Updates to the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks

(Revision date August 2023)

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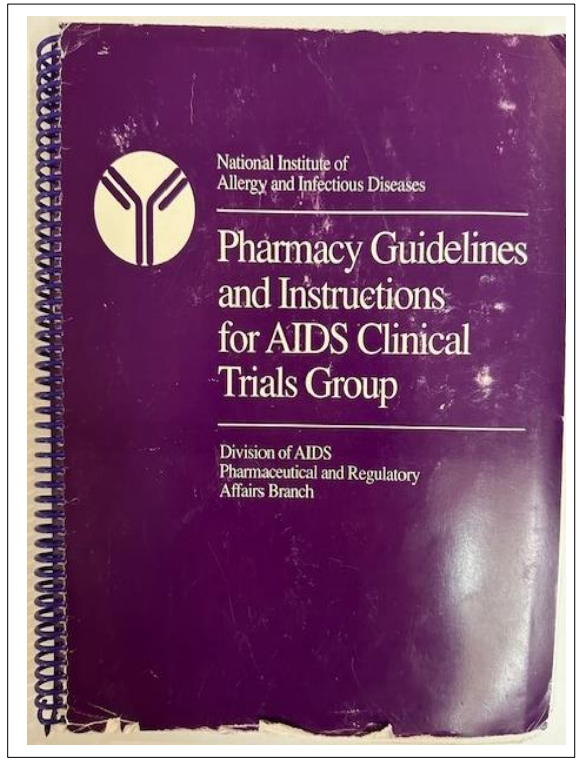
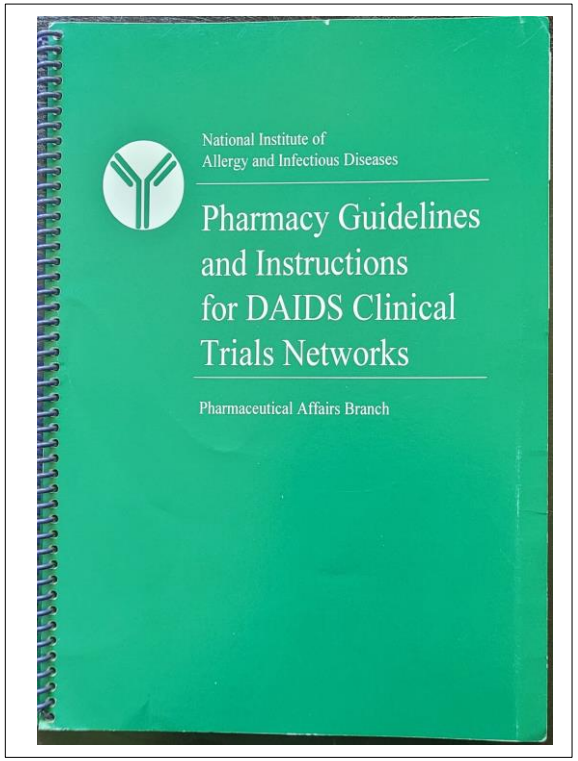
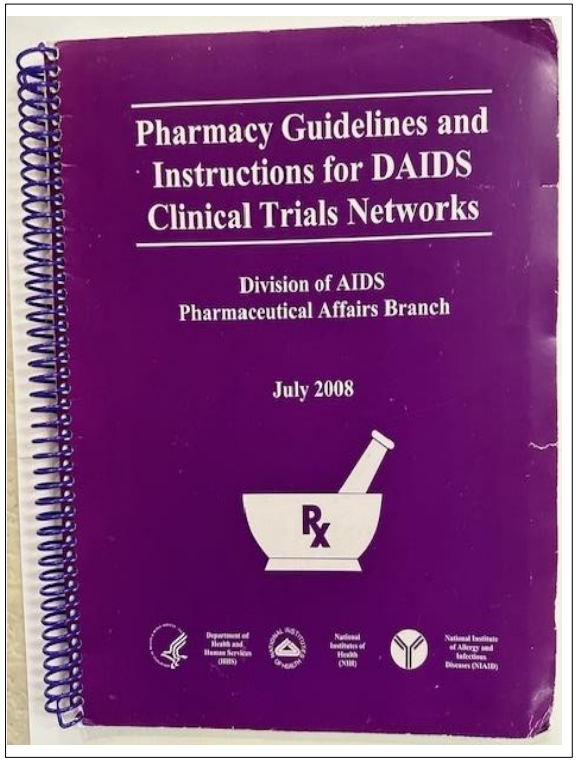
DAIDS Pharmaceutical Affairs Branch (PAB)

Office of Clinical Site Oversight (OCSO)

History of the Publication of the Pharmacy Guidelines





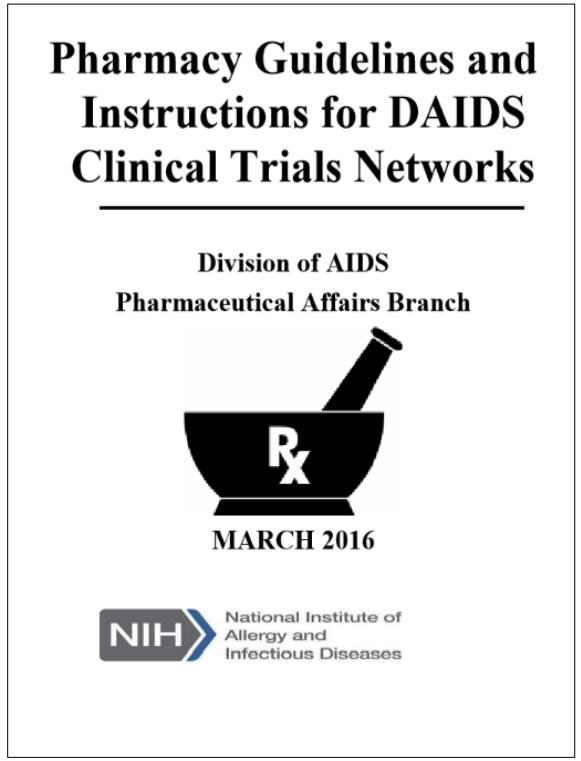


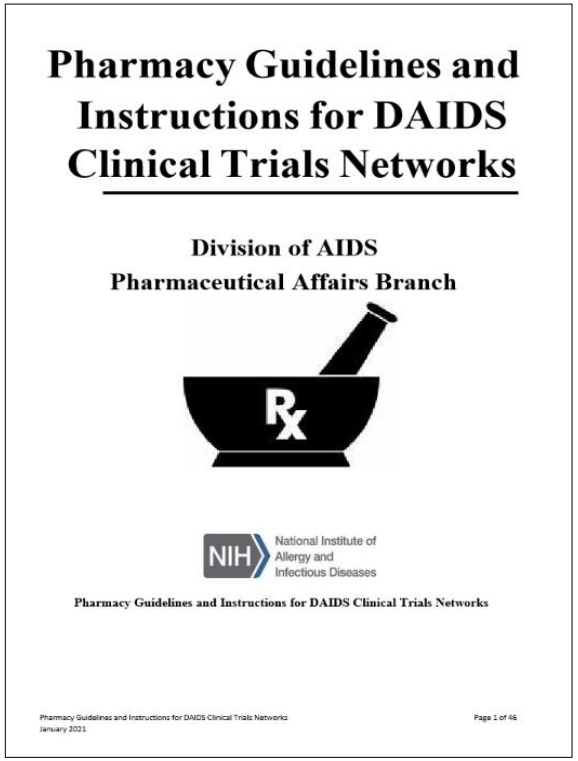
1997

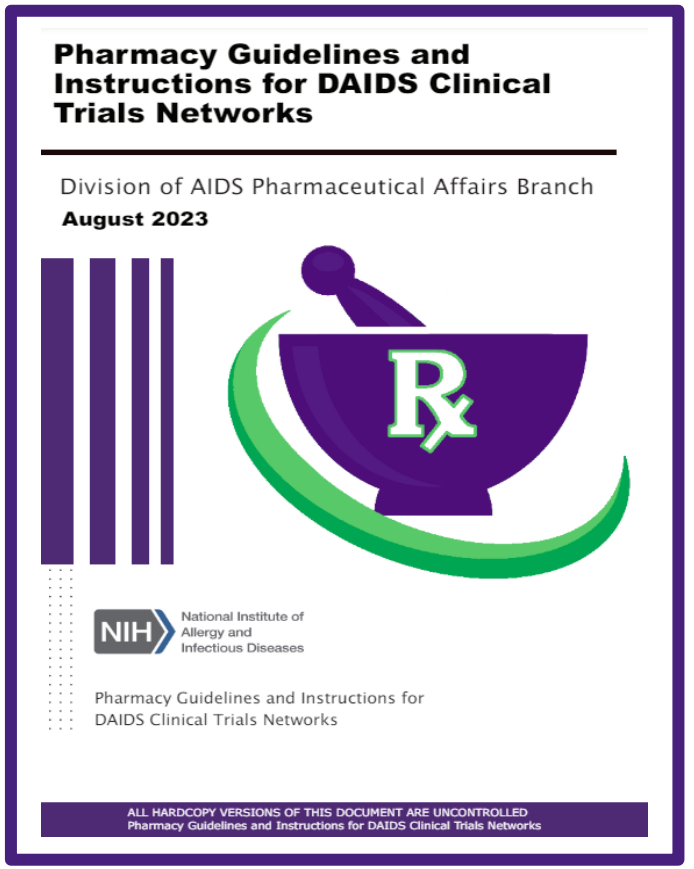
2002

2008

History of the Publication of the Pharmacy Guidelines







2016

2021

2023

Presentation Key

2021 Guidelines

- Text from the 2021 Guidelines will be displayed in a white box with black outline
- A Strikethrough will be used to show text that was removed when the Guidelines were revised in 2023:
  - ~~Example~~

2023 Guidelines

- New text from the 2023 Guidelines will be displayed in a light gray box with dark purple outline
- New text will be shown in **bold**

SECTION 1

GLOSSARY

United States Pharmacopeia/National Formulary (USP/NF) definitions were updated for consistency with current USP/NF definitions:

2021 Guidelines:

Room Temperature - The temperature prevailing in a working area.

2023 Guidelines:

Room Temperature – (also referred to as Ambient temperature): The temperature prevailing in a working environment.

SECTION 1

GLOSSARY

United States Pharmacopeia/National Formulary (USP/NF) definitions were updated for consistency with current USP/NF definitions:

2021 Guidelines:

Controlled Room Temperature – ... The following conditions also apply. Mean kinetic temperature not to exceed 25°C. Excursions between 15° and 30°C (59° and 86° F) that are ~~experienced in pharmacies, hospitals, and warehouses, and during shipping are~~ allowed. Provided the mean kinetic temperature does not exceed 25°C, transient spikes up to 40°C are permitted as long as they do not exceed 24 hours. ~~Spikes above 40°C may be permitted only if the manufacturer so instructs~~…

2023 Guidelines:

Controlled Room Temperature – ... Mean kinetic temperature (MKT) may be used during an excursion provided:
1) MKT does not exceed 25°C (77°F); 2) excursion between 15° and 30°C (59° and 86°F); 3) transient excursions are not more than 40°C (104°F); and 4) excursion time is not more than 24 hours. These limits (time and temperature) and the calculated MKT must be documented. Articles may be labeled for storage at "controlled room temperature" or at "20°–25°C", or other wording based on the same MKT…

SECTION 2

PHARMACEUTICAL AFFAIRS BRANCH

No significant changes

SECTION 3

RESPONSIBILITIES OF THE PHARMACIST OF RECORD

I. Professional

II. Oversight of Pharmacy Facilities

III. Administrative

I. PROFESSIONAL

A Training

vi **Supervision and Training of Pharmacy Staff**

2021 Guidelines:

…Training records must include the protocol version or the associated protocol-specific or site-specific document version number.

2023 Guidelines:

…Training records must include the protocol version or associated protocol-specific or site-specific document version number, **as well as, name of the trainer, training method, name and signature/initials of the trainees and training date**.

SECTION 3

RESPONSIBILITIES OF THE PHARMACIST OF RECORD

I. Professional

II. Oversight of Pharmacy Facilities

III. Administrative

II. OVERSIGHT OF PHARMACY FACILITIES

D Storage and Temperature Monitoring

ii Refrigerator and Freezer Storage of Study Products

2021 Guidelines:

The pharmacy refrigerator(s) and freezer(s) must be:

- Of adequate size and sufficient capacity for the storage and segregation of study products
- Kept in a clean and sanitary condition
- Maintained in good working order
- Capable of maintaining temperatures within the specified storage temperature range setting.

2023 Guidelines:

The pharmacy refrigerator(s) and freezer(s) must be:

- **Placed in a well-ventilated room, leaving space between the unit, ceiling, and any wall with nothing blocking the cover of the motor compartment.**
- **Equipped with a door that opens and closes smoothly and fits squarely against the body of the unit.**
- Of adequate size and sufficient capacity for the storage and separation of study products
- Kept in a clean and sanitary condition
- Maintained in good working order
- Capable of maintaining temperatures within the specified storage temperature range setting.

II. OVERSIGHT OF PHARMACY FACILITIES

E Temperature Quality Management System

i Daily Manual Temperature Monitoring and Daily Temperature Log

2021 Guidelines:

The device used for the daily manual temperature monitoring must have the capability of capturing the current temperature, and minimum and maximum temperature memory. A daily temperature monitoring log is required to manually record:

- ~~Current Temperature~~
- Minimum and maximum temperatures
- Date
- Time
- Name/Initials of person who checked and recorded the temperature
- Any actions taken if a temperature excursion occurred
- If a reading is missed, leave a blank entry in the log and add a comment as to why the reading is missing

2023 Guidelines:

The device used for the daily manual temperature monitoring must have the capability of capturing the current temperature, and minimum and maximum temperature memory. A daily temperature monitoring log is required to manually record:

- Minimum and maximum temperatures
- Date
- Time
- Name/Initials of person who checked and recorded the temperature
- Any actions taken if a temperature excursion occurred
- If a reading is missed, leave a blank entry in the log and add a comment as to why the reading is missing

II. OVERSIGHT OF PHARMACY FACILITIES

E Temperature Quality Management System

ii Continuous Temperature Monitoring and Recording

2021 Guidelines:

An electronic temperature data logger is a device that records temperatures at programmed time intervals, and should be set, ideally, with a maximum interval of ~~15 minutes~~ with more frequent recording desirable…

2023 Guidelines:

An electronic temperature data logger is a device that records temperatures at programmed time intervals, and should be set, ideally, with a maximum interval of **30 minutes** with more frequent recording desirable…

II. OVERSIGHT OF PHARMACY FACILITIES

E Temperature Quality Management System

v Temperature Deviations/Excursions Reporting and Quarantine

<u>NEW</u> 2023 Guidelines:

The PoR is required to demonstrate oversight of the temperature excursion reporting process for both permitted and non-permitted excursions. To ensure inspection readiness and demonstration of appropriate and documented oversight, both types of excursions must be reported to the Sponsor.

The PoR is responsible for ensuring that the study product is maintained at the protocol-specified, long-term temperature storage range to preserve the integrity, stability, and effectiveness of study products for each protocol (See Storage and Temperature Monitoring Section). A temperature deviation/excursion indicates a temperature reading that is outside of the specified long term temperature storage range.

II. OVERSIGHT OF PHARMACY FACILITIES

E Temperature Quality Management System

v Temperature Deviations/Excursions Reporting and Quarantine

2021 Guidelines:

When study products experience a temperature deviation or excursion, (outside the range permitted by the protocol), the study product should be immediately quarantined at the appropriate storage temperature, and the occurrence reported directly to the CRPMC, copying the PAB Protocol Pharmacist, using the DAIDS PAB Temperature Excursion Reporting Form (TERF). The PoR should await final disposition instructions from the CRPMC. The CRPMC will adjudicate the reported temperature excursion and communicate study product suitability to the CRS pharmacy.

2023 Guidelines:

When study products experience a **non-permitted** temperature deviation or excursion (outside of the range permitted by the protocol), the study product should be immediately quarantined at the appropriate storage temperature, and the occurrence reported directly to the CRPMC, copying the PAB Protocol Pharmacist, using the DAIDS PAB Temperature Excursion Reporting Form (TERF). The PoR should await final disposition instructions from the CRPMC. The CRPMC will adjudicate the reported temperature excursion and communicate study product suitability **to the PoR**.

The DAIDS uses the temperature ranges in whole numbers as specified in the USP (see Glossary of Terms Section for USP Storage Conditions Definitions). As such, any temperature recording requiring the CRPMC adjudication will be rounded to the nearest whole number.

FREQUENTLY ASKED QUESTION

Q **For study product required to be stored at 15°C to 25°C, a temperature of 25.1°C will round to 25°C and is within range for 15°C to 25°C. Is a TERF required to be submitted to the CRPMC?**

A Per the Pharmacy Guidelines "DAIDS uses the temperature ranges in whole numbers as specified in the USP (see Glossary of Terms Section for USP Storage Conditions Definitions). As such, any temperature recording requiring the CRPMC adjudication will be rounded to the nearest whole number."

- If after rounding, the rounded number is within the acceptable temperature range, no temperature excursion reporting is required.
- If after rounding, the rounded number is not within the acceptable temperature range, the temperature excursion must be reported to the CRPMC using the TERF.

II. OVERSIGHT OF PHARMACY FACILITIES

E Temperature Quality Management System

v Temperature Deviations/Excursions Reporting and Quarantine

2021 Guidelines:

Controlled Room Temperature Excursion - If the study protocol states store between 20˚C and 25˚C with excursions permitted within 15˚C and 30˚C (59˚F and 86˚F), the temperature excursion must be reported to the CRPMC using the TERF. The study product may remain in active inventory and dispensed to study participants.

2023 Guidelines:

Added information about controlled room temperature permitted and non-permitted excursions and the reporting of these excursions.

See new text in upcoming slides.

II. OVERSIGHT OF PHARMACY FACILITIES

E Temperature Quality Management System

v Temperature Deviations/Excursions Reporting and Quarantine

<u>NEW</u> 2023 Guidelines:

Controlled Room Temperature Permitted and Non-Permitted Excursions:

- If the study protocol states "*store between 20°C and 25°C, with excursions permitted within 15°C and 30°C (59°F and 86°F)*", temperature excursions occurring ***<u>below 15°C</u>*** or ***<u>above 30°C</u>*** must be reported to the CRPMC as non-permitted excursions.

- If the study protocol states store "*at 25°C, with excursions permitted within 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]*" or similar language referencing USP Controlled Room Temperature, the study product may be stored between 20°C and 25°C, with excursions permitted within 15°C and 30°C (59°F and 86°F). Temperature excursions occurring ***<u>below 15°C</u>*** or ***<u>above 30°C</u>*** must be reported to the CRPMC as non-permitted excursions.

II. OVERSIGHT OF PHARMACY FACILITIES

E Temperature Quality Management System

v Temperature Deviations/Excursions Reporting and Quarantine

<u>NEW</u> 2023 Guidelines:

Controlled Room Temperature Permitted and Non-Permitted Excursions:

- Any controlled room temperature excursion that occurs ***<u>within</u>*** the study protocol-specified, permitted temperature excursion window of *15°C and 30°C (59°F and 86°F)*, must be reported as a permitted excursion to the CRPMC using the TERF, however, **the study product may remain in active inventory and dispensed to study participants**. Reporting of these permitted excursions may occur upon identification or may be consolidated and reported upon regular review (at least monthly) of continuous temperature monitoring data.

- Note: Protocol-specified, permitted controlled room temperature excursions facilitate continued use of study products; however, they are still excursions outside of the long-term storage temperature range and must be reported to the Sponsor.

FREQUENTLY ASKED QUESTION

Q **Why do we need to report CRT excursions if they are permitted excursions?**

A An excursion indicates a temperature that is outside of the specified long term temperature storage range. As part of DAIDS Sponsor responsibilities for our clinical trials, we are required to show oversight of the temperature excursion reporting process for both permitted and non-permitted excursions. In the event of a regulatory inspection, to demonstrate appropriate and documented site and Sponsor oversight, sites are required to report both types of excursions. The permitted excursion allows for continued use of the study product.

Division of AIDS (DAIDS) Pharmaceutical Affairs Branch (PAB)

Temperature Excursion Reporting Form (TERF)

The Pharmacist of Record (PoR) or Associate Pharmacist (AP) must use this TERF to notify DAIDS PAB of permitted and non-permitted temperature excursions that occur in the Clinical Research Site Pharmacy. Please see *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for additional information regarding temperature excursions. (***NOTE:*** Refer to CRPMC instructions for temperature excursions that occur in transit from the CRPMC to the site.)

Instructions

Select the type of protocol specified excursion and attach the continuous temperature data during the time of the excursion. If this data is not available, provide the data from your daily temperature monitoring log. Any temperature recording requiring the CRPMC adjudication will be rounded to the nearest whole number.

☐ Permitted:

NOTE: Study Products may remain in active inventory and do not need to be quarantined. Permitted excursions may be consolidated and reported at least monthly.

1. Complete sections 1-3 and sign.
2. Send completed form via email to the CRPMC (crpmctempex@thermofisher.onmicrosoft.com).

☐ Non-Permitted:

NOTE: These excursions must be reported as soon as PoR/AP becomes aware. Quarantine all affected study products immediately at the appropriate storage temperature while awaiting determination of suitability for continued use. Clearly label products as "quarantined" and separate from unaffected products.

1. Complete all sections on the form and sign.
2. Send completed form via email to the CRPMC (crpmctempex@thermofisher.onmicrosoft.com).

SECTION 1

CRS Name(s):		**CRS Number(s):**	**Pharmacy Org ID#**
Pharmacist Name and Title (PoR/AP):	**Email Address:**		**Phone Number:**

SECTION 2

Protocol Number	Product Name/ Strength/Package Size	Lot/NSC Number	Exp. Date/ Retest Date/ Mfg. Date [dd-mmm-yy]	Quantity *(specify unit)*	Appropriate Temperature Storage Range *(specify °C or °F)*	Excursion Temperature *(specify °C or °F, single temp or range)*	Duration of Exposure *(specify min, hrs, days)*	Date(s) of Excursion [dd-mmm-yy]	**FINAL DISPOSITION (FOR CRPMC USE ONLY)** [dd-mmm-yy]	
								From:_____ To: _____	☐ Suitable for use ☐ Not Suitable for use	Date
								From:_____ To: _____	☐ Suitable for use ☐ Not Suitable for use	Date
								From:_____ To: _____	☐ Suitable for use ☐ Not Suitable for use	Date
								From:_____ To: _____	☐ Suitable for use ☐ Not Suitable for use	Date

Division of AIDS (DAIDS) Pharmaceutical Affairs Branch (PAB)

Temperature Excursion Reporting Form (TERF)

SECTION 3

Cause(s) for Temperature Excursion:

☐ Incorrect storage within equipment
☐ Power outage/interruption
☐ Malfunction of temperature monitoring device
☐ Prolonged opening of refrigerator/freezer
☐ Missing temperature data
☐ Routine maintenance of refrigerator/freezer
☐ Storage equipment malfunction
☐ Temperature monitoring device/probe not placed properly
☐ Protocol-specified permitted excursion
☐ Unknown cause
☐ Other, explain

SECTION 4

For non-permitted temperature excursions, have any of the study product(s) affected above experienced a temperature excursion at your site previously? ☐ YES ☐ NO
If yes, please complete the table below.

Protocol Number	Product Name/ Strength/Package Size	Lot/NSC Number	Quantity *(specify unit)*	Excursion Temperature *(specify °C or °F, single temp or range)*	Duration of Exposure *(specify min, hrs, days)*	Date(s) of Prior Excursion(s) [dd-mmm-yy]

** *Study products that have been affected by this or any non-permitted temperature excursions should be segregated and labeled following site procedures to easily identify the number of times the product(s) have experienced such excursions.*

Have any participants received the affected product? ☐ YES ☐ NO
*If yes, please inform the PI immediately. For blinded studies, be sure not to unblind the Investigator or any other study personnel.

Date: [dd-mmm-yy]

CRS Pharmacist Name and Title: _____

Signature:

CRPMC Use Only Date: [dd-mmm-yy]

CRPMC Reviewer Name and Title: _____

Signature:

CRPMC TERF ID Number

PAB TERF ID Number

II. OVERSIGHT OF PHARMACY FACILITIES

H Maintenance of Equipment

2021 Guidelines:

There must be a program for inspecting, testing, and maintaining pharmacy equipment and documenting the results. All pharmacy equipment must be maintained and evaluated for appropriate performance, in accordance with the manufacturer's instructions. All equipment should be certified or calibrated annually, or as per manufacturer's recommendations and in compliance with any local regulations. Maintenance and calibration records for all pharmacy equipment should be retained in the pharmacy and/or immediately available upon request.

<u>ADDED</u> 2023 Guidelines:

All pharmacy equipment must be labeled with a unique identifier (i.e., serial number or other identifier) and this unique identifier must also be recorded on the appropriate corresponding documentation (e.g., temperature log associated with the temperature monitoring device, certificate of calibration testing, re-calibration maintenance record, etc.).

SECTION 3

RESPONSIBILITIES OF THE PHARMACIST OF RECORD

I. Professional

II. Oversight of Pharmacy Facilities

III. Administrative

III. ADMINISTRATIVE

B Notification of Change Forms

2021 Guidelines:

Permanent Notification of Change in PoR – This form must be completed when there is a new permanent PoR at the clinical research site.

2023 Guidelines:

Permanent Notification of Change in PoR – This form must be completed when there is a new permanent PoR at the clinical research site. **For sites affiliated with a CTU, the PoR is designated as Key Personnel under the CTU grant. Any changes in Key Personnel must be submitted to DAIDS by the institution's Authorized Business Official.**

III. ADMINISTRATIVE

B Notification of Change Forms

2021 Guidelines:

Note: For sites under National Institute of Child Health and Human Development (NICHD), the site pharmacy approvals and processing of notification forms will be performed by the NICHD contractor that provides site pharmacy oversight.

2023 Guidelines:

Note: For sites under National Institute of Child Health and Human Development (NICHD), the site pharmacy approvals and processing of notification forms will be performed by the NICHD contractor that provides site pharmacy oversight. **Any site pharmacy supporting the conduct of a DAIDS-sponsored and/or supported clinical trial network protocol, must have documentation of site pharmacy approval within the time period established for a new funding cycle for the DAIDS Clinical Trials Networks.**

III. ADMINISTRATIVE

D Reports

Reports to the Pharmaceutical Affairs Branch

2021 Guidelines:

Pharmacy-related incidents that occur at a CRS pharmacy must be reported directly to PAB as soon as the PoR becomes aware of an incident or matter that could affect the outcome of a study. Incidents should be reported using the DAIDS PAB Incident Report Form (IRF), within one business day of identification.

2023 Guidelines:

Pharmacy-related incidents that occur at a CRS pharmacy must be reported directly to PAB as soon as the PoR becomes aware of an incident or matter that could affect the outcome of a study. Incidents should be reported using the DAIDS PAB Incident Report Form (IRF), within one business day of identification. **Incidents related to product complaints should be reported using the DAIDS PAB Product Complaint Resolution Form (PCRF).**

FREQUENTLY ASKED QUESTION

Q **The revised 2023 Pharmacy Guidelines includes a new reporting process for study product complaints using the DAIDS PAB Product Complaint Resolution Form (PCRF). May I request a PCRF?**

A If the PoR needs to report a product complaint regarding a study product shipped from the CRPMC, they should reach out to PAB for the PCRF.

III. ADMINISTRATIVE

E Records and Documents

ii Pharmacy Records and Documents

2021 Guidelines:

At a minimum, the following pharmacy records, and other documents that govern the practice of pharmacy at the site, must be maintained in the pharmacy:

- Copy of the current Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks that is readily accessible…

2023 Guidelines:

At a minimum, the following pharmacy records, and other documents that govern the practice of pharmacy at the site, must be maintained in the pharmacy:

- Copy of the current Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks that is readily accessible…
- **All maintenance and certification records for all pharmacy equipment**

*Full list of pharmacy records and other documents may be found in the Pharmacy Guidelines, page 40-41

SECTION 4

STUDY PRODUCT MANAGEMENT

VI. Dispensing/Preparation and Authorized Prescribers

VIII. Quality Management Plan (Quality Control and Quality Assurance)

IX. Chain of Custody

VI. DISPENSING/PREPARATION AND AUTHORIZED PRESCRIBERS

E Preparation

2021 Guidelines:

For study products requiring reconstitution, mixing, dilution and/or drawing up into a syringe, refer to the protocol and any additional protocol documents, if available, for protocol-specific instructions on preparation. Protocol documents may include the protocol, study-specific procedures, manual of operations, or a Pharmacists Study Product Management Procedures manual. In addition, requirements for preparation must also consider regulatory requirements or current quality standards (e.g., USP/NF standards) so that the integrity, stability, and effectiveness of the study products are maintained.

2023 Guidelines:

For study products requiring reconstitution, mixing, dilution and/or dose preparation, refer to the protocol and any additional protocol documents, if available, for protocol-specific instructions on preparation. Protocol documents may include the protocol, study-specific procedures, or manual of operations.

Any materials used must be inspected for appropriate packaging, labeling, and expected physical/visual appearance prior to use for the preparation of study product. All processes required for the preparation of study product (e.g., prescription review, participant-specific dispensing log, study product preparation worksheet/procedures, calculations, dose volume, time of preparation, time of expiration, etc.) must be documented and inspected for accuracy and completeness.

In addition, requirements for preparation must also consider regulatory requirements or current quality standards (e.g., USP/NF standards) so that the integrity, stability, and effectiveness of the study products are maintained.

SECTION 4

STUDY PRODUCT MANAGEMENT

VI. Dispensing/Preparation and Authorized Prescribers

VIII. Quality Management Plan (Quality Control and Quality Assurance)

IX. Chain of Custody

VIII. QUALITY MANAGEMENT PLAN (QUALITY CONTROL AND QUALITY ASSURANCE)

B Examples

2021 Guidelines:

Examples of Clinical Quality Management Plan Pharmacy Component Elements Include:

- Study Product Management Record Keeping
- Study Product Management Processes
  - Study Product Preparation Procedures
  - Study Product Dispensation Procedures
  - Study Product Chain of Custody Procedures
  - Study Product Storage and Temperature Monitoring Processes

2023 Guidelines:

Examples of Clinical Quality Management Plan Pharmacy Component Elements Include:

- Study Product Management Record Keeping
  - **Site Accountability Logs**
  - **Participant-Specific Accountability Logs**
  - **Participant-Specific Dispensing Logs**
  - **Temperature Monitoring and Recording Logs**
- Study Product Management Processes
  - Study Product Preparation Procedures
  - Study Product Dispensation Procedures
  - Study Product Chain of Custody Procedures
  - Study Product Storage and Temperature Monitoring Processes

*Full list of Examples of Clinical Quality Management Plan Pharmacy Components Elements may be found in the Pharmacy Guidelines, page 54

SECTION 4

STUDY PRODUCT MANAGEMENT

VI. Dispensing/Preparation and Authorized Prescribers

VIII. Quality Management Plan (Quality Control and Quality Assurance)

IX. Chain of Custody

IX. CHAIN OF CUSTODY

2021 Guidelines:

Throughout the conduct of the study, couriers or staff personnel, other than the PoR or other authorized site personnel, may come into possession of participant-specific study product. To ensure the integrity of the pharmacist-labeled, participant-specific study product, an unbroken trail of accountability, also referred to as chain of custody, must be documented as authorized study personnel take and relinquish its possession. Documents used to track the chain of custody must be maintained in the same manner as all other source documents. A template for creating a site-specific Chain of Custody document is available.

2023 Guidelines:

Many authorized site personnel may come into possession of a pharmacist-prepared, participant-specific study product **(e.g., PoR, AP, pharmacy staff, physicians, nurses, couriers, etc.)** throughout the conduct of a study. An unbroken trail of accountability, also referred to as chain of custody (CoC), must be documented at each point of handover of study product, recording the authorized study personnel accepting and relinquishing possession of the study product.

Documents used to track the chain of custody must be maintained in the same manner as all other source documents **and must not contain information that could unblind.** A template for creating a site-specific Chain of Custody document is available.

SECTION 5

PHARMACY VISITS

No significant changes

FREQUENTLY ASKED QUESTION

Q **With the release of the revised 2023 Pharmacy Guidelines, are pharmacists required to re-take the training on the DAIDS Learning Portal?**

A Site pharmacists are not required to re-take the “DAIDS Clinical Trials Networks Pharmacy Guidelines Training” located on the DAIDS Learning Portal. As per the notification sent to the Pharmacist of Records (PoRs) and Associate Pharmacists (APs) on August 17th, 2023, the site pharmacists are requested to complete the attestation form here acknowledging receipt of the 2023 Guidelines.

USEFUL RESOURCES

DAIDS Clinical Research Pharmacy and Study Products Management Webpage

https://www.niaid.nih.gov/research/daids-clinical-research-pharmacy-and-study-products-management

- Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks
- DAIDS PAB Chain of Custody Template
- DAIDS PAB Daily Temperature Log Template
- DAIDS PAB Study Product Accountability Record Template

QUESTIONS?

Email DAIDS PAB with any questions:

daidspab@niaid.nih.gov