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Identifying and Mitigating Risks in Manufacturing and Supply Relationships for Drug Products

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Your Presenters

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Discovery Transactions	Distribution Arrangements	Joint Ventures	Manufacture and Supply Agreements
Options to Buy or License	Product Acquisition and Disposition	Profit-Sharing Arrangements	Territory-Specific Transactions

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Manufacturing and Supply

- Critical piece of development, launch and commercialization
- Highly operational; requires attention to logistical details
- Mistakes made early are sometimes difficult to remedy (e.g., right to process, long term commitments)
- Need to consider implication for future partners and acquirors

Types of Manufacturing Arrangements

- Types of services:
  - Process development, often combined with early-stage clinical supply
  - Late-stage clinical supply, sometimes combined with commercial supply
  - Exclusive supplier, primary supplier or backup supplier
- Stages of manufacture:
  - Raw materials, cell lines and intermediates
  - Bulk drug substance
  - Fill and finish
  - Packaging and labelling

Process Development Considerations

- Existing process transfer to CMO verses CMO improvement
- CMO's incorporation of CMO background technology and third party technology and portability of process as a result
- Control in specifications and process – SOP, protocol and master batch records
- Ownership of process; ownership of IP (e.g., what is product-specific verses generally applicable)
- Portability of process – tech transfer, assistance, license, confidentiality concerns
- Yield and quality; engineering batches; when to proceed to GMP batches
- Payment structure (often time and material-based and not milestone based)

Clinical Supply Considerations I

- Forecast and ordering
- Reservation and cancellation; CMOs obligation to cover (materials and capacity)
- Shortage of supply; allocation
- Regulatory matters – assistance; change in requirements
- External laboratory management
- Audit and inspection rights

Clinical Supply Considerations II

- Compliance and quality assurance; release and release documentation (COA, COC, completed batch records, stability data)
- Acceptance and rejection; latent defect (timing and definition)
- Non-conforming batches
  - Responsible party
  - Rework, replacement or refund
  - Raw materials and drug substance replacement
- Storage and shipping

Clinical Supply Considerations III

- Supply price determination
- Payment timing
- Limitation of liability; liability caps
- Representations and warranties
- Term of agreement; termination and survival

cGMP

- The current Good Manufacturing Practices as provided for (and as amended from time to time) in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Q7 (ICH Q7), and the EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use in Volume 4 of the European Commission's Rules governing medicinal products in the European Union, the United States Code of Federal Regulations 21 C.F.R. Parts 210 and 211, or analogous set of regulations, guidelines or standards as defined by other relevant Regulatory Authority having jurisdiction over the Development, Manufacture or sale of Licensed Product in a particular jurisdiction.

Commercial Supply – Additional Considerations

- When to negotiate; how to choose a commercial supplier
- Forecast and ordering; launch predictions
- Shelf-life considerations
- Yield and pricing
- Backup supplier arrangements
- Recall

Supply Chain Management

- Logistical nightmare
- Reservation, scheduling change, and cancellation issues
- Storage and delivery
- Release responsibility; non-conformity – who is at fault?
- Loss of manufacturing intermediates and drug substance due to downstream manufacturing issues

Risk Mitigation

- Terms and conditions in the manufacturing agreement and quality agreement
- Operational management: alliance management, communication channels, audit, inspection, and man-in-plant
- IP-related communications and discussions
- Insurance considerations
  - Identify insurable risks – property damages and assumed third party liabilities
  - Crafts CMO agreements with insurance policy coverage in mind
  - Consult the professionals (e.g., Woodruff Sawyer; Steve Sawyer; ssawyer@woodruffsawyer.com)

Thank you!

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