Manufacturing and quality risk management during the vaccine development and manufacturing process

Clinical Vaccine Development and Biomanufacturing

Oxford University

Presentation by

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Presentation Outline

- Purpose of the presentation
- Brief discussion of the pharmaceutical development process
- Some background and context
- Project risk management
- CMC Development models
  - Pharmaceutical industry
  - Stage Gate Model
  - Technical Readiness Level
  - Regulatory Document Model
- Combined Knowledge and Experience
- CMC Readiness Assessment Tool
- Summary
- Parting Thoughts

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Purpose

To provide the attendee with a systematic approach to evaluate and monitor progress, risks and opportunities in Chemistry, Manufacturing and Controls (CMC) during the vaccine development and manufacturing process

Chemistry and Manufacturing Control (CMC) is the FDA term used globally to describe the data for the manufacture and testing of a medicinal product. In Europe, the ICH term, Module 3 Quality, is more commonly used. The two terms are interchangeable.

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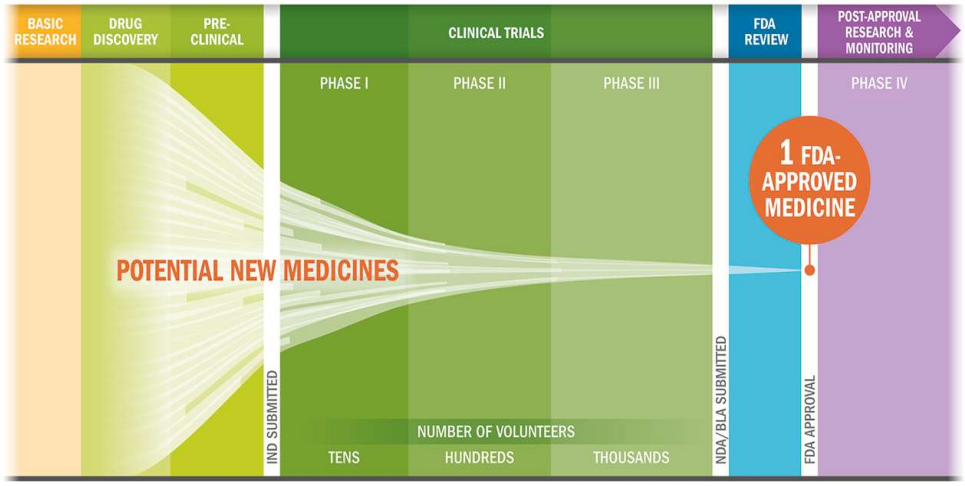
The Pharmaceutical Development Process



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

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Some background and context

- From the CMC point of view.
- Does not necessarily define the Project Critical Path.
- Allows (and encourages) input and modification by the user.

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Project Risk Management

Project Risk can be defined as 'an uncertain event or condition that, if it occurs, has a positive or negative effect on a project's objectives'.

- Project "risk" includes whether necessary tasks are completed.
- The FMEA model
  - Risk Frequency
  - Risk Consequence
  - Risk Detectability
- How do you "detect" Project Risk?
  - Development models
  - Regulatory documents

The objective of this presentation is to suggest a model to identify CMC risks to a pharmaceutical development project before they end up on "the Critical Path".

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The use of the Risk Priority Number for Project Management

Severity	5	Prevent the completion of the Objective
	3	Delay the completion of the Objective 1 to 2 months
	1	No effect on completion of the Objective
Occurrence	5	High probability of failure or difficulty
(Difficulty)	3	Medium difficulty
	1	Low/no difficulty, participant experienced in this area
Detection	5	Defect not detected until objective at completion
	3	Defect detection would delay the completion of the Objective
	1	Defect readily detected, such as completion of a document

The Risk Priority Number (RPN) is the product of the Severity, Occurrence and Detection values. The higher the number, the greater the risk is to successful attainment of the Objective. Generally, the most successful management of that risk is the application of more resources to the areas with the highest RPN

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CMC Development Models

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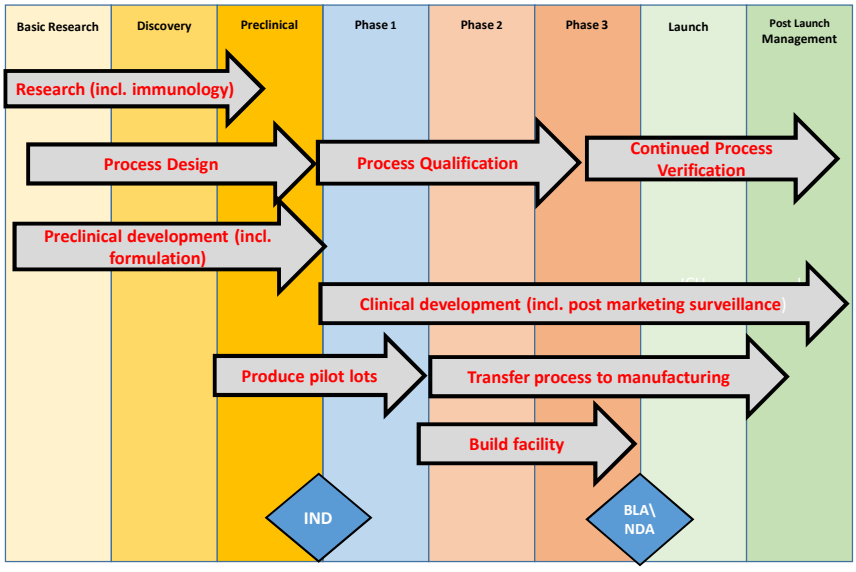
Development Model #1: Pharmaceutical Industry



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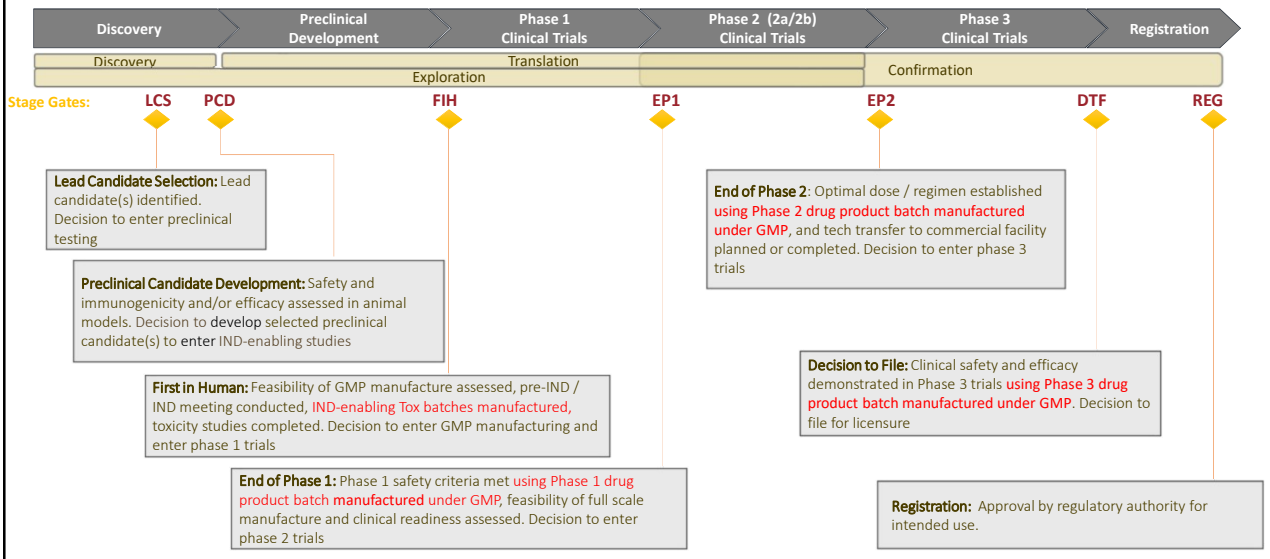
Development Model #2: The Stage Gate



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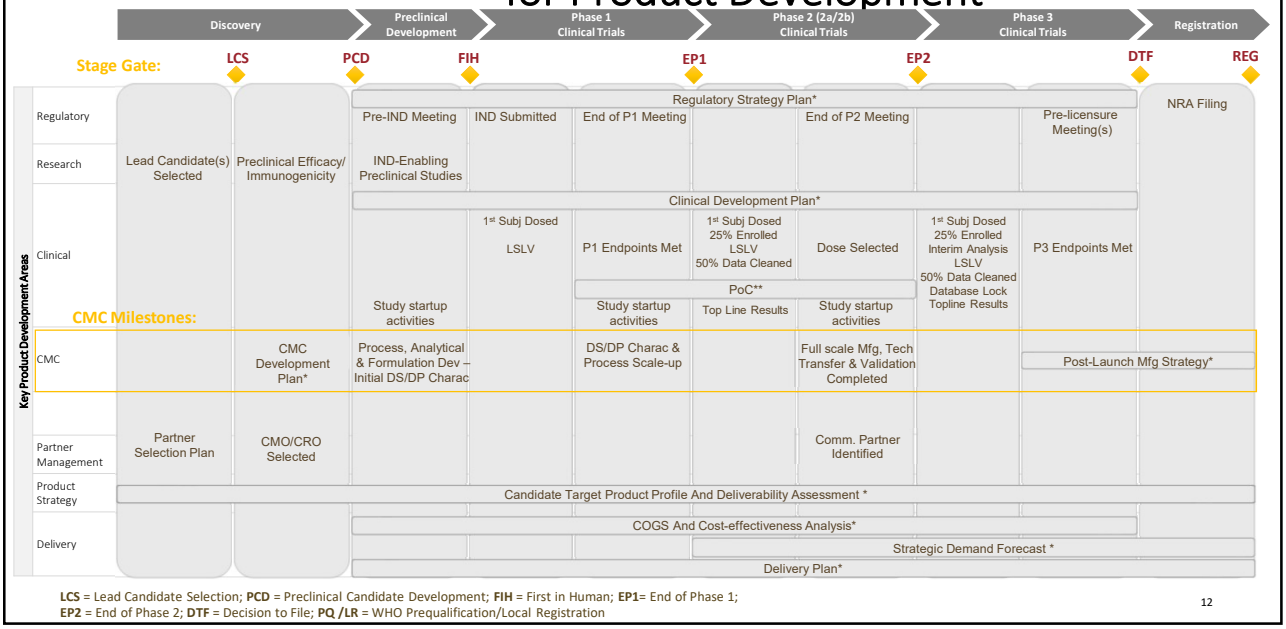
Model #2: PD Workflow Stage Gates (◆) & Milestones for Product Development



LCS = Lead Candidate Selection; **PCD** = Preclinical Candidate Development; **FIH** = First in Human; **EP1**= End of Phase 1;
EP2 = End of Phase 2; **DTF** = Decision to File; **PQ /LR** = WHO Prequalification/Local Registration

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Development Model #3: Technical Readiness Level

US Department of Defense *Technical Readiness Levels* Adapted for Pharmaceutical Development

- TRL-1: Review of Scientific Knowledge Base.
- TRL-2: Development of Hypotheses and Experimental Designs
- TRL-3: Target/Candidate Identification and Characterization of Preliminary Candidate(s)
- TRL 4: Candidate Optimization and Non-GLP In Vivo Demonstration of Activity and Efficacy
- TRL-5: Advanced Characterization of Candidate and Initiation of GMP Process Development
- TRL-6: GMP Pilot Lot Production, IND Submission, and Phase 1 Clinical Trial(s)
- TRL-7: Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)
- TRL-8: Completion of GMP Validation and Consistency Lot Manufacturing, Pivotal Animal Efficacy Studies or Clinical Trials, and FDA Approval or Licensure
- TRL-9: Post-Licensure and Post-Approval Activities

A detailed description of the TRL requirements is included in the slide "Notes" pages.

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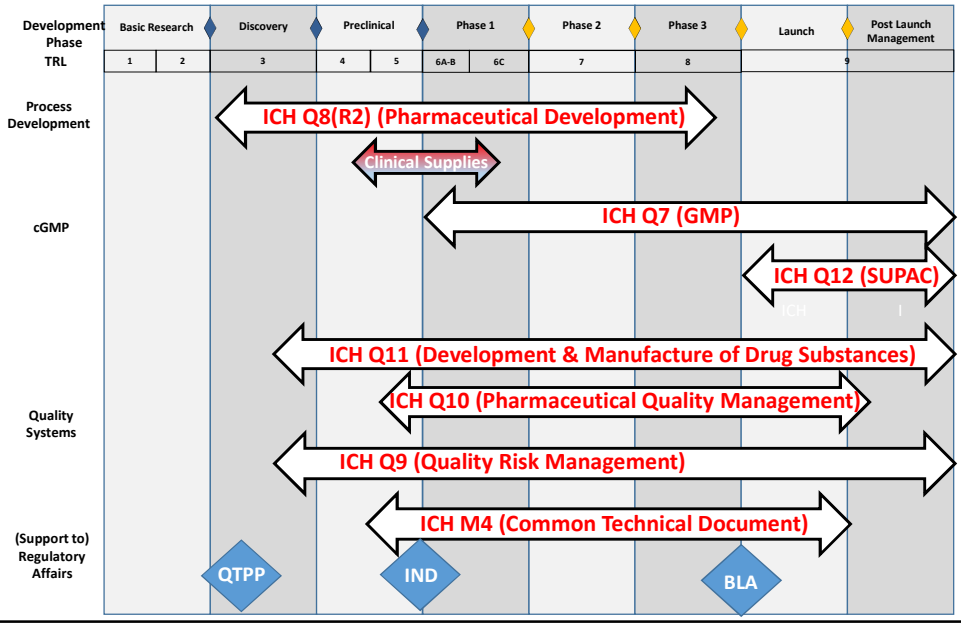
Development Model #4. Regulatory Documents



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How can we benefit from the combined knowledge and experience?

CMC-RAT	FDA Drug Development Model	Stage Gate Model	Pharmaceutical Industry Model (PHRMA)	DOD Pharmaceutical Development Model	TRL
Basic Research/ Discovery	Discovery and Development	Discovery	Basic Research	Basic Research	1
			Drug Discovery		2
	Preclinical Candidate Development			Discovery	3
Candidate Prioritization/ Preclinical Development		Preclinical Development	Preclinical	Preclinical Candidate Development	4
					5
First in Human/ Candidate Selection	Clinical Research	Phase 1	Phase 1	Phase 1	6
		Phase 2	Phase 2	Phase 2	7
Commit to Phase 3		Phase 3	Phase 3	Phase 3	8
BLA Approval/ Post Launch Management	FDA Review	BLA Approval	FDA Approval	Launch	9
	FDA Post-Market Safety Monitoring	Local Registration	Post-Approval Research & Monitoring	Post Launch Management	

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CMC Readiness Assessment Tool (CMC-RAT)

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CMC categories for evaluation

- Process development
- cGMP
- Analytical Methods
- Manufacturing
- Quality Systems
- Regulatory Affairs

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How to use the model

CMC Stages

1. Basic Research/ Discovery
2. Candidate Prioritization/ Preclinical Development
3. First in Human/ Candidate Selection
4. Commit to Phase 3
5. BLA Approval/ Post Launch Management

Slide presentation

First slide - Overall stage goal and expected outcomes

Second slide – Tasks recommended for stage completion

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1. BASIC RESEARCH / DISCOVERY

CMC Objective	Principal Outcomes
The CMC responsibility during this Stage is to develop the plans to achieve the CMC milestones for preclinical development (i.e., complete process, analytical, formulation development & initial DS/DP characterization). CMC will contribute to the development of the quality target product profile (QTPP) and Critical Quality Attributes (CQA) for the proposed product.	• Decision to move to IND-enabling studies • Critical Quality Attributes established • Preliminary DS/DP production process identified • Research-grade DS produced as comparator for future studies

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1. BASIC RESEARCH / DISCOVERY

	TASK DESCRIPTION
Process development	Develop CMC Plans for Selection of substrates required for product manufacture (cell line, virus seeds)
	Develop CMC Plans for GLP / GMP manufacturing (cell bank, virus seed, drug substance, drug product, and release) for IND-enabling preclinical studies
	Develop CMC Plans for Development of a compliant manufacturing process at suitable scale for preclinical materials (GLP) and phase 1/2a materials (GMP), including cell line development, upstream process and purification process
	Provide research-grade DS produced as comparator for future studies
cGMP	Develop CMC Plans for High level risk assessment for key CMC areas (e.g., technical development, GMP, Quality, etc.) incorporating severity of impact / probability
Analytical Methods	Develop CMC Plans for Development and qualification of analytical release and stability-determining assays to test purity, identity, concentration, stability, potency, and process- / product-related residuals of the vaccine, including acceptance criteria
Manufacturing	Develop CMC Plans for Assessment of the feasibility of full-scale vaccine manufacturing (e.g., scalability, process / product consistency)
	Develop CMC Plans for Identification and qualification of critical raw material suppliers
	Develop CMC Plans for Identification and audit of GMP compliant production site for clinical material
Quality Systems	ICH Q8(R2)
Regulatory Affairs	Assist in development of a preliminary target product profile (TPP), quality target product profile (QTPP) and DS and DP critical quality attributes (CQA) to guide future development.
	Clarify content of CTD CMC section and level of detail; provide consistent approach to key issues.

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2. CANDIDATE PRIORITIZATION AND PRECLINICAL DEVELOPMENT

CMC Objective	Principal Outcomes
Process, Analytical, Formulation Development & Initial DS/DP Characterization Completed - Assure manufacturability and quality of vaccine candidate drug substance and drug product manufacturing, assessed using qualified analytical assays, analytical standards, and the appropriate in-process, release, and stability specifications; release drug product for IND-enabling studies	• Decision to move the product to Phase 1 Clinical trials • Critical Process parameters identified • Preliminary stability and formulation studies completed • Test Articles and Controls produced and characterized • Technology Transfer Protocol to contract manufacturing facility approved • Pre IND meeting

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2. CANDIDATE PRIORITIZATION AND PRECLINICAL DEVELOPMENT

	TASK DESCRIPTION
Process development	Substrates for product manufacture (cell line, virus seeds) obtained
	GMP compliant manufacturing process fixed at required scale for delivery of preclinical materials (GLP) and phase 1/2a materials (GMP), including cell line development, upstream process, and purification process
	Developed drug substance and drug product formulations (including establishing the maximum quantities of adjuvants / excipients for clinical studies)
	Identify immune responses in GLP animal studies as necessary for regulatory filing
	Assessment of the feasibility of full-scale vaccine manufacturing (e.g., scalability, process / product consistency)
cGMP	GLP / GMP manufacturing for preclinical studies completed (drug substance, drug product, cell or virus substrates if required)
Analytical Methods	Qualified analytical release and stability-determining assays to test purity, identity, stability, concentration, potency, and process- / product-related residuals of the vaccine, including acceptance criteria, available
	Stability studies on early lots initiated (real-time and accelerated)
	Samples are retained for future analytical comparability studies
Manufacturing	Critical raw material suppliers selected and validated
	GMP compliant manufacturing site identified and audited
Quality Systems	ICH Q7 (for clinical supplies), ICH Q8(R2), ICH Q9, ICH Q10 (for GMP clinical products)
Regulatory Affairs	Update TPP and determine regulatory strategy
	Prepare and submit Pre-IND package to FDA to support development and advice on GLP studies in animal models

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3. FIRST IN HUMAN / CANDIDATE SELECTION

CMC Objective	Principal Outcomes
DS/DP Characterization Completed and Process Scale-Up Initiated – CMC work is focused on initiating development and scale-up of the manufacturing process at a qualified CMO / manufacturing partner to produce drug substance and drug product for late Ph2 / Ph 3 clinical trials, consistency lots, and post-licensure supply, assessed using qualified analytical assays, analytical standards, and the appropriate / updated in-process, release, and stability specifications; release drug product for Phase 1 clinical trials	• Phase 1 Clinical Supplies manufactured and released • IND submitted • Critical Process Parameters verified • DS and DP standards prepared for future QC use • Decision to move to Phase 2 clinical trials

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3. FIRST IN HUMAN / CANDIDATE SELECTION

	TASK DESCRIPTION
Process Development	Critical Process Parameters verified
	Development of Phase 2 / Phase 3 manufacturing process and associated analytical product characterization.
	Plan, including identification and mitigation of potential risks, to develop a full scale, post-licensure vaccine manufacturing (e.g., scalability, process / product consistency)
cGMP	GMP manufacturing for Phase 1 completed (drug substance, drug product, cell or virus substrates if required)
	Plan for the retention of sufficient DS and DP samples for future stability testing and QC use
Analytical Methods	Validate/qualify critical assays to assess product quality, in vivo, in vitro animal efficacy.
	Prepare assay method transfer protocols, if applicable
Manufacturing	Qualification and audits of CMOs / manufacturing partners to ensure manufacturing of clinical trial materials that meet specifications and quality standards and that are capable of delivering post-licensure material
Quality Systems	Compliance with ICH Q7 and Q10 expected. Full Quality agreements in place for relevant CMOs and/or suppliers
Regulatory Affairs	Provide CMC input to scientific advice/questions from regulatory authority
	Prepare and submit full CMC input to IND package to FDA to support initial clinical trials

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4. COMMIT TO PHASE 3

CMC Objective	Principal Outcomes
Full Scale Manufacturing, Tech Transfer and Validation Completed – Technology transfer to the cGMP-compliant commercial manufacturing partner is completed, including process validation with drug product batches assessed using validated analytical assays, reference standards, and finalized in-process, release, and stability specifications; release drug product for Phase 2 clinical trials	• Phase 2 clinical supplies manufactured and qualified • Decision to move to Phase 3 clinical trials • Critical Process Parameters validated.

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4. COMMIT TO PHASE 3

	TASK DESCRIPTION
Process Development	Validation of processes for manufacturing and scale-up of phase 3 materials, including fermentation / cell culture, purification, formulation, packaging and tech transfer
	Final critical quality attributes and critical process parameters validated
	Approval of process and analytical validation plan
	Tech Transfer from CMO to commercial manufacturer protocol approved
cGMP	GMP manufacturing for Phase 2 completed (drug substance, drug product, cell or virus substrates if required)
	Stability studies for DS and DP are completed
Analytical Methods	Validation of analytical release and stability-determining assays to test purity, identity, concentration, stability, potency, and process- / product-related residuals of the vaccine, including acceptance criteria
	Assays used to assess critical outcomes in clinical trials and in animal efficacy studies are validated
Manufacturing	Critical raw material supply chain secured through validation of multiple vendors
	Qualification of commercial manufacturing partner including compliance to cGMP
Quality Systems	Full compliance with ICH Q7 and Q10 expected. Full Quality agreements in place for relevant CMOs and/or suppliers
Regulatory Affairs	CMC input to prepare BLA/NDA

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5. BLA APPROVAL / POST LAUNCH MANAGEMENT

CMC Objective	Principal Outcomes
Full-Scale Post-Launch Manufacturing Strategy in Place - Development of a strategy to assess operational readiness for full-scale manufacturing post-launch, including ability to deliver projected volumes of drug substance / drug product, release assays, supply chain, and regulatory authority release.	• Phase 3 clinical supplies manufactured • Manufacturing process transferred to commercial manufacturer • Manufacturing process validated at commercial manufacturer • BLA/NDA submitted

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5. BLA APPROVAL / POST LAUNCH MANAGEMENT

	TASK DESCRIPTION
Process Development	Supports *continued process verification* requirements per ICH Q8
	Supports post-approval and scale up manufacturing changes per ICH Q12
cGMP	GMP manufacturing for Phase 3 completed to include validation consistency and bridging lots as required
	Commercial launch strategy developed / updated
Manufacturing	Complete technology (process and analytical method) transfer to commercial manufacturer
	Ongoing CMC support to ensure uninterrupted supply of high-quality DP in all markets developed / updated
	Supply chain or distribution contracts in place
Quality Systems	Quality assurance / control activities developed / updated (including Pre-Approval Readiness)
Regulatory Affairs	Provide CMC input to scientific advice/questions from regulatory authority
	Provide CMC input to submission of BLA/NDA
	Provide CMC input to questions from Phase 4 / post market surveillance commitments

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Summary

- Plan for future success.
- Understand the interactions and complexities of development.
- Bring problems/issues to the team (or management) ASAP
  - *For every problem, present a suggested solution*
- Organize your data for regulatory submissions.
- DON'T BE ON THE CRITICAL PATH!

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Whoops! I almost forgot..

<u>Where problems can begin</u>

- **Standards** [You will run out]
- **Stability** [Don't find out too late]
- **Analytical** [Do you have an acceptable potency assay to go all the way through licensure?]
- **Supply Chain** [Have you identified a reliable CMO, commercial partner?]
- **Facility** [Are there unique requirements?]

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Thank You!

Questions?

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