Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

CDC'S CHEMPACK PROJECT: NERVE AGENT ANTIDOTE STORAGE

Daniel R. Levinson
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EXECUTIVE SUMMARY

OBJECTIVES

To determine the extent to which:

1. nerve agent antidotes in the CHEMPACK project were stored at temperatures required by the Food and Drug Administration (FDA),
2. the Centers for Disease Control and Prevention (CDC) implemented procedures to ensure the quality of nerve agent antidotes in the CHEMPACK project, and
3. nerve agent antidotes in the CHEMPACK project appropriately received extended expiration dates under the Shelf Life Extension Program (SLEP).

BACKGROUND

In 2004, CDC established the CHEMPACK project as part of an approximately $3.5-billion Federal Strategic National Stockpile of drugs and medical supplies to assist States in protecting communities against the potentially deadly effects of chemical agents that attack the human nervous system (i.e., nerve agents). While nerve agent antidotes in the CHEMPACK project (hereinafter referred to as CHEMPACK drugs) are part of the Strategic National Stockpile, they are not located with other federally stockpiled drugs. Through the voluntary CHEMPACK project, CDC has placed over 1,900 containers stocked with CHEMPACK drugs in multiple locations in participating States, thereby allowing States to quickly respond to a nerve agent release. Each container is stocked with CHEMPACK drugs to treat 454 or 1,000 people, depending on the container's configuration.

When States elect to participate in the CHEMPACK project, they sign a memorandum of agreement with CDC that outlines Federal and State roles and responsibilities. For example, States are responsible for CHEMPACK drugs' security, storage, and distribution in the event of a nerve agent release. CDC retains ownership of CHEMPACK drugs and is responsible for their quality assurance, which includes temperature monitoring. To ensure that CHEMPACK drugs are stored within the temperature range required by FDA, CDC remotely monitors containers stocked with CHEMPACK drugs using temperature-recording devices called Sensaphones and notifies States when temperatures need to be corrected.

As a holder of CHEMPACK drugs, CDC is subject to current good manufacturing practice (CGMP) provisions in the Food, Drug, and Cosmetic Act (the Act). FDA considers CGMP provisions of the Act to be met if drugs are stored under temperatures required by their FDA-approved label. CHEMPACK drugs must be stored according to the definition of controlled room temperature. The definition requires a storage range of 68 degrees Fahrenheit (68°F)–77°F with brief excursions (i.e., temperature fluctuations) permitted provided the calculated mean kinetic temperature (i.e., a fixed temperature that simulates the effect of temperature variation over a period of time) does not exceed 77°F. FDA requires entities that hold drugs with controlled room temperature storage requirements to calculate mean kinetic temperature but allows for flexibility in establishing the most appropriate method of performing the calculation. FDA also requires entities that perform activities regulated by CGMP to establish and maintain a system to ensure the quality of their products. FDA provides broad quality system guidance, but the entities have the flexibility to develop and implement procedures that best attain their quality objectives while still meeting FDA requirements.

Finally, CDC participates in FDA's SLEP for selected Strategic National Stockpile drugs, including drugs in the CHEMPACK project. SLEP defers drug replacement costs by extending expiration dates. SLEP potency testing is conducted on a sample of drugs from one lot, or batch. Based on the results, the expiration dates of other drugs from the same lot may be extended, provided that they were stored according to FDA's requirements.

We reviewed CDC and FDA documents and interviewed CDC and FDA officials to assess the extent to which CDC's procedures met requirements for (1) CHEMPACK drug storage; (2) maintaining a system to ensure the quality of all Strategic National Stockpile drugs, including CHEMPACK drugs; and (3) SLEP. We focused our review on the 1-year period from December 1, 2006, to November 30, 2007.

FINDINGS

Almost one-quarter of CHEMPACK containers did not have at least three daily temperature readings in accordance with CDC procedures. Of the 1,255 CHEMPACK containers that were in State storage sites for the 1-year period we reviewed, 23 percent (288 of 1,255) did not have the minimum number of CDC-established Sensaphone temperature readings for the full year. Further, CDC did

not investigate and document most of the missing temperature readings.

CDC's storage requirements for CHEMPACK drugs were not consistent with FDA's storage requirements. CDC's procedures permitted CHEMPACK drugs to be stored between 59°F and 86°F. The storage temperature range required by FDA is 68–77°F with brief excursions permitted up to 86°F and down to 59°F, provided that the calculated mean kinetic temperature does not exceed 77°F. However, CDC did not calculate the mean kinetic temperature of CHEMPACK containers to demonstrate that their storage environment did not exceed a calculated mean kinetic temperature of 77°F.

Nine percent of selected CHEMPACK containers were not stored according to FDA's storage requirements for at least 1 month. Almost half of the 967 CHEMPACK containers that had at least three daily Sensaphone temperature readings for the 1-year period we reviewed experienced temperatures above 77°F for varying amounts of time. Using average temperature as a substitute for mean kinetic temperature, we determined that 9 percent (91 of 967) of selected containers had an average monthly temperature 1°F or more above the mean kinetic temperature permitted by FDA (i.e., at or above 78°F) for at least 1 month. In addition, 1 percent (12 of 967) of selected containers had an average temperature at or above 78°F for at least 6 months.

CDC did not consistently implement quality system procedures in the CHEMPACK project. Although CDC had established a system to ensure the quality of all Strategic National Stockpile drugs, including CHEMPACK drugs, the system was not consistently implemented. Further, the quality system lacked the procedures necessary to ensure that CHEMPACK drugs were stored under conditions that would result in their highest possible level of quality and were maintained according to CGMP.

CDC's procedures allowed CHEMPACK drugs to inappropriately receive extended expiration dates under SLEP. Our findings demonstrate variability in CHEMPACK drug storage conditions. CDC procedures permit the comingling of drugs that were stored under these variable conditions with no means to link the drugs to records of their storage temperatures. This process allowed drugs that were not stored according to FDA's requirements to receive extended expiration dates based on the potency testing results of drugs in the same lot that were stored as required by FDA. Further,

a similar process is also used to extend the expiration dates of non-CHEMPACK drugs in the $3.5-billion Strategic National Stockpile managed by CDC.

RECOMMENDATIONS

Surviving nerve agent exposure requires rapid treatment with nerve agent antidotes. CDC has distributed over 1,900 CHEMPACK containers to participating States to allow quick response to a nerve agent release. Each container is stocked with CHEMPACK drugs to treat 454 or 1,000 people, depending on the container's configuration. FDA has established minimum storage requirements to ensure that drugs are safe and effective. However, CDC procedures did not ensure that CHEMPACK drugs stockpiled in States were stored according to these requirements.

For example, CDC requirements allowed CHEMPACK drugs to be consistently stored under conditions that did not meet FDA storage temperature requirements and CGMP. In addition, CDC's SLEP procedures do not comply with FDA's requirements for drugs to receive extended expiration dates. These findings raise concerns about whether similar vulnerabilities also apply to other stockpiled CDC assets, i.e., non-CHEMPACK drugs in the $3.5-billion Strategic National Stockpile, because all assets share the same quality system and SLEP procedures.

To address our findings, we recommend that CDC:

Seek FDA guidance on whether CHEMPACK drugs that have received extended expiration dates under SLEP are appropriate for use.

Revise its CHEMPACK project SLEP procedures to comply with FDA requirements.

Revise its CHEMPACK drug storage temperature requirements to comply with FDA requirements.

Ensure that the CHEMPACK project's quality system meets CGMP requirements for drug storage.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

CDC concurred with all four of our recommendations. CDC noted several actions it has taken or plans to take to address our findings and recommendations. For example, CDC has retroactively calculated mean kinetic temperature for the same period as our evaluation and identified three CHEMPACK containers that FDA suggests may require additional testing to assure potency. However, it is unclear from CDC's comments how it accounted for CHEMPACK containers that were missing temperature readings and documentation of temperature-recording device calibrations.

Finally, CDC stated that our report did not evaluate the overall Strategic National Stockpile program and therefore should not imply that problems exist with Strategic National Stockpile non-CHEMPACK assets. Nevertheless, CDC has begun an assessment of how best to initiate an independent review of its quality system and other procedures relative to CHEMPACK containers, and the rest of the Strategic National Stockpile assets, to ensure compliance with FDA requirements.

We support CDC's efforts to address these findings and encourage it to continue making progress in these areas. We made technical changes to the report based on CDC's comments.

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INTRODUCTION

OBJECTIVES

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1. nerve agent antidotes in the CHEMPACK project were stored at temperatures required by the Food and Drug Administration (FDA),
2. the Centers for Disease Control and Prevention (CDC) implemented procedures to ensure the quality of nerve agent antidotes in the CHEMPACK project, and
3. nerve agent antidotes in the CHEMPACK project appropriately received extended expiration dates under the Shelf Life Extension Program (SLEP).

BACKGROUND

The CDC Division of Strategic National Stockpile (DSNS) maintains an approximately $3.5-billion stockpile of federally owned drugs and medical supplies to assist State and local health departments in the event of a large-scale public health emergency.[1, 2] This stockpile includes antidotes to treat people exposed to nerve agents.

Nerve agents have been used to commit acts of terrorism. For example, in 1995, the Aum Shinrikyo cult released the nerve agent sarin in five Tokyo subways, killing 12 people and injuring more than 5,000 others. Depending on the dose, nerve agents can cause immediate nervous system failure and death. Surviving nerve agent exposure requires rapid treatment with nerve agent antidotes.

In 2004, CDC established the CHEMPACK project as part of the Strategic National Stockpile to assist the 62 Bioterrorism Cooperative Agreement Project Areas—the 50 States, the District of Columbia, the cities of Chicago and New York, Los Angeles County, Puerto Rico, the U.S. Virgin Islands, and the 6 Pacific Basin jurisdictions (hereinafter referred to as States)—to protect communities against the potentially

[1] The initial authorization to create and maintain special pharmaceutical stockpiles as a national resource is described in the Fiscal Year 1999 Omnibus Appropriations Act.

[2] CDC, *Strategic National Stockpile (SNS)*. Available online at http://emergency.cdc.gov/coca/ppt/DSNS_Piester_July12008_CE.ppt#303,1,Slide 1. Accessed on March 19, 2009.

deadly effects of nerve agents.[3] Cumulative funding for the CHEMPACK project is estimated to exceed $100 million during fiscal years 2009–2013.[4]

While nerve agent antidotes in the CHEMPACK project (hereinafter referred to as CHEMPACK drugs) are part of the Strategic National Stockpile, they are not located with other federally stockpiled drugs and medical supplies. Through the voluntary CHEMPACK project, CDC places CHEMPACK drugs in multiple locations in participating States, thereby allowing States to quickly respond to a nerve agent release.[5] As of January 2009, more than 92 percent of the United States population lived within a 1-hour distance of CHEMPACK drugs, according to CDC.[6]

When States elect to participate in the CHEMPACK project, they sign a memorandum of agreement with CDC that outlines Federal and State roles and responsibilities. For example, States are responsible for CHEMPACK drugs' security, storage, and distribution in the event of a nerve agent release. CDC retains ownership of CHEMPACK drugs and is responsible for their quality assurance, which includes temperature monitoring.

CHEMPACK Drug Storage Containers

CDC assembles containers stocked with CHEMPACK drugs (i.e., atropine, pralidoxime, and diazepam) and distributes the containers to CDC-approved State storage sites. Each container is stocked with CHEMPACK drugs to treat 454 or 1,000 people, depending on the container's configuration. As of January 2009, CDC had distributed over 1,900 CHEMPACK containers to States.[7]

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[3] *CHEMPACK Program Description (June 14, 2004).* Available online at http://www.bt.cdc.gov/planning/continuationguidance/pdf/chempack-attachj.pdf. Accessed on October 1, 2007.

[4] *Implementation Plan for Chemical, Biological, Radiological and Nuclear Threats*, p. 13. Health and Human Services Public Health Emergency Medical Countermeasures Enterprise, 2007.

[5] As of January 2009, 54 of the 62 States were participating in the CHEMPACK project.

[6] CDC, *Public Health Preparedness: Strengthening CDC's Emergency Response*. Available online at http://emergency.cdc.gov/publications/jan09phprep/. Accessed on February 15, 2009.

[7] Written CDC responses to OIG questions about the CHEMPACK project, August 20, 2009.

These stocked containers cost at least $83 million—approximately $43,000 per container.[8] CHEMPACK containers are monitored by temperature-recording devices called Sensaphones. CDC programs each Sensaphone to take one temperature reading at least every 8 hours, for a minimum of three daily temperature readings.[9] A Sensaphone uses a telephone line to send the temperature readings to a CDC computer that retains the readings. CDC personnel monitor the temperature readings and notify States when action is required to correct CHEMPACK drug storage temperatures.

CHEMPACK Drug Storage Requirements

FDA has established minimum requirements, known as current good manufacturing practices (CGMP), for drug manufacturers, processors, packers, and holders to ensure that drugs are safe and effective.[10] As a holder of CHEMPACK drugs, CDC is subject to statutory CGMP provisions in section 501(a)(2)(B) of the Food, Drug, and Cosmetic Act (the Act).[11, 12] FDA considers CGMP provisions of the Act to be met if drugs are stored according to FDA-approved requirements as specified on the drug labels.[13]

CHEMPACK drug labeling requires that the drugs be stored in accordance with the United States Pharmacopeia definition of controlled room temperature.[14] This definition establishes a storage

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[8] CDC documentation of CHEMPACK container costs, dated December 20, 2007. There are two types of CHEMPACK containers, each with a different configuration and cost. To be conservative, we used the cost of the less-expensive container when calculating the total cost of the 1,937 containers.

[9] CDC has established Sensaphone alarm temperature settings. When temperatures fall outside of range, a Sensaphone may take a temperature reading more frequently than every 8 hours until the container's temperature returns within range.

[10] 21 CFR § 211.

[11] Written FDA response to Office of Inspector General (OIG) questions on CHEMPACK drug storage requirements, March 13, 2008.

[12] The Act requires that drugs be maintained to conform with CGMP, but does not specifically address what constitutes CGMP. For guidance on good practices for holders of drugs, FDA refers to 21 CFR §§ 205 and 211. Specifically, FDA refers to holding provisions in the CGMP regulations and "Guidelines for State Licensing of Wholesale Prescription Drug Distributors" in 21 CFR § 205.50. The sections of the CGMP regulations in 21 CFR § 211 that are the most applicable as guidance for the holding of drug products include subparts B (Organization and Personnel), C (Buildings and Facilities), and H (Holding and Distribution).

[13] FDA Memorandum, *Clarification Regarding SNS Medical Product Temperature Excursions*. May 18, 2005.

[14] The United States Pharmacopeia is an official public standards-setting authority for all prescription and over-the-counter medicines and other health care products manufactured or sold in the United States.

temperature range of 68 degrees Fahrenheit (68°F) to 77°F. However, the controlled room temperature definition also recognizes that temperature excursions (i.e., fluctuations) can occur in typical drug storage warehouses. As a result, drugs with controlled room temperature storage requirements are permitted to experience brief excursions as low as 59°F and as high as 86°F, provided that the calculated mean kinetic temperature (i.e., a fixed temperature that simulates the effect of temperature variation over a period of time) does not exceed 77°F. See Appendix A for the full definition of controlled room temperature.

FDA officials provided further guidance on the definition of controlled room temperature, noting that it intends for drugs to be stored primarily within the 68–77°F range. Further, FDA officials noted that drugs labeled for controlled room temperature storage should not be stored constantly at the upper excursion range because they may be exposed to a mean kinetic temperature exceeding 77°F over time.

FDA does not dictate how frequently drug storage temperatures must be recorded or the length of time over which mean kinetic temperature must be calculated. However, FDA recommends that entities follow the instructions in United States Pharmacopeia General Information Chapter 1150 for collecting temperature monitoring data and for calculating mean kinetic temperature. General Information Chapter 1150 states that temperatures for calculating mean kinetic temperature can be conveniently collected using electronic devices that measure temperatures at frequent intervals (e.g., every 15 minutes).

Finally, FDA does not require CHEMPACK drugs to be stored under controlled humidity, although CDC requires States to maintain the humidity level in CHEMPACK drug storage sites below 60 percent.[15] According to CDC personnel, this requirement was established based on input from the FDA, with legal oversight by the Office of the General Counsel at both the Departments of Homeland Security and Health and Human Services.[16]

[15] Memorandum of agreement between CDC and each participating State.

[16] Written CDC responses to OIG questions on the roles and responsibilities of the DSNS Quality Control Unit, March 25, 2008.

The Quality System for the CHEMPACK Project

FDA requires entities that perform activities regulated by CGMP to establish and maintain a system to ensure the quality of their products. FDA provides broad quality system guidance, but entities have the flexibility to develop and implement procedures that attain their quality objectives while still meeting FDA requirements.

CDC's Strategic National Stockpile quality system applies to the CHEMPACK project, as well as other stockpiled CDC assets, i.e., non-CHEMPACK drugs in the $3.5-billion Strategic National Stockpile. For the CHEMPACK project, in particular, the quality system includes procedures to ensure that (1) Sensaphones take accurate temperature readings, (2) storage temperatures are monitored to maintain CHEMPACK drugs within a CDC-established temperature range, and (3) the temperature readings are accurately retained.[17] In addition, the quality system includes procedures to correct and document out-of-range drug storage temperatures. Finally, the DSNS Quality Control Unit provides oversight of all Strategic National Stockpile drugs, including those in the CHEMPACK project, to ensure that the quality system is implemented as intended.

Ensuring accurate temperature readings. CDC procedures for the CHEMPACK project require CDC personnel to calibrate Sensaphones annually to ensure that the temperature recorded by the device reflects the actual storage environment.[18] Further, according to CDC procedures for the CHEMPACK project, CDC personnel sign and date all calibration reports before placing them on file.

Monitoring and retaining temperature readings. To ensure that CHEMPACK drugs are stored within the CDC-established temperature range, CDC personnel monitor Sensaphone temperature readings for all CHEMPACK drug storage sites. CDC also retains electronic records of Sensaphone temperature readings to document CHEMPACK drug storage conditions.

Correcting and documenting out-of-range temperatures. CDC procedures require CDC personnel to notify States when action is

[17] CDC has established a temperature range for CHEMPACK storage that is different from the temperature range required by FDA. This will be discussed in detail later in this report.

[18] Calibration is a process during which a measuring instrument is adjusted to an acceptable level of accuracy.

required to return CHEMPACK drug storage temperatures to the CDC-established range.

When CHEMPACK drug storage temperatures fall outside of the CDC-established range for less than 24 hours, CDC procedures for the CHEMPACK project require CDC personnel to create an incident ticket. In general, an incident ticket documents the steps that States have taken to correct CHEMPACK drug storage temperatures, and what may have led to the out-of-range temperatures.[19]

If CHEMPACK drug storage temperatures fall outside of the CDC-established range for longer than 24 hours, CDC personnel must create a corrective and preventive action report. A corrective and preventive action report documents the steps that State and/or CDC personnel have taken to correct temperatures outside of the established range. It also documents what may have led to the out-of-range temperatures and potential impact to the affected CHEMPACK drugs.

Overseeing quality procedures. The DSNS Quality Control Unit is responsible for overseeing the quality system for storing and monitoring all Strategic National Stockpile drugs, including CHEMPACK drugs.[20] The Quality Control Unit reports directly to the DSNS Office of the Director and its responsibilities include:

- ensuring that CDC and States comply with applicable CGMP regulations;
- conducting regularly scheduled evaluations of all CHEMPACK drug storage sites, applicable policies, and standard operating procedures;
- verifying appropriate investigation and resolution of situations and actions that do not adhere to CHEMPACK policies and standard operating procedures, e.g., out-of-range CHEMPACK drug storage temperatures; and
- ensuring that all CHEMPACK CGMP documents, e.g., Sensaphone calibration reports, records of Sensaphone temperature readings,

[19] CDC personnel also develop incident tickets to document occurrences other than out-of-range storage temperatures, such as power outages and lack of Sensaphone connectivity.

[20] CDC, *Establishment of an Independent Division of Strategic National Stockpile (DSNS) Quality Control Unit for the Storage and Movement of Finished Pharmaceuticals*. December 15, 2005.

incident tickets, and corrective and preventive action reports, are appropriately maintained.[21]

Shelf Life Extension Program

CDC participates in SLEP for selected Strategic National Stockpile drugs, including CHEMPACK drugs. SLEP is an FDA program that defers drug replacement costs by extending drug expiration dates.[22] Under SLEP, the shelf life of a drug may be doubled if the drug passes FDA potency testing. CDC has reported that for every dollar spent on SLEP costs (e.g., shipping drugs, potency testing) in 2007, it saved $13 by deferring the purchase of new drugs.[23, 24]

CDC provides FDA with a list of all lot numbers of CHEMPACK drugs that are approaching expiration.[25] From this list, FDA determines which drugs will be potency tested and requests that CDC submit samples to be tested from each selected lot of the drugs. CDC recalls, from State storage sites, the remaining drugs from each selected lot to central CDC storage, where they are held pending FDA potency test results.

CHEMPACK drugs from one lot may have been stored in multiple locations. According to FDA officials, SLEP potency testing results may be used to extend the expiration dates of drugs with the same lot number that were stored under appropriate conditions, i.e., according to FDA-approved labeling requirements. When a drug fails potency testing, all drugs with that lot number must be destroyed. Further, if drugs with any lot number were stored under conditions outside of FDA-approved labeling requirements, they should be potency tested separately or destroyed upon expiration.

As of January 2009, samples of the CHEMPACK drugs atropine, pralidoxime, and diazepam have undergone FDA potency testing and received extended expiration dates.

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[21] Ibid.

[22] *FDA/DoD [Department of Defense] Shelf Life Extension Program*. Available online at https://slep.dmsbfda.army.mil/slep/slep_infor_paper_JAN_2006.doc. Accessed on July 29, 2008.

[23] CDC SLEP cost avoidance includes both CHEMPACK and non-CHEMPACK drugs.

[24] CDC, *Online Performance Appendix*, p. 120. Available online at http://www.cdc.gov/FMO/PDFs/FY09_CDC_Online_Performance_Appendix.pdf. Accessed on April 13, 2009.

[25] A lot number identifies a particular batch, or lot, of drug product from a manufacturer.

Related Work

In 2006, OIG issued a report on early CHEMPACK project implementation and determined that CDC had opportunities to strengthen CHEMPACK deployment. OIG recommended that CDC assist States in deployment testing, develop CHEMPACK performance goals and training materials, and provide medical expertise on CHEMPACK drugs. In its comments to our report, CDC stated that it had addressed, or begun to address, OIG's recommendations.

METHODOLOGY

Scope

We determined the extent to which CHEMPACK drugs were stored at the temperatures required by FDA during the 1-year period from December 1, 2006, to November 30, 2007.[26] We also determined the extent to which CDC ensured that CHEMPACK drugs, as well as non-CHEMPACK drugs in the $3.5-billion Strategic National Stockpile, were maintained under a system to ensure their quality and appropriately received extended expiration dates under SLEP.

We did not analyze the viability of CHEMPACK drugs that were stored outside FDA-required temperatures. We also did not directly assess storage conditions for non-CHEMPACK drugs.

Data Collection

We requested that CDC provide a listing of all CHEMPACK containers that were in State storage sites for the entire year we reviewed.[27] Of the over 1,900 containers that CDC had distributed as of January 2009, 1,262 met this criterion.

In addition, we obtained written CDC policies, procedures, and records related to storing CHEMPACK drugs as well as the Strategic National Stockpile quality system and SLEP. We also obtained written FDA requirements for CDC participation in SLEP.

[26] We used Sensaphone data to determine CHEMPACK drug storage temperatures. The most recent 12-month period of Sensaphone data available at the time of our review was from December 1, 2006, to November 30, 2007.

[27] The containers were stored in 51 of the 54 States participating in the CHEMPACK project. Three States had not yet received CHEMPACK containers when we began our review.

Further, we interviewed CDC officials about their policies and procedures for CHEMPACK drug storage and Strategic National Stockpile participation in SLEP. Finally, we interviewed FDA officials on Federal storage requirements for CHEMPACK drugs and Strategic National Stockpile SLEP participation.

Data Analysis

We reviewed Sensaphone temperature records for 1,255 CHEMPACK containers that were in State storage sites for the entire 1-year period we reviewed.[28] We reviewed the Sensaphone records to determine the extent to which the 1,255 containers had at least three temperature readings for each day of the 1-year period, in accordance with CDC procedures.[29] For the containers that did not have at least three daily temperature readings for the year, we determined the total number of temperature readings that were missing. We also reviewed CDC incident reports to determine the extent to which CDC investigated and documented the missing temperature readings.

We selected the containers that had at least three daily temperature readings for the entire 1-year period for further analysis. First, using Sensaphone temperature readings, we determined the cumulative time the containers were maintained above the 68–77°F storage range for CHEMPACK drugs.[30, 31] We focused our analysis on temperatures above the storage range because they present the greatest risk of increasing a container's mean kinetic temperature above the 77°F limit specified by FDA.

Second, we calculated average temperature for the selected containers as a substitute for mean kinetic temperature for each month of the

[28] We excluded seven containers from our analysis because CDC did not provide their corresponding Sensaphone records.

[29] Sensaphones take temperature readings more frequently than every 8 hours when a container's storage temperature falls outside of the CDC-established storage range.

[30] We define cumulative time as the aggregate time that CHEMPACK containers were maintained above 77°F over the course of the entire 1-year period we reviewed.

[31] To be conservative, we did not include periods of time when a container's temperature was above 110°F because these temperature readings were questionable and/or we received CDC documentation explaining that they were not valid.

1-year period we reviewed.[32, 33] We then counted the number of months that each container had an average temperature of 78°F or higher, i.e., 1 degree or more above the mean kinetic temperature limit of 77°F permitted by FDA. See Appendix B for a description of the methodology we used to calculate average temperature.

Next, we reviewed CDC documentation to determine the extent to which CDC personnel implemented Strategic National Stockpile quality system procedures for the CHEMPACK project by developing required incident tickets and corrective and preventive action reports. First, we selected CHEMPACK containers that had at least three daily temperature readings for the entire 1-year period we reviewed. Next, we used Sensaphone records to determine the number of occurrences that each selected container's temperature was outside of the CDC-established range.[34] Finally, we reviewed CDC documentation to determine the extent to which CDC personnel developed incident tickets and corrective and preventive action reports for out-of-range temperatures lasting less than 24 hours and over 24 hours, respectively.

We reviewed CDC documentation to determine the extent to which CDC personnel filed a signed and dated annual Sensaphone calibration report, as required by CDC procedures for the CHEMPACK project, for all 1,255 containers that were in State storage for the entire year we reviewed.[35] We also reviewed the calibration reports to determine the extent to which CDC met CGMP standards when documenting the calibration procedures and results.

Finally, we determined the extent to which CDC procedures ensured that CHEMPACK drugs appropriately received extended expiration dates. We performed this analysis by comparing CDC SLEP

[32] We did not calculate mean kinetic temperature because we did not have the energy of activation, a variable required for calculation, for each CHEMPACK drug.

[33] According to FDA, the calculated mean kinetic temperature is higher than the average temperature. FDA, *Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products*, November 2003, p. 18. Available online at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf. Accessed on November 13, 2009.

[34] We define occurrences as each time a container's temperature left and then returned within range.

[35] We performed this analysis on calibration records CDC personnel developed during the period from January to December 2007.

procedures to FDA SLEP requirements, and by reviewing transcripts of interviews we conducted with CDC and FDA officials about SLEP.

Limitations

We reviewed Sensaphone temperature readings for 1,255 CHEMPACK containers that were in State storage sites during the year from December 1, 2006, to November 30, 2007. As of January 2009, there were over 1,900 containers stored in States.

We reviewed the storage temperatures of CHEMPACK drugs during a 1-year period. However, many of the drugs had been stored for periods longer than 1 year. The cumulative amount of time these drugs may have been stored outside their required storage range is unknown.

We calculated average temperature as a substitute for mean kinetic temperature because we did not have the energy of activation, a variable necessary to calculate mean kinetic temperature, for each CHEMPACK drug.

Further, FDA does not dictate how frequently drug storage temperatures must be recorded or the length of time over which mean kinetic temperature must be calculated. However, FDA does note that more frequent measurements will provide a more precise mean kinetic temperature. We calculated average temperature, as a substitute for mean kinetic temperature, for each month of the 1-year period we reviewed using all recorded temperatures for each container. Other methods may also be appropriate.

Standards

This study was conducted in accordance with the *Quality Standards for Inspections* approved by the Council of the Inspectors General on Integrity and Efficiency.

Almost one-quarter of CHEMPACK containers did not have at least three daily temperature readings in accordance with CDC procedures

Twenty-three percent (288 of 1,255) of the CHEMPACK containers in State storage sites for the entire year we reviewed did not have the three required daily temperature readings for the 1-year period we reviewed.[36] The other 967 of 1,255 containers had at least three daily temperature readings for the full year.

In most cases, the CHEMPACK containers that did not have at least three daily temperature readings were missing 1 percent or less of the required temperature readings (i.e., 11 readings or less). These missing readings represent a cumulative maximum time of approximately 3.5 days of the 1-year period we reviewed.

In some cases, these CHEMPACK containers were missing a significant number of temperature readings. For example, 2 percent of containers (23 of 1,255) were missing more than one-quarter of the required temperature readings (i.e., over 247 readings). These missing readings represent a cumulative minimum time of over 90 days of the 1-year period we reviewed.

Table 1 (on the next page) provides the number and percentage of CHEMPACK containers we determined were missing temperature readings during the 1-year period.

Table 1: CHEMPACK Containers With Missing Temperature Readings

Percentage of Missing Daily Temperature Readings in a 1-Year Period*	Number of Containers	Percentage of Containers (n=1,255)**
0.1–1%	248	20%
Over 1–5%	6	0%
Over 5–10%	4	0%
Over 10–25%	7	1%
Over 25–50%	13	1%
Over 50–75%	5	0%
Over 75%	5	0%
Total	**288**	**23%*** **

* Ranges calculated out of 1,095 expected readings in a 1-year period.

** Percentages are rounded to the closest whole number.

*** Percentages do not add to total because of rounding.

Source: OIG analysis of Sensaphone temperature readings of CHEMPACK containers.

[36] We reviewed the 1-year period from December 1, 2006, to November 30, 2007.

CDC did not investigate and document most of the missing temperature readings

CDC documented missing temperature readings for three CHEMPACK storage sites for the 1-year period we reviewed. These sites corresponded to only 4 of the 288 containers that lacked temperature readings.

CDC's storage requirements for CHEMPACK drugs were not consistent with FDA's storage requirements

FDA requires CHEMPACK drugs to be stored primarily within the 68–77°F range, with excursions permitted down to 59°F and up to 86°F provided that the calculated mean kinetic temperature does not exceed 77°F.[37]

CDC requires CHEMPACK drugs to be stored in a 59–86°F range. This requirement allows States to indefinitely store CHEMPACK drugs in temperature ranges (i.e., 59–67°F and 78–86°F) that, according to FDA requirements, are permitted for brief excursion periods only. FDA officials further noted that CHEMPACK drugs should not be constantly stored under temperatures in the upper excursion range.

CDC did not calculate the mean kinetic temperature of CHEMPACK containers

CHEMPACK drugs should not be stored under conditions that result in a calculated mean kinetic temperature that exceeds 77°F. However, CDC did not calculate the mean kinetic temperature of CHEMPACK containers during the time of our review. Without this calculation, CDC could not demonstrate that CHEMPACK drugs that experienced temperature excursions above 77°F were held according to FDA requirements.

Nine percent of selected CHEMPACK containers were not stored according to FDA's storage requirements for at least 1 month

We analyzed the temperature readings of the 967 CHEMPACK containers that had at least three daily Sensaphone temperature readings for the 1-year period we reviewed

[37] Written FDA response to OIG questions on CHEMPACK drug storage requirements, March 13, 2008.

and determined that over one-third of these containers experienced temperatures above 77°F for varying amounts of time.[38] Specifically, 36 percent (351 of 967) of these containers experienced temperatures above 77°F for a cumulative period ranging from 8 hours to over 6 months. See Appendix C for further details on this analysis.

Using average temperature as a substitute for mean kinetic temperature, we determined that 9 percent (91 of 967) of the selected containers had an average monthly temperature 1 degree or more above the maximum mean kinetic temperature permitted by FDA (i.e., at or above 78°F) for at least 1 month.[39] In addition, 1 percent (12 of 967) of the selected containers had an average temperature at or above 78°F for at least 6 months. Three of these containers had an average monthly temperature at or above 78°F for the entire 1-year period we reviewed.

Table 2 provides the number of months that the selected CHEMPACK containers had an average temperature at or above 78°F and the corresponding number and percentage of containers.

Table 2: CHEMPACK Containers With a Monthly Average

Number of Months at or Above 78°F	Number of Containers	Percentage of Selected Containers (n=967)*
1	35	4%
2	19	2%
3	14	1%
4	8	1%
5	3	0%
6	2	0%
7	3	0%
8	4	0%
11	1	0%
12	2	0%
Total	**91**	**9%****

* Percentages rounded to the closest whole number.

** Percentages do not add to total because of rounding.

Source: OIG analysis of Sensaphone temperature readings of CHEMPACK containers.

[38] Approximately 44 percent (425 of 967) of these containers had at least one temperature reading above 77°F

[39] Monthly average temperatures did not exceed 84°F.

CDC did not consistently implement quality system procedures in the CHEMPACK project

Although CDC had established a system to ensure the quality of all Strategic National Stockpile drugs, including CHEMPACK drugs, the system was not consistently implemented. Further, the quality system lacked procedures necessary to ensure that CHEMPACK drugs were stored under conditions that would maintain their highest level of quality and were maintained according to CGMP.

CDC did not validate the computer that stores Sensaphone temperature readings

CDC did not validate the computer that stores Sensaphone temperature readings to ensure that the stored temperatures were identical to the temperatures recorded by the Sensaphone. In addition, CDC did not validate the computer system to ensure that controls were in place to prevent the loss of temperature readings, or unauthorized access or changes to those readings.

CDC did not adequately document Sensaphone calibrations

According to CDC procedures, Sensaphones must be calibrated annually to ensure that the temperatures recorded by the devices reflect the actual storage environment. A calibration report must be signed and dated to document that the procedure was performed. However, 39 percent of the CHEMPACK containers (486 of 1,255) did not have a Sensaphone calibration report that was signed and dated by CDC personnel during the 1-year period of our review. Therefore, we could not determine whether the calibration had been performed annually according to CDC procedures.

The 769 calibration reports that were signed and dated contained the initials of the signatory but did not indicate whether that person had performed the calibration or was a reviewing official. In addition, these calibration reports were not signed by a second person to demonstrate that they had been independently reviewed. Further, none of the calibration reports contained necessary CGMP information about the calibration process. For example, they all lacked clearly marked precalibration and postcalibration Sensaphone readings, as well as details about adjustments made to bring the Sensaphone to an acceptable level of accuracy. In addition, none of the calibration reports documented that the Sensaphone alarm settings had been checked and were functioning as intended.

CDC did not consistently develop incident tickets and corrective and preventive action reports for CHEMPACK drug storage temperatures outside of the CDC-established range

CDC must document deviations from written CDC procedures for the CHEMPACK project to be in compliance with these procedures and CGMP. However, CDC personnel did not consistently develop incident tickets or corrective and preventive action reports to document CHEMPACK drug storage temperatures outside of the CDC-established temperature range (i.e., 59–86°F), in accordance with CDC procedures.

For all 967 containers that had at least three daily temperature readings for the 1-year period of our review, there were 6,438 occurrences when the containers' temperatures fell outside of the CDC-established temperature range and returned to that range. According to CDC procedures, CDC personnel should have developed an incident ticket or corrective and preventive action report for each of these 6,438 occurrences. However, CDC completed documentation for only 65 of these occurrences.

We performed further analysis on the occurrences when the containers' temperatures were continuously outside of the CDC-established range for at least 1 hour. Based on this analysis, there were 201 occurrences that should have been reported on an incident ticket because a container's temperature reading was outside of the CDC-established temperature range for at least one hour but less than 24 hours. However, CDC completed an incident ticket for only 32 percent (64 of 201) of these occurrences.

Similarly, CDC personnel did not develop a corrective and preventive action report each time a container experienced temperatures outside of the CDC-established temperature range for longer than 24 hours. For all 967 containers that had at least three daily temperature readings for the 1-year period of our review, there were 39 occurrences that should have led to a corrective and preventive action report. However, CDC completed a corrective and preventive action report for only 1 of these 39 occurrences.

CDC did not monitor humidity at CHEMPACK drug storage sites

As outlined in the CHEMPACK memorandum of agreement, States must maintain the humidity level of CHEMPACK drug storage sites below 60 percent. However, CDC did not monitor humidity in CHEMPACK storage sites and therefore did not notify States when

action was required to bring drug storage conditions back into the required humidity range.

CDC did not ensure that the CHEMPACK project was reviewed as required by a quality control unit

DSNS policy requires its Quality Control Unit to regularly inspect all Strategic National Stockpile storage sites, including those in the CHEMPACK project. However, the DSNS Quality Control Unit had not inspected any CHEMPACK drug storage sites since the CHEMPACK project's inception in 2004. In addition, DSNS's Quality Control Unit staff had not reviewed Sensaphone calibration reports, Sensaphone temperature records, or incident tickets and corrective and preventive action reports in accordance with CDC procedures. These reviews are necessary to ensure appropriate storage of CHEMPACK drugs as well as investigation and resolution of drug storage temperatures that did not adhere to CDC procedures and CGMP.

CDC's procedures allowed CHEMPACK drugs to inappropriately receive extended expiration dates under SLEP

CDC procedures do not ensure that CHEMPACK drugs stored outside of FDA's temperature requirements are destroyed or potency tested separately from drugs that meet those requirements, as required by FDA SLEP policy.

When CHEMPACK drugs approach expiration, they are returned from State storage sites to a central CDC location and sorted by their manufacturer lot numbers. However, according to CDC documentation, ". . . product is not sorted or sortable by its history, so the container that it came out of cannot be determined once it is comingled with other [CHEMPACK drugs] of the same lot." Therefore, once CHEMPACK drugs are returned to central storage, CDC personnel cannot determine which drugs were stored under conditions required by FDA and which were not.

Our findings demonstrate that almost one-quarter of CHEMPACK containers were missing temperature readings to document their storage conditions. Further, there was variability in CHEMPACK drug storage conditions for the containers that had the minimum number of CDC-required temperature readings. For example, 36 percent (351 of 967) of containers were maintained above the 77°F upper storage limit required by FDA for cumulative periods of

between 8 hours and more than 6 months. Further, 9 percent (91 of 967) of the selected containers had an average monthly temperature 1 degree or more above the mean kinetic temperature permitted by FDA (i.e., at or above 78°F) for at least 1 month.[40]

CDC procedures allowed CHEMPACK drugs in containers that were not maintained within the FDA required temperature range to be mixed with drugs from containers that were maintained as required. These procedures allowed CDC to extend the expiration dates of CHEMPACK drugs that were not stored according to FDA's requirements based on the potency testing results of drugs in the same lot that were stored as required. A similar process is used to extend the expiration dates of non-CHEMPACK drugs in the $3.5-billion Strategic National Stockpile managed by CDC.

[40] We calculated average temperature as a substitute for mean kinetic temperature.

Surviving nerve agent exposure requires rapid treatment with nerve agent antidotes. CDC has distributed over 1,900 CHEMPACK containers to participating States to allow quick response to a nerve agent release. Each container is stocked with CHEMPACK drugs to treat 454 or 1,000 people, depending on the container's configuration. FDA has established minimum storage requirements to ensure that drugs are safe and effective. However, CDC procedures did not ensure that CHEMPACK drugs stockpiled in States were stored according to these requirements.

For example, CDC's CHEMPACK drug storage temperature requirement allows the drugs to be consistently stored under conditions that do not meet FDA's storage temperature requirements and CGMP. In addition, CDC did not consistently implement a quality system to ensure that procedures necessary to store CHEMPACK drugs according to FDA's requirements were followed. Further, CDC procedures allow CHEMPACK drugs to inappropriately receive extended expiration dates under SLEP.

Although we did not assess non-CHEMPACK assets directly, we did review CDC procedures that pertain to other assets managed by the Strategic National Stockpile. These findings raise concerns about whether similar vulnerabilities also apply to other stockpiled CDC assets, i.e., non-CHEMPACK drugs in the $3.5-billion Strategic National Stockpile, because all assets share the same quality system and similar SLEP procedures.

To address our findings, we recommend that CDC:

Seek FDA guidance on whether CHEMPACK drugs that have received extended expiration dates under SLEP are appropriate for use

CDC cannot demonstrate that all CHEMPACK drugs that have received extended expiration dates were stored under the conditions required by FDA. For this reason, CDC should provide the necessary drug storage information to FDA officials so that they can determine whether the drugs are appropriate for use, should be destroyed, or should undergo additional potency testing.

Revise its CHEMPACK project SLEP procedures to comply with FDA requirements

CDC should coordinate with FDA to revise its SLEP procedures for the CHEMPACK project so that they comply with program requirements. CDC should also consider reviewing the SLEP procedures for other CDC drugs under SLEP, i.e., non-CHEMPACK drugs included in the Strategic National Stockpile managed by CDC. This will ensure that only drugs that are stored according to FDA's requirements receive extended expiration dates.

Revise its CHEMPACK drug storage temperature requirements to comply with FDA requirements

CDC should change its storage temperature requirements for CHEMPACK drugs to 68–77°F with excursions permitted up to 86°F and down to 59°F provided that the calculated mean kinetic temperature does not exceed 77°F. This change would also require CDC to develop a method for calculating and regularly monitoring the mean kinetic temperature of CHEMPACK drug containers. CDC should seek FDA guidance to ensure that the method used to calculate mean kinetic temperature is appropriate for the long-term storage of CHEMPACK drugs.

Ensure that the CHEMPACK project's quality system meets CGMP requirements for drug storage

CDC should conduct a complete review of its Strategic National Stockpile quality system and coordinate with FDA or other CGMP experts to ensure that CHEMPACK drugs are stored under conditions that will maintain their highest level of quality. According to FDA, the CGMP provisions most applicable to the CHEMPACK project are included in 21 CFR §§ 211 and 205.50. At a minimum, CDC should adhere to its procedures of taking at least three daily temperature readings for each CHEMPACK container, monitor Sensaphone records for missing temperature readings and anomalies, and investigate the causes when they occur. In addition, CDC could consider seeking guidance from FDA as to whether taking a minimum of three daily temperature readings is sufficient. CDC should also implement quality system procedures that include maintaining complete and accurate temperature records. This would include validating the computer that stores Sensaphone readings and conducting fully documented Sensaphone calibrations. Further, DSNS's Quality Control Unit should evaluate selected CHEMPACK drug storage sites and review CHEMPACK-related documents such

as Sensaphone calibration records, incident tickets, and corrective and preventive action reports. Finally, CDC should coordinate with FDA to review the requirement for States to maintain the humidity level of CHEMPACK drug storage sites below 60 percent. If this review determines that such a requirement is necessary, CDC should start monitoring humidity in CHEMPACK drug storage sites. If the requirement is not necessary, CDC should remove it from the CHEMPACK memorandum of agreement.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

CDC concurred with all four of our recommendations and stated that the report's findings provide important information regarding the adequacy of quality systems and procedures and CDC adherence to them at the time of the evaluation. However, CDC noted that we did not evaluate the quality of CHEMPACK drugs and that our findings do not address the viability of these drugs. CDC also noted that it has instituted a corrective action program to address our findings and recommendations and described actions it has taken. That is, CDC stated that as of September 2008, it had instituted the calculation of mean kinetic temperature using an FDA-approved methodology for all CHEMPACK containers to ensure that the product is stored under the correct temperature conditions. Additionally, CDC has retroactively calculated mean kinetic temperature for the same period as our evaluation and identified three CHEMPACK containers that FDA suggests may require additional testing to assure potency. However, it is unclear from CDC's comments how it accounted for CHEMPACK containers that were missing temperature readings and documentation of temperature-recording device calibrations.

In addition, CDC indicated that it plans to take other actions to address our findings and recommendations. For example, CDC will develop a plan to sequester CHEMPACK drugs if their storage temperatures exceed allowable mean kinetic temperature values and seek FDA testing and guidance for these drugs. Further, CDC is evaluating the feasibility of increasing the number of temperature readings taken to increase the confidence in fielded products. CDC is also outlining steps to retrospectively validate the Sensaphone computer system.

Finally, CDC stated that our report did not evaluate the overall Strategic National Stockpile program and therefore should not imply that problems exist with Strategic National Stockpile non-CHEMPACK

assets. Nevertheless, CDC has begun an assessment of how best to initiate an independent review of its quality system and other procedures relative to CHEMPACK containers, and the rest of the Strategic National Stockpile assets, to ensure compliance with FDA requirements.

We support CDC's efforts to address these findings and encourage it to continue making progress in these areas. We made technical changes to the report based on CDC's comments. For the full text of CDC's comments, see Appendix D.

APPENDIX A

The United States Pharmacopeia Definition of Controlled Room Temperature

A temperature maintained thermostatically that encompasses the usual and customary working environment of 68 degrees Fahrenheit (68°F) to 77°F that results in a mean kinetic temperature calculated to be not more than 77°F and that allows for excursions between 59°F and 86°F that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 104°F are permitted as long as they do not exceed 24 hours. Spikes above 104°F may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to 77°F," or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations.

An article for which storage at controlled room temperature is directed may, alternatively, be stored and distributed in a cool place, unless otherwise specified in the individual monograph or on the label.[41, 42]

[41] Cool temperatures are those between 59°F and 68°F.

[42] This definition is reproduced verbatim with the exception that the temperatures in the original version are in Celsius.

APPENDIX B

Methodology for Calculating Average Temperature

To calculate average temperature of the 967 CHEMPACK containers that had at least three daily temperature readings, we performed the following calculation for each container:

1. for each sequential pair of temperature readings, we multiplied the duration of time between readings by the average of the two temperatures;[43]
2. added all of the values from step one; and
3. divided the sum from step two by the total duration of time the container was in storage.

For example, if a container was stored at 74 degrees Fahrenheit (°F) at 12 a.m. day 1, 76°F at 8 a.m. day 1, 84°F at 4 p.m. day 1, and 74°F at 12 a.m. day 2, the average temperature using our methodology equals 78°F, i.e., (75°F x 8 hours) + (80° x 8 hours) + (79°F x 8 hours) = 1872 / 24 hours = 78°F.

[43] Not all containers had the same number of temperature readings because Sensaphones take temperature readings more frequently than every 8 hours when a container's storage temperature falls outside of the CDC-established storage range.

Cumulative Time CHEMPACK Containers Were Maintained Above 77°F

The table below shows the cumulative time that all 967 selected containers that had at least three daily Sensaphone readings, in accordance with Centers for Disease Control and Prevention procedures, for the 1-year period we reviewed were maintained above the storage range of 68 degrees Fahrenheit (68°F) to 77°F for CHEMPACK drugs, and the corresponding number and percentage of containers.

CHEMPACK Containers Maintained Above the Storage Temperature Range

Cumulative Time Above 77°F	Number of Containers	Percentage of Selected Containers (n=967)**
8 hours to 1 day	52	5%
Over 1 day to 1 week	114	12%
Over 1 week to 1 month*	78	8%
Over 1 month to 3 months	70	7%
Over 3 months to 6 months	25	3%
Over 6 months	12	1%
Total	**351**	**36%**

* We define a month as a total of 30 days.

** Percentages are rounded to the closest whole number.

Source: Office of Inspector General analysis of Sensaphone temperature readings of CHEMPACK containers.

AGENCY COMMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

NOV 6 2009

TO: Daniel R. Levinson
Inspector General

FROM: Director
Centers for Disease Control and Prevention

SUBJECT: Office of Inspector General's Draft Report" "The Center for Disease Control and Prevention's CHEMPACK Project: Nerve Agent Antidote Storage," OEI-04-08-00040

The Centers for Disease Control and Prevention (CDC) appreciates the opportunity to review and comment on the Office of Inspector General's (OIG) draft report, *The Centers for Disease Control and Prevention's CHEMPACK Project: Nerve Agent Antidote Storage*. Thank you for your review of this important and unique part of our medical countermeasure stockpile.

The objectives of the OIG review were to determine the extent to which (1) nerve agent antidotes in the CHEMPACK project were stored at temperatures required by the Food and Drug Administration (FDA); (2) CDC implemented procedures to ensure the quality of nerve agent antidotes in the CHEMPACK project; and (3) nerve agent antidotes in the CHEMPACK project appropriately received extended expiration dates under the Shelf Life Extension Program (SLEP).

The CHEMPACK project is a unique part of the overall function of the Strategic National Stockpile (SNS), and as such is managed differently than other SNS sites. A major challenge in managing the project occurred early in 2004 when the Administration directed CDC to significantly accelerate fielding of the CHEMPACK containers after completing just eight months of what was scheduled to be a two year pilot test. At that time, CDC was charged with simultaneously developing the policies and procedures to manage the program while fielding what would eventually total over 1,900 containers at 1,300 different storage sites across the nation. Given the manner in which the CHEMPACK project was launched and has evolved, we welcome the opportunity to continue to make improvements in SNS policies and procedures. Changes in the CHEMPACK project will need to be balanced against intended outcomes, risk, and available resources.

The report's findings provide important information regarding the adequacy of quality systems and procedures and CDC adherence to them at the time of the evaluation (November 2006 to

December 2007). CDC believes OIG findings are productive in ensuring that CDC has sound policies and procedures in compliance with FDA. However, the OIG did not evaluate the quality of CHEMPACK drugs, and its findings do not address the viability of these drugs. .

CDC takes its stewardship responsibilities for the CHEMPACK project seriously and has, therefore, instituted a corrective action program to address the OIG findings and recommendations. In particular, CDC has already taken the corrective actions noted below.

- As of September 2008, CDC came into compliance with FDA guidance to assure controlled room temperature (CRT) was maintained at the 1,300 unique CHEMPACK storage locations by routinely calculating mean kinetic temperature (MKT) for all CHEMPACK containers. CDC has also formalized its process for monitoring MKT, including developing policies and procedures for documenting and correcting any temperature problems, should they arise.

- To address the concerns about CHEMPACK containers held outside of CRT requirements, and identify any containers that would potentially need FDA testing to ensure the potency and purity of these products, CDC retroactively calculated MKT for the same time period as OIG. Our analysis identified 3 CHEMPACK containers that FDA suggests may require additional testing to assure potency. CDC is working to submit the pharmaceutical lots of these 3 (out of a total of 1,238) containers to FDA for additional testing to ensure potency and purity. The remaining 1,235 CHEMPACK containers are not at risk, per October 14, 2009, FDA guidance.

We appreciate how the OIG findings on the CHEMPACK project could cause uncertainty about the quality systems used to manage the broader SNS program of central supply and vendor-managed inventory. However, the OIG did not evaluate the overall SNS program; therefore, the OIG report should not imply that problems exist with SNS non-CHEMPACK assets. Maintaining quality systems at 1,300 CHEMPACK locations across the country is inherently different than assets stored in a limited number of facilities solely dedicated to the storage and management of medical countermeasures. Given CDC's commitment to the effectiveness of its programs and discussions already underway with Assistant Secretary for Preparedness and Response (ASPR) around improving quality systems, CDC will undertake a review of our quality systems and procedures for the broader SNS program.

Response to Individual Recommendations

OIG Recommendation 1: Seek FDA guidance on whether CHEMPACK drugs that have received extended expiration dates under SLEP are appropriate for use.

CDC concurs with the need to seek FDA guidance on the drugs in question. Over a year ago (in September 2008), CDC sought FDA guidance on this matter. FDA advised that the products stored up to the maximum excursion temperature (86 degrees) should not be at risk based on

FDA's analysis of the stability data provided by the manufacturer. Through official guidance related to this issue dated October 14, 2009, FDA recommended CDC "consider testing products stored above 80 degrees Fahrenheit for potency and purity." Based on FDA guidance, CDC needs to submit product lot samples for the three containers to FDA for testing, as previously discussed.

CDC has begun to pull and place in quarantine the content of the three CHEMPACK containers in question. This will be completed by November 30, 2009. CDC will dialogue with FDA to determine testing requirements and status of this product.

Moving forward, CDC will develop a plan to ensure that CHEMPACK drugs are sequestered if the storage temperature exceeds allowable MKT, and held until FDA tests those lots and provides guidance on their status. The agency expects to implement all quality system improvements related to this issue within six months.

CDC has already implemented a critical step in ensuring that CHEMPACK drugs are appropriate for use by instituting calculation of MKT using FDA-approved methodology for all CHEMPACK containers (as of September 2008) to ensure product is stored under the correct temperature conditions.

OIG Recommendation 2: Revise its CHEMPACK project SLEP procedures to comply with FDA requirements.

CDC concurs that more clarity from FDA is needed on the issue of SLEP procedures for CHEMPACK. Therefore, we will consult further with FDA on this matter.
Further, CDC has begun an assessment of how best to initiate an independent review of its quality system and other procedures relative to the rest of the SNS assets to ensure compliance with FDA requirements. This review will also include CHEMPACK containers.

OIG Recommendation 3: Revise its CHEMPACK drug storage temperature requirements to comply with FDA's requirements.

CDC concurs with the need to ensure CHEMPACK drug storage temperatures comply with FDA guidance. As of September 2008, CDC is complying with FDA guidance regarding temperature monitoring by calculating MKT for all CHEMPACK containers (using an FDA approved methodology).

In its report, OIG used an average temperature calculation as a substitute for MKT (OIG did not calculate MKT), as CDC was not calculating MKT at the time of the OIG review. Using this methodology, OIG determined that 9 percent of CHEMPACK containers may have fallen outside of the FDA requirements. However, as part of our corrective action, CDC calculated MKT (using an approved FDA methodology) for this same time period and determined that

approximately 99 percent of the CHEMPACK containers met FDA temperature requirements for drug viability.

Further, CDC acknowledges the need to store CHEMPACK drugs within the FDA required temperature range of 68 to 77 degrees. However, excursions are to be expected, given the variability between the 1,300 storage sites. CDC is working with the CHEMPACK storage sites on ways to minimize time that the CHEMPACK drugs spend in the excursion range and to lessen the probability of MKT rising above the allowable standard.

CDC is also evaluating appropriateness of Sensaphone alarm set points. CDC will reset alarm points and triggers based on this analysis. Where voluntary storage sites cannot be assured to maintain CRT, except for permissible excursions, CDC will work with memorandum of agreement (MOA) signatories to locate suitable alternatives.

OIG Recommendation 4: Ensure that the CHEMPACK projects quality system meets current Good Manufacturing Practices (cGMP) requirements for drug storage.

CDC concurs with the need to review CHEMPACK project quality systems. Developing the oversight structure necessary to manage the project while simultaneously fielding the containers presented a unique set of challenges. With the fielding of all CHEMPACK containers completed in March 2008, CDC has turned its attention to reexamining the quality systems in place to ensure regulatory compliance and adherence to cGMP. As an example of such, we are currently evaluating the feasibility of increasing the number of temperature readings taken in order to increase the confidence in fielded products.

The Department of Health and Human Services (HHS), Assistant Secretary for Preparedness and Response (ASPR) and CDC are working collaboratively to create an overarching quality control framework to further assure product quality and promote public confidence in CDC product management. CDC will evaluate the CHEMPACK project based on the outcomes of this overarching review and HHS guidance, and modify procedures where appropriate. CDC will also continue its internal review of the Quality Control Unit policies and procedures and update these as appropriate. To ensure oversight standards related to product quality are clearly articulated, a working group including CDC, FDA, and ASPR will provide recommendations for appropriate peer review or other reviews of SNS quality system audit findings and corrective action plans.

Below are specific corrective actions underway.

- As part of adherence to relevant cGMP guidelines, a draft plan has been developed outlining steps to conduct a retrospective validation of the Sensaphone computer system. The plan identifies functional requirements and a strategy for validation.

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- DSNS 1101 Equipment Services and Preventive Maintenance Standard Operating Procedures (SOP) outlines the Sensaphone and equipment preventive maintenance program which includes calibration and documentation through service records. This SOP is currently being revised to require the review of calibration records by the SNS Quality Control Unit.

- Based on dialogue with FDA, CDC will determine if any further modifications to Project Area MOAs related to temperature controls are needed. CDC will modify SOPs and adjust monitoring systems to ensure CHEMPACK is compliant with any new temperature monitoring requirements.

We appreciate your consideration of the comments contained in this memo as you develop the final report. We are happy to discuss any of these comments with you. Please direct any questions regarding these comments to Mr. Shaun Ratliff by telephone at (404) 639-2809, or by e-mail at iggao@cdc.gov.

/S/

Thomas R. Frieden, M.D.,M.P.H.

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