Quality Agreements for the Cell Therapy Facility
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Today’s topics

- Karen - General overview of agreements, focus on Quality Agreements and how to get started; US experience; Case Studies
- Andrea - EU experience
- All - Q & A
Cell therapy companies rely heavily on outside support

**Company A** is the sponsor of a clinical trial using a cell therapy product manufactured by **Company B**. The product is a cell/device combination requiring a product-specific scaffold manufactured by **Company C**. The cells are collected from autologous patients by apheresis using **Company D**. The sterility testing for final release is performed by **Company E**. The product is shipped from the CMO to the clinical site using **Company F**. The Clinical Research Organization managing the clinical trial is **Company G**.
What do the regulations say?

- **GTPs** - “Before entering into a contract, agreement or other arrangement with another establishment to perform any step in manufacture for you, you must ensure that the establishment complies with applicable GTP requirements”

- **GMPs** - “The QC unit shall be responsible for approving or rejecting drug products manufactured, processed, packed or held under contract by another company”

- Specific language in EU regulations and cell therapy standards
Why are Quality Agreements needed?

- Help mitigate risk; this risk can affect overall product quality

- Clarify expectations, goals and responsibilities in writing from the beginning of the relationship. Written contract in place for reference if misunderstandings or disputes occur

- Regulators expect **Quality Agreements** to be in place for good reason; need to identify who is responsible for regulatory compliance
Why are Quality Agreements needed? (2)

- It simply makes good business sense
- Failure to execute quality agreements can leave both partners vulnerable, open to regulatory noncompliance, broken contracts, and lost business
- It doesn’t matter if you are an academic cell therapy laboratory, hospital or a company: Quality Agreements are necessary. If resourced constrained, use risk-based approach (i.e. agreements with CMOs a must)
Definitions and terms

- A **Business Agreement** defines general terms and conditions of a legally binding contract between 2 parties; details may include pricing, delivery terms, confidentiality obligations, liability limitations, and dispute resolution for goods and services.

- **Business agreements** are generally written, approved, and managed by operations management, financial and legal departments.
Definitions and terms

- A **Quality Agreement** defines the quality standards related to manufacturing and testing of cell products; ensures contractors are providing services or products with consistent quality; delineates responsibilities of personnel.

- A **Quality Agreement** should be in place between the sponsor (contracting firm) and provider of **critical** services and materials.
Definitions and terms

- **Sponsor** is ultimately responsible for the product (i.e. hospital, academic institution, company)
- **Sponsor and contract supplier** both have regulatory obligations to ensure product quality, and reputations and credibility to maintain
- Agreements are a **shared responsibility** between the sponsor and contract supplier and make good business sense
How do you begin the process?

- Determine an approach to developing and managing Quality Agreements:
  - Responsibilities of key personnel; role of legal department
  - Which contractors or service providers require Quality Agreements; use risk-based approach
  - Use a standardized template
  - Include in your Quality Plan
  - Write an SOP for how Quality Agreements are written, reviewed approved.
What’s next?

- Drafting the Quality Agreement begins once the contractor has undergone a formalized qualification process, and has been approved. This typically involves due diligence on the business side and qualification of the contractor, including a quality audit.
  - Follow SOPs for performing a supplier qualification, using a standardized process and checklists.
Stand-alone or combined document?

- Determine if the Quality Agreement will be a stand-alone document or part of a supply/services business agreement.
  - The Quality Agreement can be prepared at the same time and incorporated as an appendix or schedule. This is convenient during the review and negotiation process; helps avoid redundancies and quickly identifies problem areas when reviewing both documents together.
  - However, a stand-alone document can serve as a living document, referred to as needed, updated by the parties that need to be involved, and available to regulators and other auditors during an audit.
Responsibilities

- Initiated and prepared by both parties' QA groups
- Reviewed by relevant stakeholders and experts:
  - Quality Assurance
  - Quality Control
  - Manufacturing
  - Regulatory
  - Legal
  - Business Development
More Responsibilities

- Quality Agreements are approved by management from both parties' QA and RA functional groups and both parties' Operations management.

- Legal is involved in the review process. However, try to avoid excessive legal language that makes the Quality Agreement difficult to interpret by the end users.
Basic elements in a Quality Agreement

- Purpose and scope
- Definition of terms
- Regulatory compliance
- Responsibilities of sponsor and contractor – list or matrix
- Communication
- Change control and notification
- Complaints, OOS, deviations
- Site visits, audits
## Division of Responsibilities - Example

<table>
<thead>
<tr>
<th>Elements</th>
<th>Sponsor</th>
<th>Contractor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update and revision of this document</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Compliance with GMPs and GTPs</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Manufacturing and testing of Product</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Audit Contractor</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Inform Sponsor of OOS and complaints</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Case Study - Contract Manufacturing

Company CellX is a small start-up cell therapy company (the Sponsor) with a promising new application. They do not have adequate facilities to manufacture the HCT/P in a scale adequate for the clinical trial. They send out a request for proposal (RFP) to several known contract manufacturers of HCT/P. After extensive due diligence, the contractor manufacturer is selected. The teams on both sides are assembled and work on the agreements begin.
Quality Agreement - CMO

- Scope of Work - be very specific
  - Development - scale up or scale out
  - Technology transfer
  - Engineering / pilot production runs
  - GMP Production

- Master Services Agreement (Business Contract)
  - Includes the legal protections

- Quality Agreement
Quality Agreement - CMO

- Preparation of Master Records
  » Who initiates changes
  » How changes are made and approved
  » Records management (e-records)
  » Records retention

- Raw material procurement and release
  » Material specifications
  » Supplier qualification
  » Retains
Quality Agreement - CMO

- Facility and equipment
  » Validation
  » Verification
  » Calibration
  » Change control

- Deviations, Non-conforming Materials
  » Responsibility for investigation
  » Responsibility for product (component) disposition
Quality Agreement - CMO

- Complaints
  - Communication: client, clinical site, regulators
  - Investigation
- Inspections and audit rights, responsibilities and reporting
  - Annual and ‘for cause’
  - FDA
  - Other regulatory authorities
- Audit responses and corrective actions
Quality Agreement - CMO

- Product In-process and Release testing
  - In house or 3rd party
    - Instrument calibration & maintenance
    - Method validation or qualification
    - Report and data review
    - Out of Specification results investigation and conclusions
  - Final Batch Record Review - turnaround time

_The Sponsor is always responsible for product release_
Quality Agreement - CMO

- Product shipment
  - Packaging
  - Carrier
  - Chain of Custody
Quality Agreement - Apheresis

- Facility, process and equipment
  - COBE, Baxter
  - Cleanliness, calibration, maintenance
  - Change control
- Staff training - documentation
- Patient consent administration
- Forms and paperwork
- Product shipment - chain of custody
“Your firm failed to establish and maintain the requirements, including quality requirements, that must be met by supplier, contractors, and consultants as required…”

“the ….company also had not conducted site audits or maintained a contractual agreement with the contractor to determine if it was processing..*product*..according to cGMPs.
FDA Warning Letters

- The FDA quoted the quality agreement in the warning letter to the contract manufacturer:

  “The Contract Manufacturer will not release for shipment any portion of production determined to be out of specification or defective as a result of routine testing/inspection, without a legitimate assignable cause and without conclusive evidence that the exact beginning and end of the non-conforming production has been identified and clearly segregated.”
FDA Warning Letters

- Sponsor’s responsibility:

“…the contract manufacturer for the ..product.. was changed and the new molds that were prepared failed to produce product that met specified tolerances. Despite these failures, you approved the product, and you did not define or demonstrate equivalence acceptance criteria.”
You have a Quality Agreement in place, now what?

- Remember the QA agreement is a living document, and needs to be used, not stuck on the shelf!
- Quality of product/service should be monitored.
- Quality agreement should be reviewed (i.e. annually) and updated as needed.

  *Communication is key not just to deal with urgent issues that arise, but as a means to prevent problems from occurring.* Consider establishing regular meetings to discuss performance and compliance.

- Establish quality metrics to be tracked i.e., product failure rates, OOS rates, major deviation rates, turnaround, notification and response times.
References

1. 21 CFR 211, Current Good Manufacturing Practices for Finished Pharmaceuticals
2. 21 CFR 1271, Human Cells, Tissues, and Cellular and Tissue-Based Products
3. 21 CFR 820, Medical Device Quality System Regulation
4. AABB, Standards for Cellular Processing Services, 3rd Edition
7. EU Guideline to Good Manufacturing Practices for Human and Veterinary Medicinal Products, EudraLex Vol. 4
8. FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration, 4th Edition
11. ISO 13485:2003, Medical Devices Quality Systems
12. International Conference of Harmonization, Q7, Q9 and Q10
Thank you for your attention!

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