Checklist for Preclinical Studies

CATALYZE
Accelerating Translation

Small Molecule

Notes

This workbook separates the small molecule pre-IND checklist into category-specific tabs: Technical/CMC (Drug Substance & Drug Product), Bioanalytical, Pharmacology (Primary & Secondary), Animal Efficacy, PK, ADME, and Toxicology context. Note: Completion of all studies is not required; please indicate which studies have been completed.

References include ICH Q1A(R2)/Q1B, Q3A/Q3B/Q3C, Q6A, Q8/Q11, ICH S7A/S7B, ICH S2(R1), ICH M3(R2), FDA Bioanalytical Method Validation Guidance, FDA MIST, and USP <711>.

Category	Item/Study	Purpose	Key Outputs/Acceptance Criteria	Reference/Guideline	Notes
Technical/CMC – Drug Substance	☐Chemical Identity & Structure (IR, NMR, MS)	Confirm API identity, structure, stereochemistry	Spectra match reference; no unexpected peaks	ICH Q6A; FDA Analytical Procedures Guidance	Include chiral purity if applicable
Technical/CMC – Drug Substance	☐Synthetic Route & Process Description	Define manufacturing steps and critical controls	Documented process with identified CPPs/CMAs	ICH Q11	Provide impurity generation points
Technical/CMC – Drug Substance	☐Impurity Profile (Related Substances)	Quantify process/degradation impurities	Impurities ≤ phase-appropriate limits	ICH Q3A/Q3B	Track under stress conditions
Technical/CMC – Drug Substance	☐Residual Solvents (GC)	Quantify Class 1–3 solvents	Below ICH Q3C limits	ICH Q3C	Demonstrate method suitability
Technical/CMC – Drug Substance	☐Specifications & Reference Standards ☐Salt Investigation ☐Determination of spectral data ☐Stability studies (forced degradation studies) ☐Moisture absorption ☐Polymorph Investigation ☐Particle size distribution ☐Determination of BCS Classification (solubility/permeability index) ☐Kinetic/thermodynamic solubility evaluation ☐Dissolution rate studies in biorelevant media ☐Calculation of molecular weight ☐Physical properties determination (cLogP, H-bond donors, H-bond receptors, rotatable bonds, tPSA ☐Determination of potential structural alerts in parent compound ☐Determination of formulation for GLP studies	Set phase-appropriate DS specifications and qualify standards	Specs aligned to ICH Q6A; standard COA	ICH Q6A	Plan tightening by Phase II/III
Technical/CMC – Drug Product	☐Formulation Development & Excipient Compatibility	Identify a stable, clinically suitable DP	No significant interaction/degradation	FDA Preformulation; ICH Q8 (QbD)	Screen pH, heat, humidity
Technical/CMC – Drug Product	☐Prototype DP Characterization (Dissolution, Content Uniformity)	Demonstrate performance and dose uniformity	Dissolution per USP <711>; CU within ±15% (early)	ICH Q6A; USP <711>	Align with intended route
Technical/CMC – Drug Product	☐Stability – Accelerated/Stress/Photostability	Map degradation pathways and estimate shelf-life	Defined pathways; preliminary shelf-life	ICH Q1A(R2); ICH Q1B	Include humidity stress
Technical/CMC – Drug Product	☐Container/Closure Compatibility & E/L Risk	Ensure compatibility and minimize leachables	No adverse E/L risk (phase-appropriate)	USP <1664>; FDA E/L considerations	Plan full E/L later if needed
Bioanalytical	☐LC–MS/MS Method Development & Phase-appropriate Validation	Quantify drug in plasma/serum for PK	Accuracy/precision within ±15% (±20% at LLOQ)	FDA Bioanalytical Method Validation Guidance	Assess matrix effects and stability
Pharmacology – Primary	☐Target Engagement & In vitro Pharmacology	Confirm pharmacological activity at intended target	No concerning off-target hits	ICH S7A/S7B	Prioritize cardiovascular (QT) risk per S7B
Pharmacology – Primary	☐In vivo Pharmacology / Dose-Response	Demonstrate efficacy in relevant animal model	No unsafe acute effects at relevant exposures	ICH S7A; S7B (QT/QTc)	May align with tox studies

Animal Efficacy	☐Proof-of-Concept Efficacy in Relevant Model	Demonstrate biological effect consistent with MoA	Statistically significant efficacy; biomarker changes	ICH S7A; FDA nonclinical guidance	Include dose-response and exposure mapping
PK	☐Single-Dose PK (IV and clinical route)	Characterize exposure and clearance	Cmax, Tmax, AUC, CL, t1/2	FDA Pharmacology/Toxicology; ICH M3(R2) timing	Use bioanalytical validated for purpose
PK	☐Repeat-Dose PK (aligned to tox)	Assess accumulation/steady state	Accumulation ratio; steady-state parameters	ICH M3(R2)	Embed in repeat-dose tox
Toxicology – Context	☐Genotoxicity Battery (Ames + Chromosomal)	Assess mutagenic potential prior to FIH	Negative/acceptable per ICH S2(R1)	ICH S2(R1)	Required before FIH
Toxicology – Context	☐Safety Pharmacology – QTc (in vitro hERG; in vivo ECG)	Evaluate proarrhythmic risk	No clinically relevant QT prolongation	ICH S7B	Inform clinical ECG monitoring
ADME	☐Mass Balance/Excretion (radiolabeled where feasible)	Quantify excretion routes and recovery	% dose recovered; route distribution	FDA ADME expectations; ICH M3(R2)	Support human dose and DDI planning
ADME	☐Metabolite ID & Profiling	Identify and quantify major metabolites	Metabolite structures; coverage of ≥90% radioactivity	ICH M3(R2); FDA MIST	Assess human-unique or disproportionate metabolites
ADME	☐Tissue Distribution (as needed) ☐Caco-2 Permeability ☐Protein Binding across species ☐CYP Inhibition ☐Microsomal Stability ☐Hepatocyte Stability ☐Plasma Stability across species ☐PXR Induction (potential induction of human P450 enzymes) ☐P450 Induction (CYP Induction in human hepatocytes) ☐Metabolite Identification across species ☐Reactivity (determination of reactive functionalities in drug or metabolites) ☐PK across nonclinical species (including clearance, Cmax and bioavailability) ☐Enzyme Induction Study (multiple dosing in rats for 7-14 days) ☐PK in higher animal (including clearance, Cmax and bioavailability)	Assess target organ exposure	Tissue concentration vs plasma	FDA nonclinical guidance	Support efficacy/tox interpretation