when) will:
   batch records be reviewed?
   analytical records be reviewed?
   investigations be closed out?
   differences of opinion be reconciled?
 Can drive ‘man in plant’ needs
Routine GMP Audits

You need to do them!
Another good relationship building opportunity
May need to consider intellectual property landscape
Consider auditing logistics
Contractors expect them at least annually, but too frequent, too many people, too long can be a burden (which just adds additional expense)
Agency Inspections

Widely varying interest in direct participation in agency audits
Will need some level of Sponsor involvement, min. via phone and fax, need to discuss logistics before the FDA is at the reception desk!
With agency’s systems focus to auditing, audits can quickly cross product and client lines
Contractor is, in effect, your representative during an agency inspection – make sure contractor is doing a good job representing your interests
Negotiating

Try to consider scenarios you may be faced with – best to decide how to handle the hypothetical case rather than when you’re in the middle of a real issue.

Most meaningful discussions and agreements will be made ‘Quality person’ to ‘Quality person’. Good to have the folks that will be executing the quality agreement involved in the negotiations to better understand intent.

A lot of interaction ‘work process’ will be established during the negotiating period. Try to capture.

Alignment with business agreement needs to be regularly checked. Project leader typically involved in both discussions and should provide linkage. There will likely be direct cost implications.

Work to understand each other -- great opportunity to starting building the relationship!
Execution and Maintenance

Establish routine communication channels – most information normally flows between QA and Project Leader peers in the two organizations (and they then need to communicate well between themselves and further within their organizations!)

Consider establishing a formal process to document routine communication, decisions and transfer of records between companies

Should review Quality Agreement annually, build in learning experiences.

Review/update can be coupled with the annual audit, annual product review and/or quality management system review.

Will evolved based on the business need and based on the maturity of the relationship – typically moves from one of high level of control and oversight early in the relationship to more of a partnership as the relationship matures.
Summary key points

Quality Agreements provide a framework for interaction and satisfying shared quality and regulatory obligations.

Most of the value with a Quality Agreement is the up-front discussion and mutual understanding it facilitates.

One size does not fit all -- quality agreements will look different for different situations.

Exceptions to the CMO’s standard practices will add cost – work to understand underlying needs and drivers.

Establish and reinforce routine communication channels – it’s key to an effective relationship.