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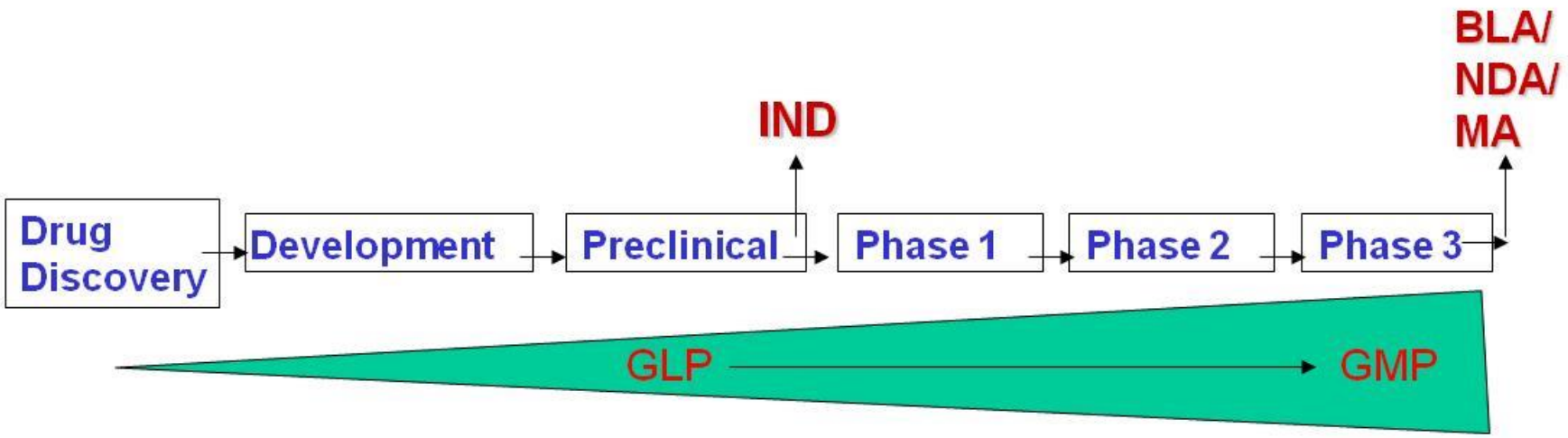
Challenges of cGMP implementation at different CMO's – The role of Quality Agreements

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This presentation will discuss the following points:

- GMP in the various development phases
- Selecting a CMO
- Key elements in the FDA and ICH draft guidance: Contract Manufacturing Arrangements for Drugs: Quality Agreement
- Examples

Product and Clinical Development



R & D	Proof of Concept	cGMPs initiated	Safety	Full cGMP
Genomics	Animal Toxicology	QA / QC	PK	QA / QC
Proteomics	Animal Metabolism	Safety, Dose	QA / QC	Efficacy
High-thru screening	studies	Production	Effectiveness	Safety
DNA Arrays	Production	Purification	Production	Production
	Purification	Formulation	Purification	Formulation
	Preparation for cGMP	Characterization, Stability	Formulation	Stability
			Stability	Release Tests
				Validation

Why Contract Manufacturing?

- Minimize the need for investing in manufacturing facilities
- CMOs can provide knowledge in development, scale up etc.

Selecting the right CMO

There are two types of CMOs:

- *Dedicated* – performs only contracted manufacturing
- *Not-Dedicated* – A Pharma / Biotec company that has its own product manufacturing and provides manufacturing services.

Dedicated CMO

PROs	CONs
Lower costs	Not enough employees
Fast	Financial awareness
Reliable (failures are not good for their reputation)	Regulatory understanding/outlook
Experience in various manufacturing situations	Schedule Issues

Non-Dedicated CMO

PROs	CONs
Experienced in Manufacturing	Manufacturing experience in one “platform” process
Expertise in Development and Scale up	Resources can conflict with internal projects
Existing Quality Systems	Systems not built to act as a CMO and requirements are not always phase-appropriate
Strong Regulatory history and expertise	Not very flexible

ICH Guidance

- Q7 Good Manufacturing Practice Guidance for APIs –

  recommends that manufacturers evaluate contractors for cGMP compliance by establishing a formal agreement that defines cGMP responsibilities, including quality measures and also by auditing the contractor's facilities.

- Q9 Quality Risk Management –

  recommends a comprehensive evaluation of suppliers and contract manufacturers through auditing and implementing supplier quality agreements.

ICH Guidance – Cont.

- Q10 Pharmaceutical Quality Systems –

  Pharmaceutical companies and contracted facilities should define the responsibilities and communication processes for quality-related activities of the involved parties, and document these in a written agreement between them.

FDA Guidance for Industry: Contract Manufacturing Arrangements for Drugs: Quality Agreements

(Draft Version)

This guidance present the need for defining, establishing and documenting the responsibilities of each party involved in the contract manufacturing of drugs subject to current GMP. And describes how the Quality Agreement can be utilized for these purposes.

What is a Quality Agreement?

"A Quality Agreement is a comprehensive written agreement that defines and establishes the obligations and responsibilities of the Quality units of each of the parties involved in the contract manufacturing of drugs subject to cGMP".

Elements of a Quality Agreement

From a cGMP perspective, the most critical elements of a Quality Agreement are the sections describing the parties' responsibilities and the discussion of change control.

The rest of this presentation will discuss some of these topics and present “real life” examples of the implications of inadequate Quality agreements.

1. Responsibilities

- Each quality Agreement should clearly document which party is responsible for cGMP activities relevant to the particular services of operations covered by the Quality Agreements.
- The assignment of particular responsibilities to either Owner of Contracted facility does not relieve any party from compliance with cGMP requirements that are not set forth in the agreement.

The following topics should be covered:

Quality Unit responsibilities

1) One of the most critical elements of the Quality Agreement
2) This section of the agreement should be clear with respect to product release – the owner is ultimately responsible for approving or rejecting drug products manufactured, processed, packed or held under contract by another company.

Final product release of finished goods for distribution must be carried out by the owner and cannot be delegated to a contracted facility under the cGMP regulations or any terms of the Quality agreement. According to the QP European regulations, the QP of a manufacturing facility has the ultimate responsibility for the release of the product.

Example

Clinical trials in Israel do not require QP release of the clinical batch prior to phase 3 trials.

Some European CMOs insist on following their internal procedures and “force” the companies to perform QP release of the batch.

Release of clinical to US sites from an European distribution center follows the QP release requirements although not applicable in the US.

Subcontracting

- CMOs may subcontract some of the manufacturing process, analytical testing, raw material supplies, etc. to third parties.
- Any sub-contracting should only be performed to approved supplier (by the CMO), in parallel – the client should request to approve any sub-contractor used for it's product manufacturing and analysis.
- Sub-contractors should be the responsibility of the CMO and in case of any deviations, the CMO will be accountable to the client

Materials Management

Who is responsible for setting specifications for raw materials? Auditing, qualifying and monitoring the suppliers of those materials? Who is responsible for conducting the required sampling and testing.

Additional issues:

- Inventory management
- Labeling, label printing & reconciliation
- Procedures for Quarantine and prevention of mix-ups and cross contamination.
- Storage under labeled conditions
- Storage conditions during material transfer

Example:

It is the responsibility of the CMO to retain sufficient raw materials samples and Product samples according to the regulatory guidelines

Product Specific Terms

This section should include specific terms related to the particular product involved, e.g. -

Product/component specifications, defined manufacturing operations, including batch numbering processes, responsibilities for expiration / retest dating, storage and shipment, lot disposition and responsibilities for process validation.

Example:

The client should be involved in Major and Critical deviations and approve the investigation report and suggested CAPAs. The CMO may prefer to submit the investigation to the client only after closure for documentation purposes.

Laboratory Controls

- This section should address the adequate laboratory facilities that the Owner and the CMO Quality units should have available to them for testing and approval (or rejection) of drug products and include procedures defining controls over sampling and testing samples.
- Qualification/Validation of methods
- Laboratory equipment – qualified , calibrated and maintained.
- Stability and reserve samples
- Communication of the results
- Investigating deviations, discrepancies, failures and Out-of-specification results

Documentation

- Owner and CMO are required to maintain documentation and records required under the cGMP regulation.
- The quality agreement should indicate procedures for the Owner to review and approve documents and any changes to SOPs, manufacturing records, specifications, laboratory records, validation documentation etc.
- Specify how records and documentation required by the applicable cGMP regulations will be made available for immediate retrieval, and how copies will be made and maintained under certification or controlled copy procedure.
- Electronic records should be stored so they will maintain their traceability, reliability and integrity throughout the required period.

2. Change Control

- Changes may be initiated by either party and should be discussed and addressed in the Quality Agreement.
- The Contracted Facility should notify the Owner of changes (e.g. in raw materials, suppliers, location, additional products manufactured, testing procedures, major manufacturing equipment etc.)
- The parties should agree and document in the Quality Agreement the types of changes which requires Owner review and approval prior to implementation and those changes that can be implemented with notification only.
- The parties should agree on procedures for conducting validation activities required to implement any changes.
- The parties should agree on the time frame for those approvals.

Regulatory submissions

- CMOs should be responsible to prepare the CMC section for regulatory submissions and support the owner in any requests from the different regulatory authorities.
- CMOs may request the owner to approve any written communication between the owner and the regulatory authorities. The CMO may approve the relevant sections for Product manufacturing and testing written by the owner, but it is in the rights of the owner to later submit it and use it as required without receiving an additional approval from the CMO.

Sentences taken from QAA

- During the development phase of the API and the IMP and up to the completion of the full validation of the Manufacturing Process of the API and the IMP, some items required by GMP may not be fully implemented or applied in the manufacturing, release and supply of the API the IMP – Client visit during manufacturing revealed that a series of manufacturing activities are being conducted with no documentation al all. Labelling of process samples was not appropriate, etc.
- CMO shall maintain the records to the Manufacturing Process and method information in local language in its own format in manufacturing batch records" – the client requested translation for approval and the CMO objected and it was later learned that the CMO doesn't create detailed appropriate batch records prior to the manufacturing of Phase 1 material.
- CMO shall maintain a local change control system that ensures compliance with GMP, regulatory submissions and with all provisions of this Quality Assurance Plan for IMP. All changes will be evaluated by competent management personnel regarding the technical implications" – in most of the cases QAA by CMOs does not mention the need for client approval.

Sentences taken from QAA

- Client will be notified on any Major unplanned Deviation within 2 working days . In case of Major unplanned Deviations Client will be involved in the investigation process and together with CMO quality assurance and regulatory affairs will evaluate the acceptability regarding GMP and the impact on conformity with regulatory submissions. This is not practicable for minor deviations during development where deviations may be needed at a daily basis. Our system only distinguishes between minor and major deviations where major includes critical.
- While the QAA states: “Deviation” means, after final assessment of CMO, any deviation occurred during the Manufacture of the Product which (i) has not affected (“Minor Deviation”); (ii) may impact (“Major Deviation”); or (iii) impacts (“Critical Deviation”) the quality of the Product. The definition of minor deviation in the MSA (Master Service Agreement is:
  - CMO shall, as the case may be, perform the Services in accordance with the Proposal, the Work Order and the Quality Agreement and to Manufacture the Product in accordance with the Standard (except for those Minor Deviations of which client shall be notified in writing as set forth in the Quality Agreement),
- Defective Product is only a product that due to CMO’s gross negligence has not been manufactured in accordance with the Standards.

Summary

Both parties should work together to ensure Quality, Safety and effectiveness of the Drug Products.

During the negotiation on the QAA, both sides (Client and CMO) should ensure that the interpretation of the agreement is clear and its implementation is feasible.