An Overview of an Emerging Biologic Company's CMC Risk

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Production Cell Line	Bulk Drug Substance	Aseptic Drug Product	Analytical & Stability	IND Submission
Use of inappropriate or uncontrolled raw materials.	Wrong CDMO process scale available or product incompatible facility design.	Wrong CDMO process scale or incompatible facility design.	Insufficient assay linearity, range, precision, sensitivity, specificity, or reproducibility in one or more of the product release and stability assays.	Failure to demonstrate biochemical and manufacturing process comparability between the development and GMP batches.
Insufficient sequence codon optimization.	Use of inappropriate or uncontrolled raw materials.	Product incompatibility with the container closure system.	Missing an assay for a manufacturing process-related impurity.	Insufficient justification of product release and stability specifications.
Insufficient product expression to support planned clinical trials.	High levels of aggregates or degradation in the final product.	Wrong vial size, product concentration, or fill volume to support clinical studies.	Missing an assay to test for a host-related impurity.	Insufficient MCB qualification testing
Genetic instability.	High levels of host cell protein or DNA in the final product	Prefiltration bioburden failure	Missing an assay to test for any product-related impurities.	Not demonstrating adequate control of adventitious agents in the bulk substance and final drug product.
Expression of significant levels of product-related impurities.	High levels of process-related impurities in the final product.	Sterility failure	One or more of the stability assays are not stability indicating.	Insufficient stability data in the IND.
Expressing excessive amounts of aggregated or breakdown products.	Decrease in titer during process scale-up.	B&F assay qualification failure	Bioassay not reflective of the product's proposed mechanism of action	Not proving that all of the assays are stability-indicating.
Growth profile unsuitable for GMP manufacturing.	Increase in product aggregation or degradation during process scale-up.	Media fill failure.	The toxicology and GMP batch release and stability results are not comparable because the analytical assays used for the toxicology batch are significantly different from the assays used for the GMP batch.	Too loose of product specifications for the FDA to feel comfortable with proceeding.
Can't show production cell line clonality.	Increase in process or host related impurities during process scale-up	Excessive amounts of visible particles in the final product.	Developing differences in post translational modifications between the toxicology and GMP batches.	Not enough information in the IND for the FDA to feel comfortable with proceeding.
Problematic parental cell line history.	Manufacturing processes causes loss of product activity.	Excessive amounts of sub-visible particles in the final product	Setting product specifications too loose to adequately control the quality and consistency of clinical material.	Too much information in the IND making future CMC changes too restrictive.
Lack of controls and documentation for clone selection and master cell bank manufacturing.	Lack of required process controls.	Product aggregation and degradation introduced during the manufacturing process.	Setting product specifications too tight to release future batches.	
Microbial or viral contamination of the master cell bank.	Significant process changes between tox and GMP batches.	Lack of process controls to ensure that the manufacturing process is robust and reproducible.	Product Infusion Stability Failure.	
	Microbial or viral contamination	Cross-contamination with other CDMO customer products.	Lack of reference standard freeze-thaw stability.	
	Insufficient process viral clearance.	Significant process changes between the engineering and GMP batches.	Drug substance, reference standard, or drug product stability failure.	
	Cross-contamination with other CDMO customer products.	Unsuitable product formulation to support room temperature drug product manufacturing and vial inspection, packaging and labeling for clinical distribution.		
	Product instability during room temperature manufacturing.			

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