Manufacturing Contracts & Quality Agreements

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What is a Quality Agreement?

- 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
- ***Business contracts*** with general terms and conditions, pricing, delivery terms, confidentiality obligations, liability limitations, dispute resolution ***are not Quality Agreements***

Why are Quality Agreements needed?

- Companies outsource many activities critical for producing a cell product, for instance:
  - ***Tissue procurement, manufacturing and testing activities, critical materials , (i.e. scaffolds, delivery systems), shipping***
- Quality Agreements help mitigate risk
  - ***Failure to clarify expectations, goals and responsibilities can affect overall product quality and patients receiving promising therapies; in addition can leave both partners vulnerable, open to regulatory noncompliance, broken contracts, and lost business***

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"*

What do the regulations say? (cont.)

- *Device QSRs – "Each manufacturer shall establish and maintain the requirements, <u>including quality requirements, that must be met by suppliers, contractors, and consultants"</u>*
- *EU GMPs - "There <u>should be a written contract</u> covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it."*
- *Also various standards: FACT, AABB, ISO, ICH all have language on evaluation of contractors, quality requirements, and contracts*

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.
- Determine if the Quality Agreement will be a stand-alone document or part of a supply/service business contract.
  - 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.

Who should prepare/review and approve a Quality Agreement?

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

Who should prepare/review and approve a Quality Agreement? (cont.)

- 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 legalese that makes the Quality Agreement difficult to interpret by the end users.

What are basic elements to consider for a Quality Agreement template?

- 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

Elements	Sponsor	Contractor
Update and revision of this document	X	X
Compliance with GMPs and GTPs		X
Manufacturing and testing of Product		X
Audit Contractor	X	
Inform Sponsor of OOS and complaints		X

You have a Quality Agreement in place - now what?

- Remember this is a living document, and needs to be used, not stuck on the shelf!
- Quality of product/service should be monitored
- ***Communication is key to deal with issues that arise.***
- 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. Draft Guidance for Industry: Current Good Tissue Practices and Additional Requirements for Manufacturers of HCT/Ps ,January 2009
5. EU Directive 2003/94/EC, Article 12
6. EU Guideline to Good Manufacturing Practices for Human and Veterinary Medicinal Products, EudraLex Vol. 4
7. FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration, 4th Edition
8. AABB, Standards for Cellular Processing Services, 3rd Edition
9. ISO 13485:2003, Medical Devices Quality Systems
10. International Conference of Harmonization, Q7 and Q10

Thank you for your attention!

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