Required Periodic FDA Submissions for IND Sponsors and Sponsor-Investigators

Submission	Timing	Regulations	Details	Support Program Templates
Annual Report	60 days of the anniversary of the IND effective date	21 CFR 312.33 Annual Report	A sponsor shall submit a summary of the study status and progress, enrolled subjects' demographics, current subject status, summary of discontinued subjects, interim results, summary of all adverse events/safety reports, other study related updates.	Cover Letter, Annual Report
Change in Protocol*	Prior to implementation	21 CFR 312.30 Protocol Amendments	A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. *	Cover Letter, Summary of Changes
Informational Amendment**	As necessary but no more frequent than 30 days	21 CFR 312.31 Informational Amendments	A sponsor shall report any essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report.**	Cover Letter, Summary of Changes, FDA form 1572
IND Safety Report (1)***	ASAP within 15 calendar days from notification	21 CFR 312.32 FDA Guidance: Safety Reporting Requirements	A sponsor shall submit any serious and unexpected suspected adverse reactions (SUSAR), findings from other studies, findings from animal or in vitro testing.*** Sponsor must also notify all participating investigators and IND cross references of IND Safety Reports.	Cover Letter, FDA Form 3500A or Narrative
IND Safety Report (2)	ASAP within 7 calendar days from notification	21 CFR 312.32 Safety Reports	A sponsor shall submit any unexpected fatal or life-threatening suspected adverse reaction. Sponsor must also notify all participating investigators and cross references.	Cover Letter, FDA Form 3500A or Narrative
New Investigator	30 days of adding investigator	21 CFR 312.30	A sponsor shall submit notification of new investigators who will carry out a previously submitted protocol (exception: a treatment protocol under 312.315 or 312.320). Investigational drug may not be shipped and investigation may not begin prior to FDA notification.	Cover Letter, FDA Form 1572
New Protocol	Prior to implementation	21 CFR 312.30	A sponsor shall submit any new protocol that is not covered by a protocol already contained in the IND. IRB approval is also required prior to implementation.	Cover Letter
Protocol Closure	At time of annual report		A sponsor shall submit a final report for a protocol that has closed. Content of submission includes items required for the Annual Report 21 CFR 312.33.	Cover Letter, Final Report
Protocol Closure for Increased Risks	Promptly and no more than 5 working days	21 CFR 312.56(d)	A sponsor shall discontinue investigations and adhere to 21 CFR 312.38 as well as notify all investigators who have at any time participated in the investigation of the discontinuance, and furnish FDA with a full report of the sponsor's actions.	Cover Letter, Final Report
IND Withdrawal	Promptly if for safety reasons	21 CRF 312.38	A sponsor shall promptly inform FDA, participating investigators, all IRBs, and any IND cross referenced of reason for withdrawal and adhere to below requirements.	Cover Letter, Final Report
IND Withdrawal	Upon fulfilling IND requirements	21 CRF 312.38	All clinical investigations conducted under the IND shall be ended (*closed with IRB*), all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with 312.59. Cross referenced IND Sponsors should also be notified.	Cover Letter, Final Report

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* **Protocol Amendments**: The following are examples of amendments that must be submitted to the FDA prior to implementation:

(i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

** **Informational Amendments**: The following are examples of informational amendments:

(1) New toxicology, chemistry, or other technical information; or

(2) A report regarding the discontinuance of a clinical investigation.

*** **IND Safety Reports**: The following are examples of IND Safety Reports that require FDA reporting in 15 calendar days:

i. *SUSAR (Serious and unexpected suspected adverse reactions)*:

(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently or with greater severity in the drug treatment group than in a concurrent or historical control group.

ii) *Findings from other studies*.

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

(iii) *Findings from animal or in vitro testing*.

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

(iv) *Increased rate of occurrence of serious suspected adverse reactions*.

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

Gregory M Podsakoff, M.D.

Digitally signed by Gregory M Podsakoff, M.D.
DN: cn=Gregory M Podsakoff, M.D., o=Children's Hospital of Philadelphia, ou=IND-IDE Support Program, CRSO, email=podsakoff@chop.edu, c=US
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