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

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Introduction

A recent publication[1] reported on the Shelf Life Extension Program (SLEP) which supports the Medical Readiness Strategic Plan developed by the US Department of Defense (DOD) Health Affairs and US Military Medical Departments. The SLEP program is administered by the US Food and Drug Administration (FDA) for DOD and the Strategic National Stockpile (SNS). Various local government agencies have acquired stockpiles of pharmaceutical agents as provisions for an emergency response to bioterrorism; however, these supplies are not covered under the SLEP program. The cost of replacing these agents prior to the end of their useful life is prohibitive for local government agencies; therefore, a program for assessing stability of specific agents beyond the expiry date was investigated.

Materials

Mark I Nerve Agent Antidote Kits (NAAK, Meridian Medical Technologies, NSN 6505-01-174-9919) consisting of atropine sulfate injection (AtroPen® Auto-Injector, Lot 1S4395, exp 10/06) and pralidoxime chloride injection (Lot 1T5333, exp 09/06) 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% (allowable non-conforming items) calculated via Statistical Quality Control.[2]

Military Standard 105E (ANSI/ASQ Z1.4, ISO 2859, BS6001, DIN40.080, NFX06-022, UN148-42, KS A 3109) is a generally recognized representative sampling standard for batches having a defined lot size and which will be assessed against a defined AQL. The relationship between batch size and sample size is the Inspection Level. Special Inspection Levels are available employing reduced sample sizes when a history of high quality exists, the risk of reduced testing is understood and/or testing of greater quantities is prohibitively expensive. Twenty-six (26) randomly chosen samples were obtained from both fixed and mobile (transported) stock (based on deployed stock of 1,638 fixed and 1,482 transported Mark I units). Thirteen (13) samples were randomly selected from each supplied sample set for initial testing. If no non-conforming results are obtained the entire lot is 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 either the first or second phase of testing, the lot is considered to no longer meet specifications.

Analytical Methods

Standards and samples were prepared in accordance with the analytical methods provided in the United States Pharmacopeia (USP).[3] The high performance liquid chromatography (HPLC) conditions specified were modified as indicated to improve resolution and data were analyzed using Dionex Chromeleon Client software (v. 6.70 SP3 Build 1884).

The assay limit specified in the USP for atropine sulfate injection is +/- 7% of the labeled content (2 mg). The assay limit specified in the USP for pralidoxime chloride injection is +/- 10% of the labeled content (300 mg/mL)

Atropine Sulfate Injection

Atropine Sulfate USP reference standard was dissolved in purified water, to provide standards with concentrations of 0.096, 0.080 and 0.064 mg/mL of atropine sulfate. The concentrations of USP standards represent 120, 100, and 80% values of the atropine sulfate injection 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 water. The injection is labeled as containing 2 mg for each 1 mL injection, and the dilution with purified water provides a final concentration of 0.080 mg/mL.

Atropine Sulfate USP and injection were assayed on a Dionex Ultimate 3000 series HPLC using the following conditions.

- Guard Column: Apollo C18 5 µm, 7.5 x 4.6 mm
- Column: Supelcosil LC-18, 5 µm, 300 x 4.0 mm
- Column Temperature: Controlled at 25ºC
- Injection Volume: 100 µL
- Flow Rate: 1.3 mL/min
- Run Time: 28 min
- Mobile Phase: Solvent A (15 mM Acetate, 15 mM Tetrabutylammonium hydrogen sulfate Buffer pH=5.5/5% Acetonitrile) + Solvent B (Acetonitrile)
- Gradient:

Time (min)	% B
0	0
10	0
15	90
18	0
28	0

- Detector Wavelength: 254 nm

A representative chromatogram of the reference standard atropine USP is provided in Figure 1.

Figure 1 – Atropine Sulfate USP Reference Standard

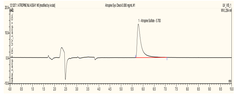
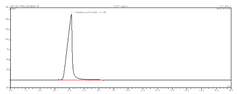


Figure 2 – Pralidoxime Chloride USP Reference Standard



Pralidoxime Chloride Injection

Pralidoxime Chloride USP reference standard was oven-dried at 105 ˚C for three hours prior to preparing standards in purified water with concentrations of 0.288, 0.24, and 0.192 mg/mL of pralidoxime chloride. These concentrations represent 120, 100 and 80% values of Pralidoxime Chloride concentrations after dilution.

Pralidoxime chloride injection samples were prepared for assay by firing the injector into a 25 mL volumetric flask and diluting to volume with purified water. The Pralidoxime injection is labeled as having 2 mL with a concentration of 300 mg/mL, and the dilution with purified water provides a final concentration of 0.24 mg/mL.

Pralidoxime Chloride USP and injection were assayed on an Aglient 1100 series HPLC using the following conditions:

- Guard Column: Apollo C18 5 µm, 7.5 x 4.6 mm
- Column: Zorbax ODS, 5 µm, 250 x 4.6 mm
- Column Temperature: Controlled at 25ºC
- Injection Volume: 15 µL
- Flow Rate: 1.4 mL/min
- Run Time: 28 min
- Mobile Phase: 48% Solvent A (3.0 mM H3PO4, 2.0 mM Tetraethylammonium chloride) + 52% Solvent B (Acetonitrile)
- Detector Wavelength: 270 nm

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

Results & Discussion

Atropine Sulfate Injection

Fixed Stock

Samples of the fixed stock of atropine sulfate injection were analyzed at 17 mos beyond expiry and had a faint brown discoloration; thus, degradation of the active ingredient was suspected. HPLC analysis of the first five of the thirteen samples indicated an average assay value of 77% of label claim, which is well below the minimum of 93% specified in the USP (allowable range 93-107%). A corresponding increase in identified total impurities was also observed (average 27%). A representative chromatogram is provided in Figure 3, showing the main atropine peak and multiple impurity peaks.

Mobile (transported) Stock

Samples of the mobile stock of atropine sulfate injection were analyzed at 17 mos beyond expiry and had a light brown to brown discoloration; thus, degradation of the active ingredient was suspected. HPLC analysis of the first five of the thirteen samples indicated an average assay value of 77% of label claim, which is well below the minimum of 93% specified in the USP (allowable range 93-107%). A corresponding increase in identified total impurities was also observed (average 34%). A representative chromatogram is provided in Figure 4, showing the main atropine peak and multiple impurity peaks.

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

Figure 3 – Atropine Sulfate Injection, Fixed Stock (17 mos post-expiry)

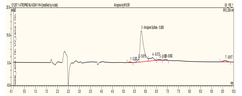
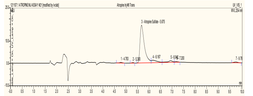


Figure 4 – Atropine Sulfate Injection, Transported Stock (17 mos post-expiry)



Pralidoxime Chloride Injection

Fixed Stock

Samples of the fixed stock of pralidoxime chloride injection were analyzed at 18 mos and 42 mos beyond expiry and had a faint yellow to yellow color, which was deemed to be normal. HPLC analysis of thirteen of the samples yielded an average assay value of 107% and 102% of label claim at 18 mos and 42 mos after expiry, respectively; both of which are within the allowable range of 90-110% as specified in the USP. All individual results also fell within this range. The average level of total impurities was 2.4% and 2.0% at 18 mos and 42 mos after expiry, respectively. A representative chromatogram of pralidoxime chloride in fixed stock samples at 42 mos after expiry is provided in Figure 5.

Mobile (transported) Stock

Samples of the mobile stock of pralidoxime chloride injection were analyzed at 18 mos and 42 mos beyond expiry and had a yellow color, which was deemed to be normal. HPLC analysis of thirteen of the samples yielded an average assay value of 104% of label claim at 18 mos beyond expiry and 95% of label claim at 42 mos beyond expiry, both of which are within the allowable range of 90-110% as specified in the USP, although one individual result at 42 mos beyond expiry was outside of the acceptable range at 61.1%.

The level of total impurities averaged 3.1% at 18 mos beyond expiry and 5.9% at 42 mos beyond expiry. Since one sample result fell outside of the acceptable range at 42 mos beyond expiry, a second set of 13 samples was assayed. This set had an average assay value of 98% of label claim, which is within the allowable range. All individual results also fell within this range and the level of total impurities averaged 5.7%. A representative chromatogram of pralidoxime chloride in mobile stock samples tested at 42 mos beyond expiry is provided in Figure 6.

Figure 5 – Pralidoxime Chloride Injection, Fixed Stock (42 mos post expiry)

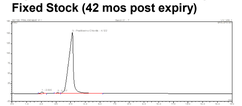
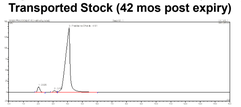


Figure 6 – Pralidoxime Chloride Injection, Transported Stock (42 mos post expiry)



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 post-expiry and a second analysis was conducted 42 mos post-expiry. Assuming the supplies were at 100% of label at the time of manufacture and that the time of manufacture was 12-18 mos prior to the labeled expiration date, regression analysis of the results from these three timepoints indicates that the supplies are projected with 90% probability to meet specifications until 73 mos post-expiry for the fixed stock (Figure 7) and 57 mos post-expiry for the transported stock (Figure 8).

Figure 7 Fixed Stock - Content Assay

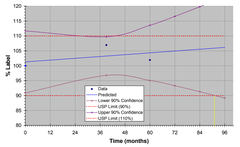
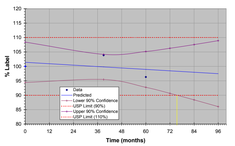


Figure 8 Transported Stock - Content Assay



Conclusions

Initial testing of atropine sulfate injection and pralidoxime chloride injection was conducted at 17 mos and 18 mos beyond expiry, respectively, and indicated that the atropine sulfate injection did not meet specifications and should be replaced. The pralidoxime chloride injection met specifications and was retested again at 48 mos beyond expiry and extrapolation indicated the supplies should last for at least another 15 mos with 90% confidence.

Local government agencies can control costs and extend the life of their bioterrorism stockpiles by implementing a testing program to assess the stability on a lot-by-lot basis and using the data for selective replacement. The agencies also must comply with FDA regulations regarding Emergency Use Authorization[4] and labeling[5].

References

1. RC Lyon, et al., Stability Profiles of Drug Products Extended beyond Labeled Expiration Dates, Journal of Pharmaceutical Sciences, Vol 95, No. 7, July 2006.
2. SQC Online at www.sqconline.com
3. USP 28 / NF 23, United States Pharmacopoeial Convention, Inc., Rockville, MD, 2005
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5. 21 CFR 211.137 and 21 CFR 201.17