SOPP 8206: Discontinuing Investigational and Related Applications (IRAs)

Version # 1

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1. Purpose

The purpose of this document is to describe the procedures and policies for Center for Biologics Evaluation and Research (CBER) staff to use for discontinuing Investigational and Related Applications (IRAs): Investigational New Drug Applications (INDs), Investigational Device Exemptions (IDEs), Master Files (MFs), and Emergency Use Authorizations (EUAs).

2. Definitions

- ***Cancelled***: An emergency IRA number was granted and the sponsor failed to submit the required forms, or the sponsor has notified CBER that the drug was never shipped. This status is also used for IRAs that would have otherwise been Voided except there were communications entered into the file.

- ***Closed:*** Applicable only to Master Files, this is equivalent to withdrawal of an IND.

- ***"Discontinued"***: This is a generic, non-regulatory term used in this SOPP to mean that the IND, IDE, MF, or EUA has a "final" action, i.e., Cancelled, Closed, Exempted, Terminated, Voided, or Withdrawn.

- ***Exempt***: An IND submission is not required to conduct the proposed studies, and FDA will not accept the IND for review (21 CFR 312.2(b).

- ***Inactivated***: At the request of the sponsor, or on FDA's initiative, the IND was placed in an inactive status because it had no subjects entered into clinical studies for 2 years or more, or it has been on HOLD for 1 year or more (21 CFR 312.45). The sponsor is not required to submit periodic reports on an Inactive IND. The IND may be reactivated by the sponsor by submission of a protocol amendment. *For purposes of this SOPP, this is not considered a discontinued status since it is not a final status for the IND.*

- ***Reactivated:*** At the request of the sponsor, and upon submission of required information [21 CFR 312.45(d)] an inactive IND is made "active." Upon receipt of the request, the status of the IND is changed to Pending or Hold/Partial Hold depending on what the status was before inactivation.

- ***Reinstated:*** If FDA terminates an IND because of an immediate danger [21 CFR 312.44(d)], FDA may reinstate the IND. This is the only circumstance by which an IND may be reinstated. Reinstatement changes the IND status to Active.

- ***Sponsor***: "The person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization" (21 CFR 312. 3). "Sponsor" for purposes of this document also includes IND sponsor-investigators (21 CFR 312.3), Master File holders (21 CFR 314.420), IDE sponsors or sponsor-investigators (21 CFR 812.3), and EUA applicants.

- ***Terminated***: The IND was *terminated* due to any of the reasons in 21 CFR 312.44, including if it was on Inactive status for 5 or more years (21 CFR 312.45 (e)). An IND can not be *terminated* unless a pre-termination letter is sent. "*Terminated - EUA*" for EUAs means the emergency has been terminated; the EUA is not considered discontinued.

- ***Voided***: The IRA number was assigned to a submission erroneously and it was not caught in time to use the number for another IRA. Examples would include where an amendment is inadvertently logged in as an original submission, or the document was never intended to be any kind of an IRA submission. Another use of VOIDED is if the IRA was sent to CBER by mistake, i.e., the product is under the jurisdiction of the Center for Drug Evaluation and Research (CDER) or the Center for Devices and Radiological Health (CDRH).

- ***Withdrawn***: The sponsor has requested that their EUA, IND or IDE be Withdrawn, because the studies are complete, they are not showing effectiveness, there has been a safety issue, or other reasons, and FDA has acknowledged the withdrawal (21 CFR 312.38 – for INDs; there is no corresponding IDE or EUA regulation). *Note that this is not the same as withdrawal of approval of an IDE (21 CFR 812.30(c)), which is an FDA initiated action.*

3. Background

The process for discontinuing IRAs varies depending on the application type and governing regulations. The regulations aren't always clear or comprehensive enough in this regard, so policies are necessary to fill the gaps. This SOPP establishes those policies, and details the procedures for discontinuing IRAs.

4. Policy

IRAs that are left active when in fact they should be discontinued cause unnecessary administrative work and distort CBER's workload picture. CBER will rigorously manage IRAs to assure that they are discontinued appropriately and promptly.

5. Responsibilities

The application review offices (Office of Blood Research and Review [OBRR], Office of Compliance and Biologics Quality [OCBQ], Office of Cellular, Tissue, and Gene Therapies [OCTGT], and Office of Vaccine Research and Review [OVRR]) are responsible for managing their assigned IRA files, including requesting overdue periodic reports from sponsors and following up to discontinue the IRAs when appropriate.

Once the status has been changed to one that is discontinued, it is the Document Control Center‘s (DCC’s) responsibility to assure proper storage and, ultimately, disposition of the IRA file.

6. Procedures

The process of discontinuing an IRA may be initiated in response to a request from the sponsor, as a result of failure to submit required periodic reports, or because of a safety issue.

Discontinuance of an IRA is documented by a letter to the sponsor, a telecon summary, or a memorandum to the file.

The chart below summarizes the processes and communication requirements for discontinuing the various types of IRAs. When the appropriate communication type (telecon, letter, etc.) and category are entered in CBER’s Biologics Investigational and Related Applications Management System (BIRAMS) and the record saved, the system will automatically update the status of the IRA (except for ***Voided*** IRAs where the Regulatory Information Management Staff [RIMS] will update the status).

IRA Type	Annual Report Required?	Discontinued Status(es)	BIRAMS Communication Required to Change to a Discontinued Status
IND	Yes – 21 CFR 312.33 (unless Inactive – 312.45)	***Emergency Use Denied***	Telecon
IND	Yes – 21 CFR 312.33 (unless Inactive – 312.45)	***Exempt***	Letter or Telecon
IND	Yes – 21 CFR 312.33 (unless Inactive – 312.45)	***Withdrawn***	Letter or Memo to File (only if the sponsor’s whereabouts are unknown, or this is an Old Action – see below under special situations)
IND	Yes – 21 CFR 312.33 (unless Inactive – 312.45)	***Voided***	RIMS sets manually, and adds a note in Comments Field in the Original Submission screen on why and when the IND was ***Voided***.
IND	Yes – 21 CFR 312.33 (unless Inactive – 312.45)	***Cancelled***	Letter or Telecon (for emergency IND) or Memo to File

IRA Type	Annual Report Required?	Discontinued Status(es)	BIRAMS Communication Required to Change to a Discontinued Status
IND	Yes – 21 CFR 312.33 (unless Inactive – 312.45)	***Terminated***	Letter (a Pre-termination letter must precede) or Memo to File (only if the sponsor's current whereabouts are unknown, i.e., the required pre-termination letter has been returned, AND only if the termination is for failure to submit progress reports).
IDE	Yes – 21 CFR 812.150(b)(5)	***Exempt***	Letter or Telecon
IDE	Yes – 21 CFR 812.150(b)(5)	***Voided***	RIMS sets manually, and adds a note in Comments Field in the Original Submission screen on why and when the IDE was ***Voided***.
IDE	Yes – 21 CFR 812.150(b)(5)	***Cancelled***	Memo to the File
IDE	Yes – 21 CFR 812.150(b)(5)	***Withdrawn***	Letter or Memo to the File
MF	No – but requested in CDER's 1989 Guideline for Drug Master File	***Closed***	Letter or Memo to the File (only if the MF holder's current whereabouts are unknown).
MF	No – but requested in CDER's 1989 Guideline for Drug Master File	***Voided***	RIMS sets manually, and adds a note in Comments Field in the Original Submission screen on why and when the MF was ***Voided***.
EUA	No – but authorization expires in one year automatically.	***Voided***	RIMS sets manually, and adds a note in Comments Field in the Original Submission screen on why and when the EUA was ***Voided***.
EUA	No – but authorization expires in one year automatically	***Withdrawn***	Letter or Memo to the File (only if the applicant's current whereabouts are unknown)

The following are procedures for handling special situations with regard to discontinuing IRAs.

Special Cases	Situation	Applies to:	Procedure
Missing Sponsor	A letter sent to an IRA sponsor's contact is returned by the Postal Service indicating that the addressee is no longer at that address, and no forwarding address is available.	INDs	If the contact person is the sponsor, the RPM should call the institution to which the letter was sent to find out, if possible, where the sponsor has moved to. It should also be clarified during the telephone call that the clinical study(s) had not continued at that institution after the departure of the sponsor. If the contact person is different from the sponsor, the sponsor should be contacted to determine who the new contact person is, and where the communication should be sent. If a new address is obtained, the letter should be revised appropriately and sent out again. If a new address can not be obtained, it may be appropriate to contact the manufacturer of the investigational product to find out if they are continuing to supply the sponsor, and if so, where it is being sent. If the whereabouts of the sponsor still can not be determined, the undeliverable letter and the envelope should be placed in the IND file along with a memorandum documenting the efforts to contact the sponsor, and terminating the IND for failure to submit progress reports (assuming none has been submitted for more than a year) effective on the date of the memorandum
Missing Sponsor	A letter sent to an IRA sponsor's contact is returned by the Postal Service indicating that the addressee is no longer at that address, and no forwarding address is available.	IDEs	The procedure is the same for IDEs and for INDs, except the memorandum should be created with a ***Withdrawn*** category instead of ***Terminated***.

Special Cases	Situation	Applies to:	Procedure
Missing Sponsor	A letter sent to an IRA sponsor's contact is returned by the Postal Service indicating that the addressee is no longer at that address, and no forwarding address is available.	MFs	If the contact person is the sponsor, the RPM should call the institution to which the letter was sent to find out, if possible, where the sponsor has moved to. It should also be clarified during the telephone call that the clinical study(s) had not continued at that institution after the departure of the sponsor. If the contact person is different from the sponsor, the sponsor should be contacted to determine who the new contact person is, and where the communication should be sent. If a new address is obtained, the letter should be revised appropriately and sent out again. If the whereabouts of the sponsor still can not be determined, the undeliverable letter and the envelope should be placed in the MF file along with a memorandum documenting the efforts to contact the sponsor and the memorandum is filed. The file status is automatically changed to ***Closed*** via the memorandum category of ***Closed***. Whenever a MF is ***Closed***, there should be a cross check for any active IRAs that may still be referencing the file.

Special Cases	Situation	Applies to:	Procedure
Missing Sponsor	A letter sent to an IRA sponsor's contact is returned by the Postal Service indicating that the addressee is no longer at that address, and no forwarding address is available.	EUAs	If the contact person is the sponsor, the RPM should call the institution to which the letter was sent to find out, if possible, where the sponsor has moved to. It should also be clarified during the telephone call that the clinical study(s) had not continued at that institution after the departure of the sponsor. If the contact person is different from the sponsor, the sponsor should be contacted to determine who the new contact person is, and where the communication should be sent. If a new address is obtained, the letter should be revised appropriately and sent out again. If the whereabouts of the sponsor still can not be determined, the undeliverable letter and the envelope should be placed in the EUA file along with a memorandum documenting the efforts to contact the sponsor and the memorandum is filed. The file status is automatically changed to ***Withdrawn*** via the memorandum category of ***Withdrawn***.

Special Cases	Situation	Applies to:	Procedure
Sponsor Death	CBER is notified by an amendment to an IND or IDE or by a returned letter that a sponsor has died.	INDs	If a sponsor of an active IND dies, the IND is no longer in effect/approved. When the Center is notified of the death of the sponsor, the institution where the sponsor was conducting the studies should be contacted to determine the status of the studies. If the studies are ongoing under a co-investigator and the co-investigator wishes to continue the studies, a new, complete IND must be submitted by the new sponsor. The old IND can not be referenced since no one has authority to permit it. In cases where the studies are ongoing, the appropriate reviewer(s) will have to make a decision as to whether the studies may continue pending receipt of the new IND (i.e., essentially granting an "emergency" IND). If it is determined that no studies have continued after the sponsor's death, the IND should be ***Terminated*** for failure to submit progress reports via a memorandum to the file.
Sponsor Death	CBER is notified by an amendment to an IND or IDE or by a returned letter that a sponsor has died.	IDEs	The procedure is the same as for INDs, except the IDE should be ***Withdrawn*** rather than ***Terminated***.
Sponsor Death	CBER is notified by an amendment to an IND or IDE or by a returned letter that a sponsor has died.	MFs	The procedure is the same as for INDs, except the MF should be ***Closed*** rather than ***Terminated***. Whenever a MF is ***Closed***, there should be a cross check for any active IRAs that may still be referencing the file.
Sponsor Death	CBER is notified by an amendment to an IND or IDE or by a returned letter that a sponsor has died.	EUAs	The procedure is the same as for INDs, except the EUA should be ***Withdrawn*** rather than ***Terminated***.

Special Cases	Situation	Applies to:	Procedure
Sponsor out of Business	CBER is notified (usually by returned letter) that the Sponsor or MF Holder has gone out of business, or the institution is defunct	INDs	An attempt should be made to determine whether anyone else has acquired the rights to the IND. If so, that person, company, or institution should be contacted about the status of the IND. If it appears after reasonable checking that no one has the rights to the IND, and it is not likely that any studies are continuing, a ***Termination*** for failure to submit progress reports memo should sent to the file to discontinue the IND.
Sponsor out of Business	CBER is notified (usually by returned letter) that the Sponsor or MF Holder has gone out of business, or the institution is defunct	IDEs	The procedure is the same as for INDs, except the memorandum to the file should use the category of ***Withdrawn*** rather than ***Terminated***
Sponsor out of Business	CBER is notified (usually by returned letter) that the Sponsor or MF Holder has gone out of business, or the institution is defunct	MFs	The procedure is the same as for INDs except the memorandum to the file should be ***Closed*** instead of ***Terminated***. Whenever a MF is ***Closed***, there should be a cross check for any active IRAs that may still be referencing the file.
Sponsor out of Business	CBER is notified (usually by returned letter) that the Sponsor or MF Holder has gone out of business, or the institution is defunct	EUAs	The procedure is the same as for INDs except the memorandum to the file should be ***Withdrawn*** instead of ***Terminated***.
Old Actions	It is discovered that a request for inactivation (IND), withdrawal (IND or IDE) or closure (MF) which came in to CBER several years ago was never acted on.	INDs	For INDs where the sponsor has requested or agreed to inactivation/withdrawal, more than two years ago, a memorandum to the file indicating the date of inactivation/withdrawal (using the date FDA received the request) is sufficient to complete the action, i.e., it isn't necessary to send an inactivation/withdrawal acknowledgement letter to the sponsor. However, if there is any doubt as to the sponsor's intention, the sponsor should be called.

Special Cases	Situation	Applies to:	Procedure
Old Actions	It is discovered that a request for inactivation (IND), withdrawal (IND or IDE) or closure (MF) which came in to CBER several years ago was never acted on.	IDEs	The procedure is the same as for INDs, except it applies to requests for withdrawals only.
Old Actions	It is discovered that a request for inactivation (IND), withdrawal (IND or IDE) or closure (MF) which came in to CBER several years ago was never acted on.	MFs	The procedure in the same as for INDs, except it applies to closures only. Whenever a MF is ***Closed***, there should be a cross check for any active IRAs that may still be referencing the file.
Old Actions	It is discovered that a request for inactivation (IND), withdrawal (IND or IDE) or closure (MF) which came in to CBER several years ago was never acted on.	EUAs	The procedure is the same as for INDs, except it applies to requests for withdrawals only.

Special Cases	Situation	Applies to:	Procedure
Reinstatement	A sponsor has requested reinstatement of their IND	INDs	***Terminated*** INDs may be reinstated, but only when the IND was ***Terminated*** under 312.44(d) because of an immediate danger. All other terminations are permanent, and clinical studies may be resumed again only upon the submission of a new IND. For this reason, it is especially important that every effort be made to assure that the sponsor is aware that termination of his/her IND is in progress. ***Withdrawn*** INDs, or INDs ***Terminated*** for failure to submit progress reports should not be reinstated; a new IND should be submitted by the sponsor. If a sponsor makes the request to "reinstate" an IND immediately after the withdrawal or termination of the IND (e.g., the withdrawal/termination was not actually intended by the sponsor), the status of the IND should be returned to what it was before the withdrawal/termination, i.e., the ***Withdrawn*** status should be deleted and an explanation entered in the comments for the communication to the sponsor acknowledging the status reversion.
Reinstatement	A sponsor has requested reinstatement of their IND	IDEs	IDEs are not ***terminated***. ***Withdrawn*** IDEs should not be reinstated; a new IDE should be submitted by the sponsor. If a sponsor makes the request to "reinstate" an IDE immediately after the withdrawal (e.g., the withdrawal was not actually intended by the sponsor), the status of the IDE should be returned to what it was before the withdrawal, i.e., the ***Withdrawn*** status should be deleted and an explanation entered in the comments for the communication to the sponsor acknowledging the status reversion.

Special Cases	Situation	Applies to:	Procedure
Reactivation	A sponsor has requested reactivation of their IND	INDs	Inactivated INDs may be reactivated by the sponsor, but only after certain required information is submitted [312.45(d)]. A letter acknowledging the action should be sent.
Referencing Discontinued IRAs	A sponsor references a discontinued IRA.	INDs, IDEs, MFs, EUAs	Sponsors may not reference discontinued IRAs. This is because the sponsor of the non-active application has no obligation to submit reports or to update the file. *Sponsors may reference an inactivated IND only if the sponsor of the referenced IND reactivates that application.*

7. References

Guideline for Drug Master Files; CDER; September 1989

8. History

Written/Revised	Approved	Approval Date	Version Number	Comment
Roger Eastep RMCC	Robert Yetter	March 12, 2008	1	First Version

9. Effective Date

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