# A CMC Development Roadmap For an Injectable AAV Gene Therapy – What to Do When

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| Pre-IND | Phase 1 | Early Phase 2 | Late Phase 2 | Phase 3 |
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| Choose the AAV serotype and design the transfer plasmid. Ensure the CDMO has stocks of Helper and Rep/Cap plasmids.<br>Develop the transfer plasmid and viral vector manufacturing processes.<br>Develop assays for plasmid and vector product release and stability testing.<br>Perform plasmid and vector formulation studies and choose final formulations.<br>Qualify assays. Validate sterility, endotoxin, and other critical assays. Ensure assays are stability-indicating.<br>Make engineering batches.<br>Perform viral clearance studies on the vector manufacturing process.<br>Create and characterize transfer plasmid and viral vector reference standards.<br>Establish the viral vector drug product manufacturing process and produce an engineering batch.<br>Set initial product specifications. Initiate plasmid, vector, drug product and reference standard stability studies.<br>Perform clinical administration method compatibility and stability studies<br>Create and qualify the transfer plasmid and packaging cell line master cell banks.<br>Produce clinical material if the engineering batches were not GMP.<br>Have a pre-IND meeting with the FDA.<br>Write and submit the IND. | Justify and document all changes to the manufacturing process and analytical assays.<br>Think about potential future changes in raw materials and manufacturing processes that could impact product quality.<br>Gather and trend analytical data from batch release and stability studies. | If not already done, create plasmid and packaging cell line working cell banks and use them both before phase 3.<br>If a stable viral vector producing cell line will be used for commercial manufacturing create the stable viral vector producing cell line and use it before phase 3.<br>Refine all product specifications.<br>Analyze stability data to get an indication of product degradation pathways and eventual product expiry.<br>If the final commercial bioassay is not already in place, start to develop it now and gain experience with it before starting phase 3. | Get all commercial manufacturing sites at final commercial scale online.<br>Create and test the end-of- production cell bank.<br>Establish and qualify downscale manufacturing process models.<br>Perform impurity clearance studies.<br>Continue to refine product specifications. Finish validating all analytical assays.<br>Request an end of phase 2 meeting with the FDA.<br>Define the process validation strategies for the viral vector bulk and drug product manufacturing processes.<br>If a stable viral vector producing cell line will not be used for commercial manufacturing, define the validation strategy for the transfer plasmid manufacturing process.<br>If required and the CDMO doesn't already have a DMF on file, define the manufacturing process validation strategies for the Helper and Rep/Cap plasmids.<br>Create and start to use a cell line specific HCP assay.<br>Prepare to present all proposed commercial manufacturing process validation strategies to the FDA at the end of phase 2 meeting.<br>After the phase 2 study is complete and before phase 3 begins, have an end of phase 2 meeting with the FDA. | All manufacturing processes and analytical assays should be finalized, only minor changes until commercial.<br>Multiple lots must be on stability that are tested with validated assays.<br>Continue to narrow, refine, and justify specifications. Justify the elimination of redundant QC tests.<br>Continue investigating process impurities. Perform forced degradation studies determine the final product degradation profile.<br>Perform HCP fingerprinting analysis. Identify and determine control strategies for any significant HCP contaminants.<br>Validate all manufacturing processes, analyze process validation batches, perform comparability testing to clincial batches. Determine column cycle limits. Perform expanded viral clearance studies.<br>Perform extractable and leachable studies.<br>Perform packaging, photostability, and shipping studies.<br>Analyze all analytical data from batch release and stability and set final specifications.<br>Address any FDA issues from the end of phase 2 meeting.<br>Have the FDA pre-BLA meeting.<br>Write and submit the BLA. Schedule the PAI. |