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

CDER-Regulated Small Molecule Drug 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, or biological characteristics and evidence supporting structure and identity of the active pharmaceutical ingredient(s).	At a minimum, provide nomenclature, structure, and general properties.	Comprehensive characterization using multiple orthogonal methods is not expected
Name and address of manufacturer	Name and address of manufacturer	N/A	N/A
General method of preparation of the drug substance	Brief description of the general method of preparation of the drug substance, including a list of the reagents, solvents, and catalysts used. More information may be needed to assess the safety of drugs extracted from human or animal or plant sources.	Manufacturers of drug substances should implement CGMP appropriate to the stage of clinical development. 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. Designation of regulatory starting materials and establishment of commercial synthetic route are 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**
Acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance	The acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of the drug substance, with a brief description of the test methods used (e.g., Nuclear Magnetic Resonance, Infrared, UV spectra to prove the identity, and High-Performance Liquid chromatograms to support the purity level and impurities, etc.). Submission of certificates of analysis is also suggested.	The observed and potential impurities, including potential mutagenic impurities, should be outlined. As applicable[1], see Phase 1-specific ICH M7 recommendations regarding information on potential mutagenic impurities (i.e., focus on Class 1, Class 2, and cohort-of-concern for studies ≤ 14 days, as well as Class 3 impurities for longer studies). It is understood that specifications are likely to change as development proceeds, as the manufacturing process is optimized, and more experience is gained. Preferably representative clinical and toxicological batch data are provided to enable comparison of impurity profiles.	For IND applications, levels of specified and unspecified impurities are not expected to be within the relevant ICH Q3A qualification and identification thresholds. Risk assessments for elemental impurities and nitrosamine impurities are not expected. Analytical method validation data are not expected.

[1] ICH M7 does not apply to drug substances and drug products intended for advanced cancer indications as defined in the scope of the ICH S9 guidance. Additionally, there may be some cases where a drug substance intended for other indications is itself genotoxic at therapeutic concentrations and may be expected to be associated with an increased cancer risk. In these cases, mutagenic impurities can be treated as nonmutagenic impurities.

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	Data from a representative lot to support stability of the drug substance during the planned clinical studies. Stability protocols and a commitment for on-going and future stability studies (testing conditions, quality attributes, analytical methods, and acceptance criteria), with the resulting data to be submitted in the initial IND/future quality amendments/annual reports.	Stability data from the specific clinical lot to be used may not be required. The amount of stability data should be proportionate to the duration and scope of the proposed Phase 1 study and adequate to support patient safety. For example, for very short-term Phase 1 studies (such as those lasting only 7 days), the supporting stability data can be correspondingly limited.	If available data do not cover the duration of the proposed clinical studies, provide information to support the stability of the DS during toxicological studies and the planned clinical studies. Establishment of DS retest period is not expected.

Drug Product (DP)[2, 3]			
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.	If applicable, list novel excipients and associated controls (tests and acceptance criteria) used to ensure safety. If applicable, list excipients of human or animal origin, risk assessment, and controls (tests and acceptance criteria) used to ensure safety.	Selection of the final/commercial dosage form or formulation is not expected.
Name and address of manufacturer	Name and address of manufacturer	N/A	N/A
A brief general description of the manufacturing and packaging procedure as appropriate for the product	Brief general description of the manufacturing process (the format of a flow diagram is suggested) and packaging procedure, as well as other relevant tests, as appropriate for the product.	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.

[2] If DP is powder in capsule or powder in bottle (API with no excipients), FDA can generally rely heavily on DS information/data, as needed.
[3] The same general expectations and flexibilities apply to product-specific diluent, as applicable. If a commercial product-specific diluent is to be used (e.g., USP supply or FDA-approved product), inclusion of a source statement is generally sufficient.

Drug Product (DP)[2, 3]			
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	The acceptable limits and analytical methods used to ensure the drug product safety, identity, strength, quality, and purity of the drug product. For injectable products, sterility and pyrogenicity tests, endotoxin levels and particulate matter should be included. Submitting a copy of the certificate of analysis of the clinical batch is also suggested.	If there are no new degradation products observed in the drug product relative to the drug substance, generally, this may simply be stated in the IND. It is understood that specifications are likely to change as development proceeds, the manufacturing process is optimized, and product understanding is gained. If clinical batch data are not available, sufficient specification and batch data for representative batches can generally serve to demonstrate the ability to manufacture product of adequate quality.	DS process specific impurities and quality attributes that are not expected to be impacted by DP manufacture are not expected to be controlled for DP. Risk assessments for elemental impurities and nitrosamine impurities are not expected. Analytical method validation data are not expected.
Information sufficient to assure the product's stability during the planned clinical studies	Data from a representative batch to support stability of the drug product during the planned clinical studies. Stability protocols and a commitment for on-going and future stability studies (testing conditions, quality attributes, analytical methods, and acceptance criteria), with the resulting data to be submitted in the initial IND/future quality amendments/annual reports.	Stability data from the specific clinical lot to be used may not be required. The amount of stability data should be proportionate to the duration and scope of the proposed Phase 1 study and adequate to support patient safety. For example, for very short-term Phase 1 studies (such as those lasting only 7 days), the supporting stability data can be correspondingly limited.	If available data do not cover the duration of the proposed clinical studies, provide information to support the stability of the DP during the toxicological studies and the planned clinical studies. Establishment of DP shelf life is not expected.

Placebo, Comparator, Co-Administered Agents (As Applicable)			
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. 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 generally 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