Regfo

FDA IND Submission Checklist

Phase 1 small molecule IND requirements.
Organized by CTD module. Linked to ICH/FDA sources.

Based on 21 CFR 312.23 · ICH M3(R2)

48 checklist items · 10 clinical hold triggers · 9 regulatory sources

FREE — NO EMAIL REQUIRED

■ **Required** FDA requires for filing
◆ **Conditional** Depends on drug/route
○ Optional Recommended
— N/A Not needed for Phase 1

Module 1: Administrative Forms & Documents

☐	ITEM	PHASE 1	GUIDELINE	LINKS
☐	**Form FDA 1571** IND application cover sheet — 12-item content checklist	■ Required	21 CFR 312.23(a)(1)	Regfo · FDA form
☐	**Form FDA 1572** Statement of Investigator — one per clinical site	■ Required	21 CFR 312.23(a)(6)(iii)(b)	Regfo · FDA form
☐	**Form FDA 3674** ClinicalTrials.gov registration certification	■ Required	42 USC 282(j); FDAAA §801	Regfo · FDA
☐	**Cover letter** Identifies submission type, drug name, IND number, contact	■ Required	21 CFR 312.23(a)(1)	Regfo
☐	**Table of contents** Paginated index of all documents in submission	■ Required	21 CFR 312.23(a)(2)	Regfo
☐	**Introductory statement & general investigational plan** Rationale, indication, planned studies Year 1, estimated subjects	■ Required	21 CFR 312.23(a)(3)	Regfo
☐	**Financial disclosure** Per investigator — disclose financial interests	■ Required	21 CFR 54	Regfo · eCFR
☐	**Debarment certification** Certify no debarred persons involved	■ Required	21 USC 335a	Regfo
☐	**Environmental assessment / categorical exclusion** Most drugs qualify for categorical exclusion	■ Required	21 CFR 25	Regfo · eCFR
☐	**Pre-IND meeting minutes** Strongly recommended for first-time sponsors. Include FDA responses.	◆ Conditional	FDA Formal Meetings Guidance	Regfo · FDA
☐	**eCTD format submission** FDA requires electronic submission in eCTD format. File naming, bookmarks, module placement matter.	■ Required	FDA eCTD Guidance	FDA

Module 2: CTD Summaries

☐	ITEM	PHASE 1	GUIDELINE	LINKS
☐	**Quality Overall Summary (QOS)** Summary of CMC data — recommended for complex products	○ Optional	ICH M4Q(R1)	Regfo · ICH
☐	**Nonclinical Overview** Summary of pharmacology/toxicology per 312.23(a)(5); may be in IB	◆ Conditional	ICH M4S(R2)	Regfo · ICH
☐	**Clinical Overview** Not applicable for initial Phase 1 IND	— N/A	ICH M4E(R2)	

Module 3: CMC (Chemistry, Manufacturing, Controls)

☐	ITEM	PHASE 1	GUIDELINE	LINKS
Drug Substance (3.2.S)				
☐	**Description & characterization** Structure, physical properties, identification	■ Required (minimal)	ICH Q6A	Regfo · ICH Q6A
☐	**Manufacturing process** Brief description, reagents, solvents, catalysts	■ Required (minimal)	21 CFR 312.23(a)(7)	Regfo · eCFR
☐	**Specifications & analytical methods** Preliminary specs, identity, purity, potency tests	■ Required (minimal)	ICH Q6A	Regfo
☐	**Stability data** Encouraged but not mandated for Phase 1	○ Optional	ICH Q1A(R2)	ICH Q1A
Drug Product (3.2.P)				
☐	**Formulation composition** All components with amounts and rationale	■ Required	21 CFR 312.23(a)(7)(ii)	Regfo · eCFR
☐	**Manufacturing process description** Brief description, sterilization if sterile product	■ Required (minimal)	21 CFR 312.23(a)(7)	Regfo
☐	**Specifications & certificates of analysis** Batch data for clinical material	■ Required	ICH Q6A	Regfo
☐	**Container closure system** Description, materials, suitability	■ Required	21 CFR 312.23(a)(7)	Regfo
☐	**Stability data** Encouraged but not required for Phase 1	○ Optional	ICH Q1A(R2)	
☐	**Batch analysis (1-2 batches)** Analytical data for material used in tox and/or clinical	■ Required	21 CFR 312.23(a)(7)	
☐	**Impurity profile & characterization** Identify and control impurities; genotoxic impurities per ICH M7	■ Required (minimal)	ICH Q3A(R2), ICH M7	Regfo

Phase 1 CMC note: Full cGMP not required, but appropriate manufacturing controls must be documented. Full analytical validation not required — phase-appropriate data is sufficient. See FDA Phase 1 CMC Guidance.

Module 4: Nonclinical Studies (IND-Enabling Package)

☐	ITEM	PHASE 1	GUIDELINE	LINKS
Pharmacology				
☐	**Primary pharmacodynamics** Mechanism of action, target binding, in vivo efficacy models	■ Required	ICH M3(R2)	Regfo · ICH M3
☐	**Secondary pharmacodynamics** Off-target receptor binding, selectivity panels	○ Optional	ICH M3(R2)	Regfo
☐	**Safety pharmacology core battery** Cardiovascular (including hERG), CNS, respiratory — all GLP	■ Required	ICH S7A / S7B	Regfo · ICH S7A · S7B
Pharmacokinetics (ADME)				
☐	**Absorption, Distribution, Metabolism, Excretion** Two species. Basic characterization for Phase 1.	■ Required (basic)	ICH M3(R2)	Regfo
☐	**Plasma protein binding** In vitro binding — needed for dose calculation	■ Required	ICH M3(R2)	Regfo
☐	**Analytical methods & validation (PK)** Bioanalytical methods for measuring drug levels	■ Required	ICH M3(R2)	Regfo
Toxicology				
☐	**Single-dose toxicity** Can be addressed within repeat-dose design; standalone not always required	◆ Conditional	ICH M3(R2) §4	Regfo · ICH M3
☐	**Repeat-dose toxicity** Two species, GLP. Duration ≥ planned clinical dosing (ICH M3 Table 1)	■ Required	ICH M3(R2) Table 1	Regfo
☐	**Genotoxicity — in vitro battery** Standard battery Option 1: Ames + mammalian cell assay + in vivo micronucleus	■ Required	ICH S2(R1)	Regfo · ICH S2
☐	**Genotoxicity — in vivo (micronucleus)** Option 2 alternative: Ames + in vivo micronucleus + in vivo Comet. Both options require an in vivo test.	■ Required (standard battery)	ICH S2(R1)	Regfo
☐	**Local tolerance** If parenteral, inhaled, or topical route of administration	◆ Conditional	ICH M3(R2) §9	Regfo
Reproductive Toxicology				
☐	**Fertility & early embryonic development** Not required for Phase 1 (required Phase 3)	— N/A	ICH S5(R3)	Regfo · ICH S5
☐	**Embryo-fetal development** Only if enrolling women of childbearing potential (WOCBP)	◆ Conditional	ICH S5(R3)	Regfo
Other Studies				

☐	ITEM	PHASE 1	GUIDELINE	LINKS
☐	**Immunotoxicity** Optional Phase 1, required Phase 3	○ Optional	ICH S8	Regfo · ICH S8
☐	**Carcinogenicity** Not applicable for Phase 1 (required Phase 3)	— N/A	ICH S1A / S1B	Regfo
☐	**Phototoxicity** If drug substance absorbs UV/visible light (290-700nm)	◆ **Conditional**	ICH S10	

GLP requirement: All pivotal in vivo and in vitro tox studies must comply with Good Laboratory Practice (GLP) per 21 CFR Part 58. Non-GLP pivotal studies = automatic clinical hold.

Module 5: Clinical

☐	ITEM	PHASE 1	GUIDELINE	LINKS
☐	**Clinical protocol(s)** Objectives, endpoints, design, population, dosing, safety monitoring	■ Required	21 CFR 312.23(a)(6)	Regfo · eCFR
☐	**Informed consent form (ICF)** Must disclose all known risks from animal studies	■ Required	21 CFR 50	eCFR
☐	**Investigator's Brochure (IB)** Compiled nonclinical + clinical data for investigator reference	■ Required	ICH E6(R2)	Regfo · ICH E6
☐	**IRB approval documentation** Protocol and ICF must be IRB-approved before dosing	■ Required	21 CFR 56	eCFR
☐	**Investigator CVs and qualifications** Training records, medical license for each PI	■ Required	21 CFR 312.23(a)(6)(iii)(b)	
☐	**Dose escalation scheme & stopping rules** DLT definitions, escalation rules, maximum tolerated dose criteria	■ Required	21 CFR 312.23(a)(6)	Regfo
☐	**Starting dose justification** NOAEL → human equivalent dose (HED) → safety margin (≥10x)	■ Required	FDA Starting Dose Guidance	FDA guidance
☐	**Previous human experience** Summary of prior trials, or explicit "no prior human experience"	■ Required	21 CFR 312.23(a)(5)	

After filing: FDA has 30 days to review (21 CFR 312.40). IND becomes effective on Day 30 unless clinical hold is issued. Post-IND: safety reports per 312.32, annual reports per 312.33, protocol amendments per 312.30.

Top 10 Clinical Hold Triggers

Based on 21 CFR 312.42 and publicly reported FDA actions. Avoid these and you avoid most delays.

#	WHAT GETS YOU HELD	HOW TO PREVENT IT
1	Missing non-rodent toxicology species	Run both rodent + non-rodent tox before assembling IND. CRO large-animal slots book months out — plan early.
2	Non-GLP hERG assay submitted as pivotal	Always run hERG under GLP. Costs ~$30-40K. Non-GLP = clinical hold, no exceptions.
3	Tox study duration shorter than clinical dosing	Match tox duration to planned clinical exposure. ICH M3(R2) Table 1 has the exact mapping.
4	Insufficient starting dose justification	Show NOAEL → HED → safety margin calculation. Standard: ≥10x for non-cancer small molecules.
5	CMC: batch inconsistency or insufficient characterization	Provide batch analysis for clinical material. Demonstrate comparability to tox batch if process changed.
6	Incomplete genotoxicity standard battery	Ames test + mammalian cell chromosomal assay is the minimum. Both under GLP.
7	Protocol doesn't address known animal findings	Clinical monitoring plan must cover every target organ identified in tox studies.

#	WHAT GETS YOU HELD	HOW TO PREVENT IT
8	Informed consent doesn't disclose all known risks	ICF must list every adverse finding from nonclinical studies. Omission = immediate hold.
9	Missing ClinicalTrials.gov registration	Register trial and submit Form FDA 3674 before filing. Commonly forgotten.
10	Tox batch ≠ clinical batch (comparability gap)	Plan manufacturing timeline so tox and clinical use same process. Document any changes.

Key Regulatory Sources

DOCUMENT	WHAT IT COVERS	LINK
21 CFR 312	IND application rules — the law	eCFR
ICH M3(R2)	Which nonclinical studies by phase	ICH
ICH S7A	Safety pharmacology core battery	ICH
ICH S7B	QT prolongation / hERG testing	ICH
ICH S2(R1)	Genotoxicity testing strategy	ICH
ICH S5(R3)	Reproductive toxicology	ICH
FDA Phase 1 CMC	What CMC data is enough for Phase 1	FDA
FDA Starting Dose	First-in-human dose calculation	FDA
21 CFR Part 58	Good Laboratory Practice (GLP) requirements	eCFR