Production Assistance for Cellular Therapies

Educational Web Seminar
Academic and Industry Partnerships – The Next Generation –
Thursday, June 8, 2017
12:00 noon – 1:00 PM ET

Speakers
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CE Credit and certificates of attendance provided upon request
Today’s web seminar presentation slides are available publicly at www.pactgroup.net

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<th>Faculty Name</th>
<th>Involvement</th>
<th>Affiliation</th>
<th>Financial Interest</th>
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<td>Diane Kadidlo</td>
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<td>Hannah Cady</td>
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<td>Jodi Brenden</td>
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Description

In this web seminar, speakers will discuss aspects of successful academic and industry partnerships. Expanding indications for cell therapy in medicine are driving the need for increasing numbers of early and late phase clinical trials. Academic and industry partnerships are becoming instrumental in managing the pace of discovery with the cost of approved therapies. Speakers will address crucial points to consider when entering into a contractual relationship between academia and industry for cell therapy development and manufacturing to support clinical trials. Topics to be covered include points to consider when choosing your partner, key elements in developing a failsafe contract, structuring a quality agreement and executing technology transfer and cell manufacturing on time and on budget. Successful delivery on expectations is victory for both partners and patients.

Objectives

1. Identify key elements to consider when developing contracts
2. Examine the components of a quality agreement and some of the obstacles and challenges faced with technology transfer and scale-up that will affect the scope of work identified in the contract
3. Identify elements that are essential in executing a successful technology transfer process

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Contract Development

Diane Kadidlo
8 June 2017

Partnerships

- Basic and translational research
- Expertise in trial design
- Patients and clinical care
- Clinical trial network
- Data analysis
- IRBs

- Study design and regulatory approval
- Expediting review process of breakthrough therapies

First Steps

- What are the expectations for the academic institution?
  - On site manufacturing
    - Product development
    - Validation
    - Clinical manufacturing of a fully developed product
  - Minimal to no site manufacturing
    - Collect
    - Receive
    - Infuse
Know Your Partner

- Vetting your industry partner
  - Scientific
    - Technical expertise
    - Publications
    - Clinical trial experience
  - Financial Status
  - Track Record

Product Development Process

Project Evaluation

- Does it fit our mission?
- What are the unknowns?
  - How well is the product developed?
- What are the risks?
  - Inability to transfer technology
  - Meet development/production timelines
- Sufficient Resources
  - Staff
  - Space
  - Equipment
- Safety concerns
Contract Team

- PI
- Legal
- Finance
- CT Lab Administrator
- CT Medical Director
- Clinical coordinator
- Quality Assurance
- Contract Officer
- Office of Technology & Commercialization

CT Agreements

- Material Transfer Agreement
  - Transfer of biologics (cells, proteins, plasmids etc.), pharmaceuticals, data
- Research Agreement
  - Research and or Preclinical work --tech transfer, process develop, validation, tox studies
- Clinical Supply Agreement
  - Manufacturing of a clinical product not involving clinical trial on site.

CT Agreements

- Industry Sponsored Clinical Trials Agreement
  - Covers entire clinical trial patient, donor, product manufacturing, start-up, monitoring, PI effort
- External Sales
  - Exchange of product no research, no IP, no clinical trial on sight
- Quality Agreements
  - Agreements between manufacturer and sponsor relating to compliance and quality expectations
Material Transfer Agreements

- Legal agreement for material that is transferred from one party (provider) to another party (recipient).
  - Biological materials (e.g., cultures, cell lines, plasmids, nucleotides, proteins, transgenic animals or plants, or pharmaceuticals), or information in various forms (e.g., data, databases, or computer source code).
- MTA governs:
  - Ownership of the transferred material and any of the modifications and derivatives made by the recipient;
  - Any limits on the recipient’s use of the material and reimbursements for any costs of providing the material;
  - Protection of either institution from legal liability as a result of the use of the material by others;
  - Confidentiality of information relating to the material, and any issues regarding publications;
  - Rights to inventions and use of research results, including protection of related intellectual property rights or valuable know-how.
- Typically these are unfunded agreements whereby no money is exchanged.

Contract Elements

- Project Scope
  - Statement of work – the overall goal
    - Research plan, process development, practice runs, validation, shipping studies, clinical trial
    - Define minimum number of experiments/ runs
    - Consider a phased approach especially in pre-clinical product optimization
- Confidentiality
  - A non-disclosure agreement (NDA) outlines confidential material, knowledge, or information that the parties
  - Separate or incorporated other agreements

Agreement Elements

- Publicity and Publications
- Intellectual Property
  - Rights to technology, inventions, data, licensing
- Indemnification & Liabilities
- Representation & Warranties
- Regulatory compliance
- Budgets
- Timeline
Budget

- Budget
  - Supplies
  - QC Testing
  - Facility fees
  - Labor
    - Production
    - Document development (SOPs, protocols, validation)
    - Meetings/calls
    - Audits
    - Easily underestimated - Keep track of time

Budget & Timeline

- Budget for Failures
  - Incorporate language in the contract identifying the potential for failure and who is responsibility for cost
- Cost Reimbursement vs Fixed Pricing
  - Preclinical vs clinical manufacturing
- Timelines
  - Realistic
  - Establish milestones
  - Periodic review

Take Home

- Know your product
- Know the risks
- Build in flexibility
- Remember it’s a Partnership
Academic and Industry Partnerships

Technology Transfer and Scale-Up

Stewart Abbot
8th June 2017

Disclosure

• Stewart Abbot is an employee and shareholder of Fate Therapeutics Inc.

• Fate Therapeutics Inc. has an ongoing collaboration with the Regents of the University of Minnesota

Academic and Industry Partnerships Technology Transfer

Guiding principles

• Ask not what your partner can do for you, but what you can do for your partner
  – after all it’s a marriage…of sorts

• Bear in mind that each partner may have different priorities
  – Publications
  – Patents
  – Trade-secrets
  – Risk-tolerance
  – Timelines
  – Funding

• Assume it the process will take longer than the initial Gantt chart

• TPPs are useful
  – Target Product Profile
  – Target Process Profile

• Put the patients first
Academic and Industry Partnerships
Technology Transfer

Target Product and Process Profiles
- A basic statement of expectations of product form and function
- US FDA: "The TPP embodies the notion of beginning with the goal in mind"
- Selected Attributes: T Product P's
  - Product description: Brief description and/or current product name
  - Mechanism of action: The mechanism by which the product produces an effect on a living organism (Efficacy / Potency).
  - Indication for use:
  - Expected Dosage
- Selected Attributes: T Process P's
  - Process "feedstock"
  - Process yields
  - Process / product identity & purity
  - Process residuals

Academic and Industry Partnerships
Technology Transfer

Key Considerations (Context: IND and FIH study enablement)
- Direction of Technology Transfer
  - Technology developed in academic setting transferred to commercial partner or license holder
  - R&D conducted in a commercial setting transferred to an academic partner for clinical manufacture and clinical trial
- Stage and Environment of Development
  - Stage of technology R&D prior to transfer
  - Level of process understanding
  - Expected / necessary stage of development after transfer
  - i.e. what level of process development will be required during transfer?
  - Expected time required for process development / transfer
  - Academic R&D environment ≠ Biotech R&D Environment ≠ Pharma R&D Environment
    - Process Understanding, nature and level of documentation
- Elements to be Transferred
  - Process complexity
    - Process AND Process QC

Academic and Industry Partnerships
Technology Transfer

Challenges and Approaches
- Typical Challenges
  - Overestimation of process understanding and control prior to transfer
  - Technology transfer is a great way of finding out what elements of a process are variable / not sufficiently controlled
  - Potential need to conduct "process development" during transfer
  - "Language" barriers e.g. different understanding of TLAs (QBD, CTQ, TRL etc.)
  - Aggressive sponsor timelines
  - Forgetting that QC assays may have to be transferred ahead of the process
- Typical Approaches (assumes legal agreements in place)
  - Transfer and review process documentation
    1. Research, Development, Manufacturing, IQ & QA
    - Mutual definition of success metrics is CRITICALLY important
    2. Onsite review and performance of process at site of process establishment ("see one" or more)
    - Onsite review and performance of process at site of process establishment ("do one" or more)
    - Perform engineering runs (selected unit operations or entire process)
    - Perform Process Qualification (PQ) runs on entire process
Terminology

• Scale-up e.g. monoclonal antibodies
  – Traditional approach to creating product supply for clinical studies
  – Few product batches created at an ever increasing scale of production
  – Few manufacturing centers with national / international distribution

• Scale-out e.g. HSCT
  – Increasingly popular approach for patient-specific therapies
  – Ever increasing number of product batches created at a similar (single-patient) scale of production
  – Potential for multiple manufacturing centers with national / international distribution

Scale-up versus Scale-out (excluding ultra-orphan indications)

• Phase 0/1 studies: ~12 patients
  – Single or few clinical sites within country
• Phase 2 studies: 60+ patients ± control population
  – >1 potentially 10s of sites in different countries
• Phase 3 studies: 100+ patients ± control population
  – Likely >10s of sites in different countries
• Commercialization: likely 1000’s, 10,000’s of patients
  – Ideally globally

Types of Processes

• Typical donor or patient-derived therapy
  – Requires manufacturing scale-out; ideally with automated unit operations
Academic and Industry Partnerships
Process Scale-Up & Scale-Out

Types of Processes

- Typical highly expanded-allogeneic therapy

  - Small part of the process is repeated for every patient
  - Requires manufacturing scale-up (elements in red conducted once / few times per product life)


Technologies (Cell-based Therapies)

- Scale-up
  - Increasing use of process analytical technologies
  - Increasing use of complex bioreactors to achieve required scale
  - Predominant use of single use disposable
  - Investment of process-development time to define CQAs to ensure scalability

- Scale-out
  - Increasingly use of automation to achieve throughput and scale
  - Increasing use of simple bioreactors to achieve scale
  - Almost complete reliance on single use-disposable systems
  - Investment of process-development time to define patient-to-patient (batch-to-batch) variability

System / Process Control

- The ability to control a process during scaling can only be as good as the ability to measure the process
- Measurements (QC) should define critical to quality (CQAs) attributes of the process
  - e.g. transduction efficiency, cell expansion, cell identity, product purity & functional attributes (efficacy)
- Long-term process variation should be determined, but might be expected to be ~3x short-term variation

### Key Considerations

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<tr>
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<th>Scale-up</th>
<th>Scale-out</th>
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<tbody>
<tr>
<td>Changes in unit operations with increasing scale</td>
<td>Modest to major</td>
<td>Minor</td>
</tr>
<tr>
<td>Utilization of labor with increasing scale</td>
<td>Increasingly efficient</td>
<td>Modest efficiency gains</td>
</tr>
<tr>
<td>Cost and consequence of batch failure</td>
<td>Major</td>
<td>Minor (depending on indication)</td>
</tr>
<tr>
<td>Process development required to increase scale</td>
<td>Major</td>
<td>Modest</td>
</tr>
<tr>
<td>Quality control</td>
<td>Simple</td>
<td>Complex</td>
</tr>
<tr>
<td>Compatibility with highly complex processes</td>
<td>High</td>
<td>Low</td>
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### Academic and Industry Partnerships Technology Transfer Conclusions

- Ask not what your partner can do for you, but what you can do for your partner
- Each partner may have different priorities and terminologies
- Assume tech. transfer will take longer than initially expected
- TPPs are useful (start with the end goal in mind)
- The larger the scale (scaled-out or -up) the better the process understanding needs to be to control variation
- When in doubt put the patients first

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Thank You

stewart.abbot@fatetherapeutics.com
Managing Quality Assurance Expectations
Fran Rabe
Director of Quality Assurance
University of Minnesota
Molecular and Cellular Therapeutics

Establishing Expectations
the Players

- **Contractee**: The entity/establishment holding an agreement for services with a **Contractor**
- **Contractor**: The entity/establishment providing a product and/or services related to the manufacture process
- **Subcontractor**: An entity/establishment the **Contractor** utilizes to perform product analytics or manufacturing functions.

Pre Contract and Agreement Expectations

Perform Due Diligence Assessment to Establish Expectations of Both Parties
- Initiate formal “capabilities” versus “needs” discussion
- Perform audit with a general (open) exchange related to current capabilities
  - Contractor should be forthcoming related to current and future capabilities
Managing Expectations versus Capabilities

- Determine gaps between contractee’s expectations and contractor’s capabilities
  - Openly discuss options for “closing the gaps”, assuming that is the path both entities choose to continue to pursue
  - Discuss options for compromise, for example:
    1) Issue: Contractor does not have capability to store retainers
    2) Issue: Contractor has limited material storage capacity
    3) Issue: Schedule of Contractor annual facility shutdown
    4) Issue: Contractee required manufacture start date

Generate a Mutually Agreed Upon Quality Agreement

Quality Agreement Purpose
- Defines specific quality and regulatory parameters (requirements)
- Assigns responsibility to each quality/regulatory parameter
- Should be separate from an overall contract
- Should be in place prior to initiating activity

Quality Agreement Contents
Preamble
Purpose
Scope
Policy Statements
Definitions
Term of Quality Agreement
Survival Clause
*Responsibilities
Approved Subcontractors
Contractor and Contractee Communication Contacts
**Responsibilities**

- Regulatory Authorization
- Equipment, Facilities, Personnel
- Documentation
- Receipt and Storage of Materials
- Product Related Manufacture
- Testing and Analysis
- Storage and Shipment

**Responsibilities Continued**

- Product Disposition
- Records
- Change Control
- Deviations, Investigations and CAPA
- Complaints
- Retrieval of Product
- Contractor and Contractee Site Audits
- Regulatory Agency Inspections

**Quality Agreement Approach**

1. Generate a basic QA agreement template (version controlled)
2. Determine contractor and contractee expectations up-front
3. Modify your template per the specific agreed upon contractee/contractor approach (version controlled)
4. Amend the QA Agreement, as needed.
Alternate Approach with Consolidation:

Rather than Modifying Each QA Agreement Utilize “Not Applicable”

Successful Quality Agreement

1) Do you home work upfront related to capabilities
2) Contractor and Contractee must partner to ensure success
3) Compromise (when appropriate) related to QA Agreement content
WORKING TOGETHER TO ACHIEVE SUCCESS
Q & A Session

Academic and Industry Partnerships
–The Next Generation–

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