Regulatory Flexibilities and Clarifications:
Chemistry, Manufacturing and Control (CMC) Information for Original First in Human (FIH) Phase 1 INDs

CDER-Regulated Recombinant Biological Products

Drug Substance (DS)			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
A description of the drug substance, including its physical, chemical, or biological characteristics	Description of physical, chemical, and biological characteristics (including proposed mechanism of action) and evidence supporting structure (primary, secondary and higher order structure) and identity of the active pharmaceutical ingredient(s).	N/A	Full characterization using multiple orthogonal methods is not expected.
Name and address of manufacturer	Name and address of manufacturer	N/A	N/A

Drug Substance (DS)			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
General method of preparation of the drug substance	Brief general description of raw materials and associated controls used to ensure safety • List of raw materials of biological origin used directly or indirectly in the process • General description of controls for raw materials Brief general description of cell substrate and associated controls used to ensure safety • A short description of expression system • A short description of cell line development history (source, media adaptation, procedure for producing clonal mammalian cell bank, etc.). Single tier cell bank is sufficient. • Safety testing performed on production cell line/cell bank, as appropriate. For example, - Identity - Purity - Bioburden - Adventitious viruses - Applicable species-specific viruses (e.g., bovine viruses, porcine viruses) - Retroviruses - Mycoplasma	Manufacturers of drug substances should implement CGMP appropriate to the stage of clinical development. See *Guidance for Industry: CGMP for Phase 1 Investigational Drugs*. Stable clonal cell pool may be sufficient.	Derivation of clonally derived cell bank is not expected. Two-tiered cell bank system is not expected. Amplification steps such as 21-day or 28-day cultivation duration are not expected for in vitro adventitious agent testing of cell banks. Process controls that are not directly related to product safety are not expected to be specified.

Drug Substance (DS)			
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General method of preparation of the drug substance	Viral and non-viral adventitious agents safety evaluation • Applicable risk assessment (e.g., BSE/TSE) and/or test results for materials of animal origin • Viral clearance study results (using model virus x-MuLV) for manufacturing processes using animal-derived production cell lines (not expected for those using E. coli, yeast, plant production cells).	Product-specific viral clearance study results are not expected if appropriate prior knowledge can be leveraged.	N/A
General method of preparation of the drug substance	Brief description of drug substance (DS) manufacturing process and process controls used to ensure product safety. • Unprocessed bulk harvest (UPB) safety testing specifications (mycoplasma, bioburden, adventitious viruses, applicable species-specific viruses, retrovirus) and results • Bioburden testing • Applicable process controls to ensure viral inactivation and removal (for animal-derived expression system). For example, - Low pH viral inactivation pH and duration - Resin contact time (bed height and flow rate) - Viral filtration pressure/flow rate and product load	Complete UPB Safety testing results (e.g., for mycoplasma) may be submitted during the 30-day review cycle upon Pre-IND agreement.	Amplification steps such as 21-day or 28-day cultivation duration are not expected for in vitro adventitious agent testing of UPB.

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General method of preparation of the drug substance	Brief description of major changes (e.g., scale up) made to manufacturing processes used for development, nonclinical (toxicology lot) and clinical materials, as applicable. Comparability assessment of safety, impurity, and potency test results between toxicology and clinical lots, as applicable, to ensure continuous safety.	N/A	N/A

Drug Substance (DS)			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
Acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance	Brief description of analytical tests and acceptance criteria to ensure the safety, identity, purity, and potency [using an assay(s) that is relevant to mechanism of action (MOA)] for lot release and stability. For example, • Identity • Protein concentration • Size variants • Charge variants • Glycosylation (as applicable) • Applicable process related impurities (e.g., residual Protein A, host cell protein and DNA, etc.) • Target binding or specific enzymatic activity (as applicable) • Safety tests (bioburden, endotoxin, etc.) Batch analysis for nonclinical/toxicology and clinical lots.	Potency assay is not expected for simple proteins demonstrated to have no higher order structure. Potency characterization results may be sufficient to initiate the FIH Phase 1 clinical trial if method development for quality control cannot be completed by the time of IND submission.	Method validation results are not expected. Cell-based potency assay(s) that is reflective of MOA is not expected.
Acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance	Brief description of reference standard/material used in quality control assays, including source of material, preparation, characterization, intended use and storage.	N/A	Two-tiered reference standard system is not expected.

Drug Substance (DS)			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
Information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies	Stability protocols for ongoing and future stability studies (testing conditions, quality attributes, analytical methods, and acceptance criteria).	A minimum of 1 month stability data from a representative DS lot, when no degradation is observed, is generally expected. Stability data/update may be submitted during the 30-day review cycle upon Pre-IND agreement.	Stability data from clinical DS lot may not be needed if they are not available by the time of IND submission.

Drug Product (DP)			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage.	Brief description of dosage form, presentation, and strength. Describe the composition of the drug product (DP) including the name of each ingredient, quality (e.g., applicable compendial standards), and quantity.	N/A	N/A
Name and address of manufacturer	Name and address of manufacturer	N/A	N/A

Drug Product (DP)			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
A brief general description of the manufacturing and packaging procedure as appropriate for the product	Brief description of DP batch formula, manufacturing process, including container closure system. Description of process controls used to ensure product sterility and safety. Brief description of major changes (e.g., scale up) made to manufacturing processes used for development, nonclinical (toxicology lot) and clinical materials, as applicable. Comparability assessment of safety, impurity, and potency test results between toxicology and clinical lots, as applicable, to ensure continuous safety.	Phase 1 investigational drug products are generally exempt from complying with 21 CFR part 211 (See 21 CFR 210.2(c)). See *Guidance for Industry: CGMP for Phase 1 Investigational Drugs*.	Process controls that are not directly related to product safety are not expected to be specified. Extractable/leachable (E/L) evaluation is not expected.

Drug Product (DP)			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
A brief general description of the manufacturing and packaging procedure as appropriate for the product	Information on compatibility (in-use stability) study design and results to support preparation and administration procedures to ensure patient safety. • In-use stability study should be designed to reflect the preparation and administration procedure provided to the clinical site(s) (e.g., pharmacy manual). • Product quality data (e.g., protein recovery, visible and subvisible particulates, potency, size variants) from in-use stability studies should be provided. • Microbial challenge data to support extended storage and infusion duration should be provided.	Microbial challenge data are not expected if prepared solution stored at 2-8°C for ≤24 hours and 25°C for ≤4 hours after product container closure is breached.	N/A

Drug Product (DP)			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
Acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product	For the control of compendial excipients: • A list of quality standards (e.g., USP/NF, Ph.Eur., J.P.) applied to ensure quality and safety of excipients. • If applicable, list excipients of human or animal origin, risk assessment, and controls (tests and acceptance criteria) used to ensure safety. • If applicable, list novel excipients and associated controls (tests and acceptance criteria) used to ensure safety. For the control of DP: • A brief description of analytical tests and acceptance criteria used to ensure drug product safety, identity, purity, and potency [using an assay(s) that is relevant to MOA] for lot release and stability. DP specific quality attributes (e.g., color, clarity, visible and subvisible particulate matter, sterility) should be included, as applicable. • A brief description of analytical procedures (compendial and non-compendial methods). • Batch analyses for nonclinical/toxicology and clinical lots	Potency assay is not expected for simple proteins demonstrated to have no higher order structure. Potency characterization results may be sufficient to initiate the FIH clinical trial if method development for quality control cannot be completed by the time of IND submission.	Method validation data are not expected. Cell-based potency assay(s) that is reflective of MOA is not expected.

Drug Product (DP)			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
Information sufficient to assure the product's stability during the planned clinical studies	Stability protocols for ongoing and future stability studies (testing conditions, quality attributes, analytical methods, and acceptance criteria).	A minimum of 1 month stability data from a representative DP lot, when no degradation is observed, are generally expected. Stability data/update may be submitted during the 30-day review cycle upon Pre-IND agreement.	Stability data from clinical DP lot may not be needed if they are not available by the time of IND submission.

Placebo			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.	This section is expected to include a brief general description of the composition, manufacture, and control of any placebo formulation, comparator, or co-administered agent to be used in the proposed clinical study. The description may be structured similarly to the description of the drug product recommended above. The same expectations apply to product-specific diluent that is not commercially sourced, as applicable. Note: For Placebo, the Quality Control test will include the absence of the active pharmaceutical ingredient(s). The physical characteristics of the placebo formulation should be comparable to the actual drug product to enable effective blinding.	If proposing the use of a commercial product (e.g., USP supply or FDA-approved product), a source statement is sufficient.	N/A

Labeling			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
A copy of all labels and labeling to be provided to each investigator.	A copy of representative immediate package label to be provided to participating clinical site(s) that contains a statement “Caution: New Drug—Limited by Federal (or United States) law to investigational use”.	N/A	N/A

Environmental Assessment			
21 CFR 312.23 Requirement	**General Expectation**	**CMC Flexibilities for FIH Phase 1 IND**	**CMC Information Generally Not Needed at the Time of FIH Phase 1 IND**
A claim for categorical exclusion under 21 CFR 25.30 or 25.31 or an environmental assessment under 21 CFR 25.40.	Include an assessment of effects of the investigational product on the environment. Environmental Assessment may be obtained from the IND product manufacturer.	Most CDER-regulated products qualify for a categorical exclusion from such an assessment. For additional information on environmental assessments consult *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications*	N/A

Resources

1. 21 CFR 312.23 for IND content and format
2. 21 CFR 312.6 for Labeling of an investigational new drug
3. 21 CFR 25.40 and 21 CFR 25.31 for environmental assessment or claim for categorical exclusion, respectively
4. Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products
5. Guidance for Industry: CGMP for Phase 1 Investigational Drugs
6. Guidance for Industry: IND Meetings for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information
7. Guidance for Industry: Botanical Drug Products
8. Guidance for Industry: INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information
9. Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies
10. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics
11. Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer
12. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications