Re-Testing of Stockpiled Drug Products for Emergency Use to Extend Shelf Life

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Since the initial results for both ﬁxed and transported stock samples were substantially below the compendial speciﬁcation, statistical sampling was not completed. Based on a statistical sampling having greater than one sample outside of predictions, the recommendation was that these supplies be replaced.

Materials
Mark I Nerve Agent Antidote Kits (NAAK, Meridian Medical Technologies, NSN 6505-01-388-9563, Lot 1T5333, ex 10/05) and pralidoxime chloride injection (Lot 7T5333, exp 05/10) were tested in this study.

Methods
Sampling Plan
Sample sizes were selected according to Military Standard 105E, General Inspection Level I. Reduced sampling, at an Acceptable Quality Level (AQL) of 1% (non-conforming items) were evaluated on Statistical Quality Control 7. Military Standard 105E (ANSI/ASQ Z1.4, ISO 2859, BS6001, DIN4064, NF09/02, UN1494, K.S A1309) is a generally recognized representative sampling standard for batches having a deﬁned lot size and for which it will be assessed at a deﬁned AQL. The relationship between batch size and sample size is determined by the AQL and the inspection level. Special Inspection Levels (SIL) are used for products that are employing reduced sample sizes when a history of high quality standards can be demonstrated. Thirteen (13) samples were randomly selected from each stockpile sample set for initial testing. If no non-conforming results are obtained the entire lot is to be deemed to meet speciﬁcations. If only one of the initial samples does not conform to speciﬁcations, the remaining samples should be tested. If two or more non-conforming samples are obtained in the ﬁrst or second phase of testing, the lot is to be considered not to meet new speciﬁcations.

Analytical Standards
Standards and samples were prepared in accordance with the specifications of the United States Pharmacopeia (USP). The high performance liquid chromatography (HPLC) technique was modiﬁed as indicated to improve resolution and data were analyzed using Dionex Chromatography Client (version 4.4 Build 49919) software.

The assay limit speciﬁed in the USP for atropine sulfate injection was 1 mg/mL and 105% of the labeled content (2 mg). The assay limit speciﬁed in the USP for pralidoxime chloride injection was 90-110% of the labeled content (300 mg).

Atropine Sulfate Injection
Atropine Sulfate USP reference standard was dissolved in purified water to provide standards with concentrations of 0.08, 0.10, 0.24, 0.28, 0.42, and 1.02 mg/mL of pralidoxime sulfate concentrations after dilution.

Atropine Sulfate injection samples were prepared for assay by ﬁring the AtroPen® injector into a 25-mL volumetric flask and diluting to volume with purified Medical Water. The injection is containing 2 mg for each 1 mL and the dilution with puriﬁed water was performed to the mark.

Atropine Sulfate USP and injection were assayed on a Dionex Ultimate 3000 series HPLC using the following conditions:
- Column: Supelco LC-18 5 μm, 30 x 4.6 mm
- Column Temperature: Controlled at 25ºC
- Injection Volume: 10 μL
- Flow Rate: 1.3 mL/min
- Detector Wavelength: 254 nm
- Gradient: 80% Water, 20% (Acetonitrile)
- Run Time: 28 min

A representative chromatogram of the reference standard atropine chloride USP is provided in Figure 2.

Pralidoxime Chloride Injection
Pralidoxime Chloride USP reference standard was oven-dried at 105 ºC for 10 hours to constant weight. The pralidoxime chloride samples were prepared in purified water with concentrations of 0.28, 0.42, and 1.02 mg/mL of pralidoxime chloride concentrations after dilution.

Pralidoxime chloride injection samples were prepared for assay by dissolving a 1:1 mixture of AtroPen® and pralidoxime chloride injection by ﬁring the AtroPen® injector into a 25-mL volumetric flask and diluting to volume with purified Medical Water. The injection is containing 0.75 mg/mL of each and having 2 mL with a concentration of 300 mg/mL, and the dilution with purified water was performed to the mark. A representative chromatogram of the reference standard pralidoxime chloride USP is provided in Figure 2.

Since the initial results for both ﬁxed and transported stock samples were substantially below the compendial speciﬁcation, statistical sampling was not completed. Based on a statistical sampling having greater than one sample outside of predictions, the recommendation was that these supplies be replaced.

Based on a statistical sampling of the ﬁxed stock having all thirteen samples meet USP speciﬁcations and the transported stock having only one sample of the 26 tested outside of speciﬁcations the recommendation was that these supplies continue to be used in the ﬁeld. The initial testing was conducted 18 mos beyond expiry and a second analysis was conducted 42 mos post-expiry. Assuming the initial test was valid, the 42 mos post-expiry results would indicate that the time of manufacture was 12-18 mos prior to the labeled expiry date, retesting of the sample was indicated. The analysis of thirteen samples in this three trimester interval of the supplies are rejected with 99% probability to meet speciﬁcations until 75 mos post-expiry for the ﬁxed stock and 75 mos post-expiry for the transported stock (Figure 8).

Conclusions
Initial testing of atropine sulfate injection and pralidoxime chloride injection was conducted at 17 mos and 16 mos beyond expiry, respectively, and indicated that the atropine sulfate injection did not meet speciﬁcations and should be replaced. The pralidoxime chloride ion injection speciﬁcations were met again at 48 mos beyond expiry and extrapolation indicated the supplies should last for at least another 15 mos with 95% conﬁdence.

In subsequent germination agencies can control costs and extend the life of their bacteriologic stockpiles by implementing a testing program to screen out non-conforming lots and by using the results of testing to make a selective replacement. The agencies also must comply with FDA regulations regarding Emergency Use Authorization 4 and labeling 5.

References
2. PDC Online at www.pdc-online.com
3. USP 28/ NF 23, United States Pharmacopeial Convention, Rockville, MD, July 2005
4. Emergency Use of Authorized Medical Products, FDA, Rockville, MD, July 2007
5. 21 CFR 11.37 and 21 CFR 11.201

Figure 1 – Atropine Sulfate Injection
Figure 2 – Pralidoxime Chloride Injection
Figure 3 – Atropine Sulfate Injection, Mobile (Transported) Stock
Figure 4 – Atropine Sulfate Injection, Fixed Stock (17 mos post expiry)
Figure 5 – Pralidoxime Chloride Injection, Fixed Stock (16 mos post expiry)
Figure 6 – Pralidoxime Chloride Injection, Mobile (Transported) Stock (12 mos post expiry)
Figure 7 – Atropine Sulfate Injection, Mobile (Transported) Stock (42 mos post expiry)