National Institute of Allergy and Infectious Diseases / Division of Microbiology and Infectious Diseases/ Office of Regulatory Affairs	Work Instruction **Process for Temperature Excursions**
No: ORA - WI – 004 Effective date: 16-July-2012	Version: 1.0

1.0 Purpose:

To describe the procedures pertaining to temperature excursions for products associated with Division of Microbiology and Infectious Diseases (DMID) - supported clinical trials

2.0 Scope: This Work Instruction (WI) pertains to:

2.1. DMID, Office of Regulatory Affairs (ORA), and Program staff who manage DMID-supported clinical trials.

2.2. The DMID Regulatory Affairs Contractor (RAC) and Clinical Agent Repository (CAR).

2.3. DMID-supported clinical trials.

3.0 Background:

The ICH Guideline for Good Clinical Practice (E6) states that "the sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations. Further sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s))" [Section 5.13.2 and 15.14.3].

DMID clinical protocols / Manual of Procedures (MOP) state the storage conditions (including the temperature requirements) under which the study product should be stored in an effort to preserve the quality, strength, purity and identity of the product. These conditions are determined via controlled studies, and are either supported by the label for licensed product or by the stability data (based on the manufacturer's specifications) for an investigational product. The study products must be transported, handled and stored in a manner that ensures that the temperature requirements defined in the protocol/MOP can be maintained. Excursions from the pre-defined temperature range may not only affect study product performance and stability, but also impact trial participants' safety.

When temperature excursions occur, the clinical site should quarantine the study product from clinical use and investigate the root cause. DMID Product Support Team (PST) will assess the details of the temperature excursion and decide if the product is acceptable for use or it should be returned or destroyed. The PST makes this assessment using stability data and recommendations provided by the manufacturer. The PST's role is to obtain and file the appropriate information; and to make a final decision based on the manufacturer's feedback.

This WI addresses communication channels and proper documentation needed to resolve a temperature excursion situation.

4.0 Definitions:

Product: A product is defined by DMID as any drug, biologic, device, or combination product that is provided for the study or identified in the protocol as a study product, including any diluents or placebos provided for use during the study.

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial as well as provides the background and rationale for the trial

Temperature Excursion: A documented event whereby a clinical product is shipped or stored at a temperature outside of its temperature range as defined in the protocol/MOP. A temperature excursion may occur in transit, at the repository, or at the site.

Quarantine: Effective restriction of the availability product for use until released.

5.0 Responsibilities:

Role	Responsibility
DMID Clinical Project Manager	• Notifies DMID Product Support Team of temperature excursions • Notifies the site of Temperature excursion status
DMID Product Support team	• Serves as POC for the initial temperature excursion information • Logs Temperature excursion information • Reviews temperature excursion • Notifies the CAR of the temperature excursion • Contacts the manufacturer for recommendation regarding the temperature excursion • Maintains temperature excursion documentation • Provides manufacturer recommendation memos to the CAR when requested • Executes product disposition plan if needed as a result of the temperature excursion
Clinical Agent Repository	• Communicates temperature excursions that occur at the CAR or in transit to the CAR • Quarantines products
Clinical Site	• Communicates temperature excursion • Provides supporting documentation for temperature excursion • Quarantines products

6.0 Implementation/Procedures:

6.1 If a temperature excursion occurs at the site, or in transit to the site:

6.1.1 The site will contact the DMID Product Support Team (PST) with the details of the temperature excursion including:

- Highest or lowest temperature recorded during the excursion. DMID uses the temperature ranges in whole numbers as specified in the USP. As such, any temperature recording requiring the PST assessment will be rounded to the nearest whole number.
- Length of time that the excursion occurred
- Any temperature monitoring data and/or supporting information

6.1.2 The site will quarantine the product until the temperature excursion is resolved and product disposition is confirmed.

6.1.3 The PST will serve as the POC for the temperature excursion.

6.1.4 The PST notifies the CPM of the temperature excursion if he/she hasn't been notified by the site, with a copy to other appropriate Program staff as per discussion with Program.

6.1.4.1 If the site has notified the CPM and provided temperature excursion information, the CPM should provide such information to the PST, as well as the contact information of the manufacturer.

6.1.5 The PST reviews the temperature excursion information and may make a decision based on known stability data or a previous temperature excursion.

6.1.5.1 The PST may consult Regulatory Affairs Specialists or other Program Points of Contact (POCs) who are involved in product development and support, if needed, to make a decision.

6.1.6 If sufficient information is not available to make a recommendation, the PST contacts the manufacturer in order to determine if the product has adequate stability data to support continued use of the product after the excursion.

6.1.6.1 The manufacturer may provide product specific forms to the PST, who in turn forwards these to the site (copies the CPM) with instructions for completion.

6.1.6.2 The site completes the forms and sends back to the PST for forwarding to the manufacturer.

6.1.6.3 The PST will request written documentation from the manufacturer in order to close-out the temperature excursion. The written documentation indicates if the product is still suitable for use or not based on available stability data.

6.1.7 The PST should send the original copy of the documentation to the site or the CAR, depending on where the excursion occurred. If the decision is made without contacting the manufacturer as outlined in step 6.1.5, the PST should include the source of the stability data or the date of the previous temperature excursion.

6.1.7.1 If the product is deemed unacceptable based on the temperature excursion, the PST will recommend disposition and re-ordering of the product if

needed (See DMID-ORA-009 Process for Investigational Disposition at the Clinical Reagent Repository).

6.1.7.2 If the product is deemed acceptable based on the evidence investigated for the temperature excursion, the product will be released from quarantine

6.1.8 The PST uploads all temperature excursion related documents to the appropriate branch folder under ORA Product Management in equationASP including:

- Emails or Documents containing temperature excursion information
- Manufacturer recommendation
- Product-specific clinical complaint forms from the manufacturer

6.1.9 The PST logs the temperature excursion information in the Temperature Excursion Log (see attachment A as an example), including site name, protocol, dates, CPM, and outcome.

6.2 If an excursion occurs at the CAR or in transit to the CAR, the CAR will quarantine the product and contact the PST with information about the temperature excursion. The PST will follow the process above.

7.0 References:

7.1 U.S. Code of Federal Regulations 21 CFR 312: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

7.2 U.S. Code of Federal Regulations 21 CFR 812: "Investigational Device Exemptions": http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812

7.3 International Conference on Harmonisation E6, Section 6: "Good Clinical Practice: Clinical Trial Protocol and Protocol Amendments": http://www.ich.org/LOB/media/MEDIA482.pdf

7.4 DMID Standards and Guidelines for Clinical Study Product Management

8.0 Inquiries:

DMID Product Support Team
Office of Regulatory Affairs
DMID/NIAID/NIH
DMIDProductSupportTeam@niaid.nih.gov

9.0 Availability:

This document is available electronically by way of:

DMID internet:
(http://www.niaid.nih.gov/labsandresources/resources/dmidclinrsrch/Pages/investigational.aspx)

10.0 Attachments:

Attachment A: Temperature Excursion Log Example

11.0 Change Summary:

Version number	Date of Revision: DD/MMM/YYYY	Replaces	Effective Date: DD/MMM/YYYY	Description of Revision/Retirement
1.0	N/A	N/A	16-July-2012	N/A

Attachment A:

Temperature Excursion Log

ID	Protocol No.	Issue Type	Site	Location of Issue	Manufacturer	Product	Product Opened date	Status	Priority	Description	Last Action	Last Action Date	DMID Contact, CPM or other	Stability Note
1	10-1014	Temperature Excursion	University A	Site	Pharm X	Antiviral X	1-Jun-10	Closed	High	12 hours of undocumented temp tracking	Pharm x rejected product	14-Jun-11	Mary Smith	
2	11-1015	Temperature Excursion	University A	Site	Pharm B	antiviral Z	2 Feb-11	Resolved	High	12 hours of undocumented temp tracking	Pharm b sent memo to Fisher	9-Mar-11	Jane Doe	
3	11-1015	Local Transport cold chain	University B	Site	Pharm B	antiviral Z	5-Feb-11	Closed	Normal	15 minutes transport without probe	Sent DMID recommendation to DMID pharmacist	10-Feb-11	DMID Pharmacist	
4	12-1000	Temperature Excursion	Primary Physician Research Group	Transit	Pharm K	Antibody B	6-Jan-12	Resolved	Normal	temperature reached 8.3° for 1 hr 35 min	Contacted Pharm K- Pharm K sent instructions	9-Jan-12	Jim Anders	8-25°for 72 hrs