A CMC Development Roadmap For an Injectable Protein Biologic - What to Do When

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Pre-IND	Phase 1	Early Phase 2	Late Phase 2	Phase 3
Transfect CHO cells and select final clone. Create and qualify the master cell bank. Develop the drug substance manufacturing process. Develop analytical assays for product release and stability testing. Perform product formulation studies and choose the formulation. Qualify assays. Validate sterility, endotoxin, and other critical assays. Ensure assays are stability-indicating. Make pilot/engineering batch. Perform viral clearance studies. Create and characterize a reference standard. Establish the drug product manufacturing process. Set initial product specifications. Initiate drug substance, drug product, and reference standard stability studies. Perform product infusion stability and compatibility studies. Produce clinical material if the pilot/engineering batch was not GMP. Have a pre-IND meeting with the FDA. Write and submit the IND.	Justify and document all changes to the manufacturing process and analytical assays. Think about potential future changes in raw materials and manufacturing processes that could impact product quality. Gather and trend analytical data from batch release and stability studies.	If not already done, create a working cell bank and use it before phase 3. Refine the product specifications. Analyze stability data to get an indication of degradation pathways and eventual product expiry. If not already in place, start to use the bioassay.	Get all commercial manufacturing sites at final commercial scale online. Create and test an end-of- production cell bank. Establish and qualify downscale manufacturing process models. Perform impurity clearance studies. Continue to refine the product specifications. Finish validating all analytical assays. Create and start to use a cell line specific HCP assay. Request an end of phase 2 meeting with the FDA. Map out drug substance and drug product process validation strategies to present to the FDA at the end of phase 2 meeting. After the phase 2 study is complete and before phase 3 begins, have an end of phase 2 meeting with the FDA.	The manufacturing processes and analytical assays should be finalized with only minor changes until commercialization. Multiple lots must be on stability that are tested with validated assays. Continue to narrow, refine, and justify specifications. Justify the elimination of redundant QC tests. Continue investigating process impurities. Perform forced degradation studies and provide the final product degradation profile. Perform HCP fingerprinting analysis. Identify and determine control strategies for any significant HCP contaminents Validate the bulk drug substance and drug product manufacturing processes, analyze process validation batches and perform comparability testing to clincial batches. Determine column cycle limits. Perform expanded viral clearance studies. Perform extractable and leachable studies. Perform packaging, photostability, and shipping studies. Analyze all analytical data from batch release and stability and set final specifications. Address any FDA issues from the end of phase 2 meeting. Have the pre-BLA meeting with the FDA. Write and submit the BLA. Schedule the PAI.