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Considerations for External Partnership: Chemistry, Manufacturing, and Controls

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Objectives and Disclaimers

- This presentation aims to address the use of contract organizations in the development of drugs and biologics
  - Contract Research Organizations (CRO)
  - Contract Manufacturing Organizations (CMO)
  - Contract Development and Manufacturing Organizations (CDMO)
- Not a ‘one size fits all’ approach to outsourcing elements of drug development
- Cost estimates vary greatly from organization to organization and are highly dependent on the complexity of the activity and type of drug or biologic

Background

- A large amount of work has been done to estimate the investment needed to bring a new therapeutic to the US market
- The nonpartisan Congressional Budget Office (CBO) report showed:
  - the estimated cost of developing a therapeutic and taking it to market approval ranges from less than $1B (biologics) to over $2B (some drugs)
  - Small drug companies (<$500M in revenue) account for >70% of the 3000 drugs in Phase 3 trials
  - About one-third of the new drugs approved have been developed by pharmaceutical firms with annual revenues of <$100 million since 2009.
  - Large drug companies (>$1B in revenue) still account for >50% of the drug approvals since 2009
  - The likelihood of approvals (LOAs) from phase I clinical trials remains at ~10%.

Purpose of CMC

- The drug/biologic must be manufactured.
- To assure that the drug/biologic sold to the public will have quality attributes similar to those of a drug/biologic demonstrated to be safe and effective.
- To assure that the quality of the drug /biologic meets appropriate standards and is consistent.
- To assure that the drug/biologic you are using is the drug described on the label.

Chemistry, Manufacturing and Controls Legal Basis 21 CFR 312.23(a)(7)

- **Chemistry Manufacturing and Controls (CMC**) concerns the composition, manufacture, and control of the drug substance and the drug product

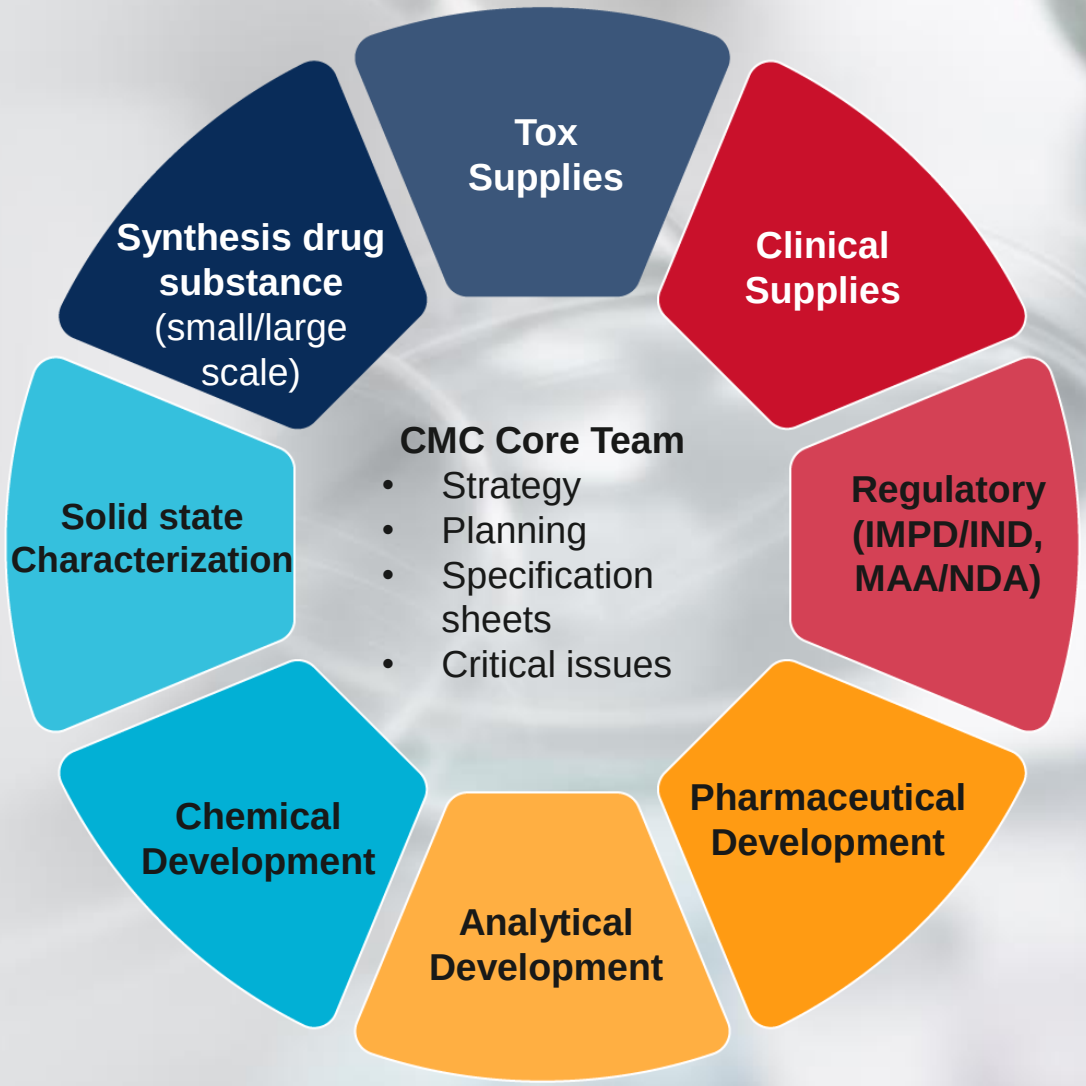
- **Drug substance** is an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3)

- **Drug product** means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo. (21 CFR 210.3(b)(4))

Plan for Success with the Right Expertise on the CMC Team

For an effective and efficient development program, the CMC team should consist of an interdisciplinary team with expertise focused on specialized disciplines.

To fulfil this need, start-up pharmaceutical companies often use CMC consultants and/or a small number of employees with expertise covering several disciplines.



Critical Elements of CMC

How and where is the drug/biologic made?

How are raw materials tested and monitored?

What control procedures are in place to assure product consistency and quality?

Are (critical) quality attributes adequately identified and characterized for the product?

Are the test methods used to monitor product quality appropriate?

What controls/How long does the product maintain its quality after it is made (shelf life/expiry)?

Key Considerations: Control of Raw Materials

- **Develop manufacturing processes with pharmaceutical grade materials (e.g., USP, NF, JP, EP aka Ph.Eur.)**

- **cGMP/pharmaceutical grade raw materials are tested and comply to more stringent quality requirements than research grade.**
  - Define grade and purity of raw materials via specifications with the vendor
  - Avoid materials of animal origin and obtain BSE/TSE certification
  - Perform use tests

- **Identify and qualify multiple suppliers of key raw materials**

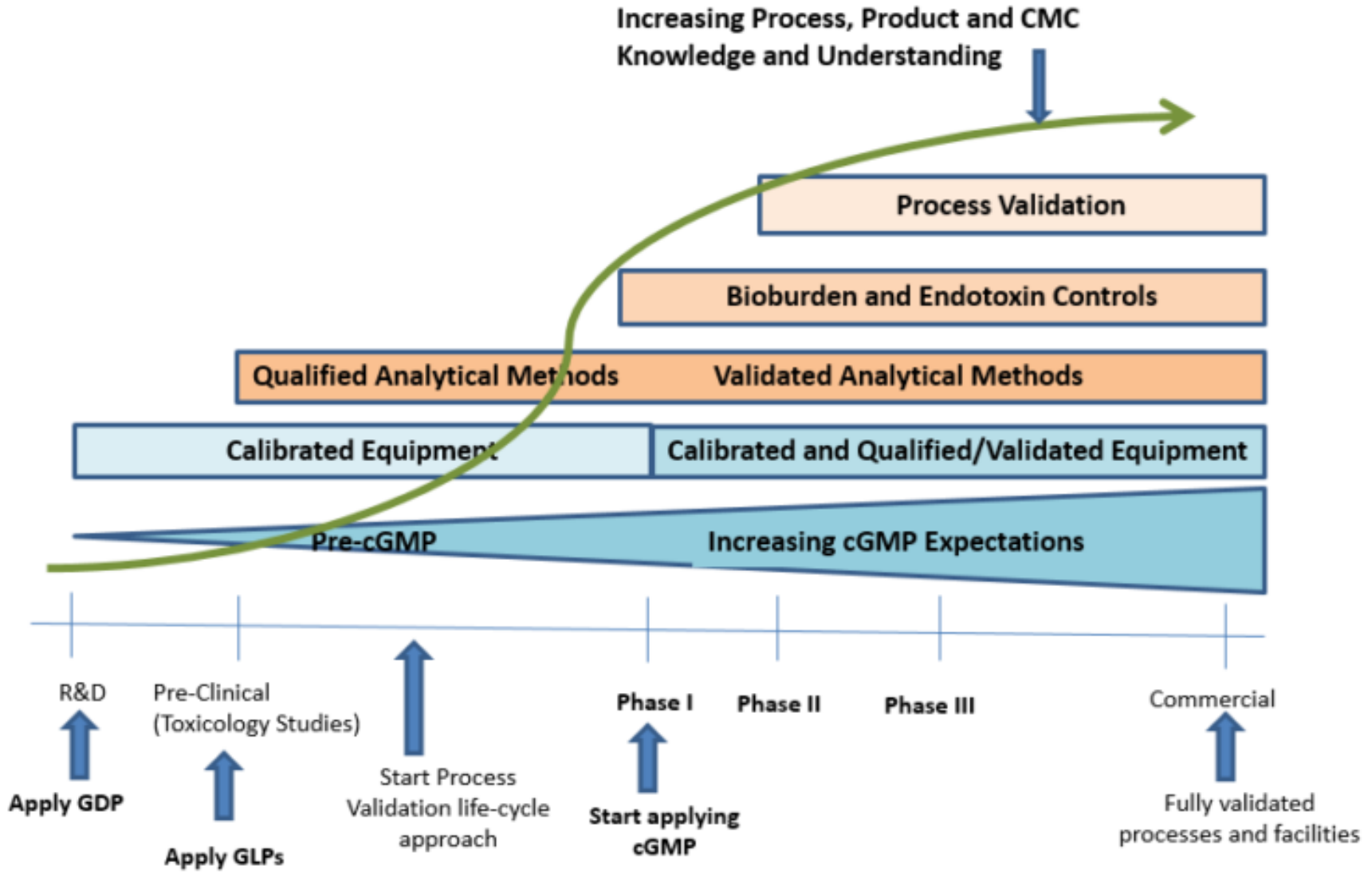
Key Considerations: Analytical Testing (QC)

- Define Critical Quality Attributes (CQA) of the drug substance and drug product
- CQAs are characteristics that should be maintained within a limit or tight range to ensure desired product quality
- Analytical methods must be able to identify and confirm strength and purity of the drug substance and drug product manufactured
- Analytical testing can involve in-process and release testing of the drug substance and drug product after manufacturing

Additional CMC Testing Is Specific to the Product

- **Sterile injectable product** – sterility and endotoxin concentration
- **Controlled release product** – release profile of active ingredient over time
- **Oral tablet** – dissolution profile
- **Soluble powder for drinking water** – moisture content as powder, solubility in water
- **Inhaled product** – particle size
- **Cell and gene therapy product** - sterility
- **Transdermal product** – release profile

Phase Appropriate cGMPs for CMC (Generic)



Key Considerations: Manufacturing

Define manufacturing processes that are readily scalable:

- Consider changes in equipment processing parameters between laboratory, pilot and commercial manufacturing scale
- Define critical process parameters (CPPs) and determine proven acceptable ranges (PARs)

Process Validation:

- The FDA defines process validation as, *"…the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product"*.

Key Considerations: Quality Assurance (QA)

- **Releases drug substance (DS) and drug product (DP) batches manufactured for non-clinical and clinical use, final CoA**

- **Numerous other activities and oversight**

CMC Contract Organizations

Typical CMO Services

- Manufactures stable intermediates, drug substance
- Produces drug product based on batch formula.
- Contract fill/finish - Provides mixing, final pH adjustment, filtration, vial/bottle filling.
- Contract packaging/labeling – Provides final label for vial, carton/container, bottle, blister pack, etc.
- Conducts lot release testing on stable intermediates, DS, DP, final bulks, and/or overall final product.
- Conducts stability and sterility testing.

Typical CDMO Services

- Tends to be more flexible than a routine manufacturing operation and allows a designer to fabricate one component of their product or take a concept and turn it into a reality.
- Justified as more economical and efficient to outsource than invest in competence, equipment, and resources.
- A CDMO handles the outsourced manufacturing of drugs and biologics as well as all of the innovation and development work that occurs prior to GMP manufacturing.

CMO Vendor Selection Criteria

- Technical
- Regulatory
- Innovation

- Clear project scope
- Updates on progress
- Recommendations
- Reports on development and manufacture work

- Proficiency at implementation
- Do what they say, when they say they'll do it

- Modify plans in line with project requirements

How to Choose a Contract Organization

Expertise & Experience

- Specific area you are looking for support in, whether it's conducting clinical trials or running laboratory tests.
- Assess organization's track record or the types of clients they have worked with in the past to assess their level of expertise.

Quality & Compliance

- Demonstrate a strong commitment to quality and compliance by providing evidence of their compliance with relevant regulations and standards.
- Review a CRO's quality management system, SOPs, and any certifications they have to determine their levels of quality and compliance.

Cost & Value for Money

- Should be competitive and provide real value for money.
- Ask for cost estimates for the services you are interested in and compare them to other CROs.

How to Choose a Contract Organization (continued)

- **Communication & Collaboration**
  - Must communicate effectively and collaborate with your team throughout the project.
  - Ask for references from other clients and to speak with the CRO's team directly to assess their communication and collaboration skills.
- **Timeliness & Flexibility**
  - Deliver the services you need in a timely manner and should be flexible enough to adapt to any changing needs or requirements.
  - Ask about the CRO's availability and their approach to managing project timelines to get a better idea of whether or not they can meet deadlines and remain flexible in the face of changes.
- **Facility Locations**
  - Location where the work will be done is an important consideration when selecting a partner.
    - If the drug you are developing together is expected to enter multi-national trials, it will be beneficial, perhaps even necessary, to hire a CRO that has experience with the quality required for each nation.
    - Facilities and staff positioned in the target location will ensure knowledge about local regulations for clinical studies and approval.
    - The starting reagents will also need to be qualified or USP, EP, JP quality. Import/export issues and reagent availability will matter.
  - Comparing global CROs and local CROs and assessing how much supervision will be needed can help you understand whether location will be important in your selection.

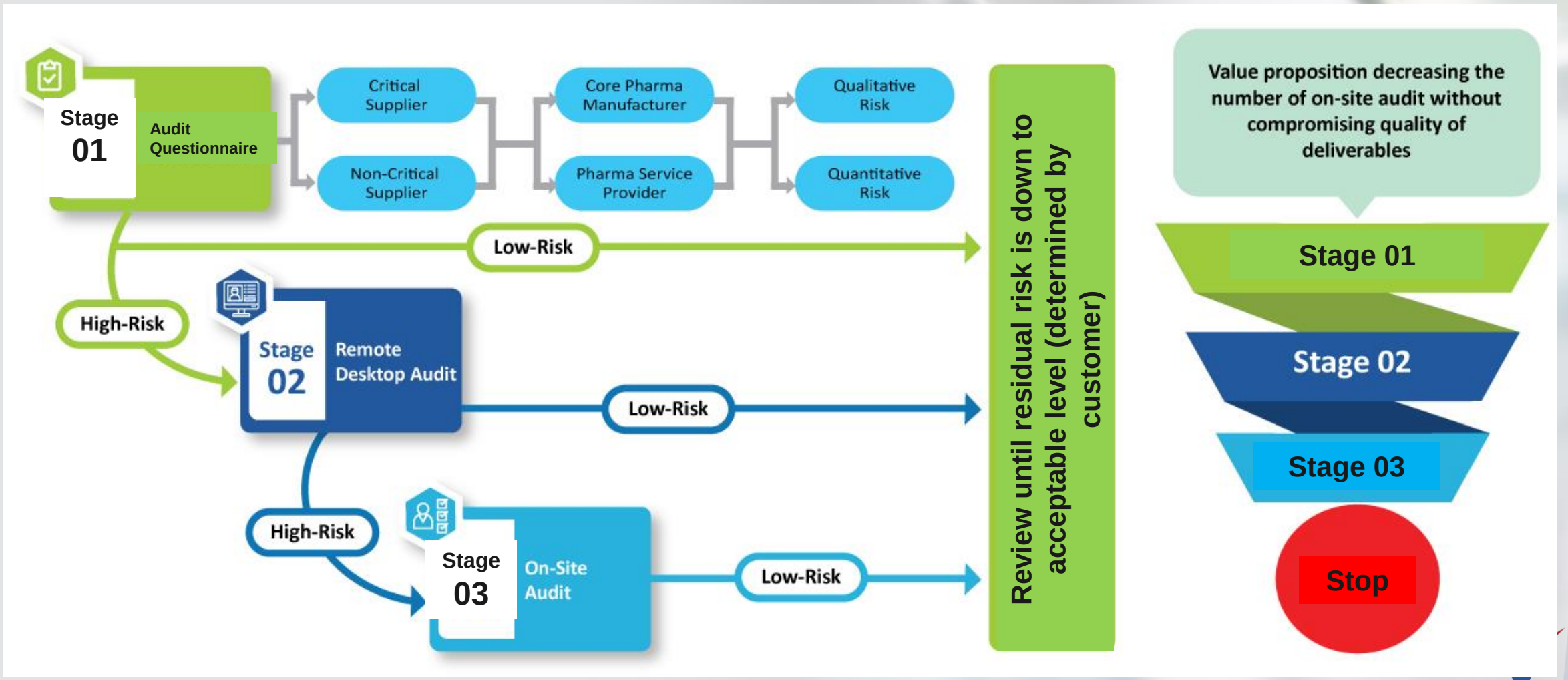
cGMP Requirements for Vendor Qualification

- Selected vendors are evaluated for compliance against regulations.
- Results of audit reviewed and need for a site follow-up visit.
- Site qualifications are done on a cyclical basis (every 24 months).
- Stringency of process increases as development program advances.

- **Benefits**

- Ability to evaluate systems vendor uses to produce a regulated product.
- Identify gaps in quality systems and ask for corrective action.

CMO Audit Process



Types of Contract Manufacturing Agreements

- **Private Label Agreements**
  - Long-term contracts for producing part or all of a product.
    - CMO creates products that the business sells as their own with their brand name
    - Private label manufacturing
    - End-to-end manufacturing
    - Select component creation.
- **Agreements for Services and Materials**
  - Involves deals for labor and access to equipment.
  - CMO's team and facilities used but you run the manufacturing operations.
  - Not all CMOs use the same equipment and materials.
  - Agreements may be needed for more than one CMO to acquire best quality for different things from each party.
- **International Agreements**
  - Like the above options but third-party supplier is overseas.
  - Unique issues for packaging and shipping into the United States.
  - May prove less expensive, depending on your specific requirements.

Benefits of Contract Manufacturing Organization

- Cost savings
- Time savings
- Access to advanced technical skills
- GMP qualified facilities
- Regulatory inspection track record
- Internal product knowledge
- **Ensure that the signed master services agreement covers all of your intellectual property, quality, timeframe, and other needs.**

Benefits of Contract Manufacturing Organization (continued)

- Higher quality product
- Expertise
- Increase scalability
- Improve supply chain management
- Established infrastructure
- Reduced labor
- Better allocation of talent
- Dedicated project management
- End-to-end options
- Partnership

Top 10 Contract Manufacturing Mistakes

- Poor Handling of Unanticipated Project Delays and Manufacturing Capacity Constraints
- No Rights to Audit in Contract
- Losing Flexibility and Responsiveness
- Not Basing Some % of Payment on Quality of Material or Right to Refuse Based on Specifications not Being Met or Regulatory Inspection Results (Form 483)
- Scale-up Issues

Top 10 Contract Manufacturing Mistakes (continued)

- Giving Away Too Much Product Control During Contract Negotiation
- Forgetting the Benefits of a Good Contract Manufacturing-Client Relationship
- Being Lenient on Setting the Raw Material Quality Standards
- Risking Intellectual Property Loss
- Not Anticipating Overseas Cultural Differences, Challenges, and Meeting Scheduling

Helpful Links

- cGMPs for Phase 1 Investigational Drugs https://www.fda.gov/media/70975/download
- Content and Format of INDs for Phase 1 https://www.fda.gov/media/72057/download
- ICH Q6B Specifications https://www.fda.gov/media/71510/download
- ICH M4Q(R1) https://www.gmp-compliance.org/files/guidemgr/MEDIA556.pdf

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Q&A