



Brief Report

Oseltamivir for pandemic influenza preparation: Maximizing the use of an existing stockpile



Twisha S. Patel PharmD ^a, Sandro Cinti MD ^b, Duxin Sun PhD ^c, Siwei Li PhD ^c,
Ruijuan Luo PhD ^c, Bo Wen PhD ^c, Brian A. Gallagher JD ^{d,e}, James G. Stevenson PharmD ^{a,c,*}

^a Pharmacy Services, University of Michigan Health System, Ann Arbor, MI

^b Infectious Diseases, University of Michigan Health System, Ann Arbor, MI

^c University of Michigan College of Pharmacy, Ann Arbor, MI

^d Marshall University School of Pharmacy, Huntington, WV

^e Joan C. Edwards School of Medicine, Huntington, WV

With the threat of significant morbidity and mortality following an influenza pandemic, stockpiling of antiviral agents such as oseltamivir is recommended. Shelf-life extension was explored to maximize use of an existing stockpile. This analysis demonstrated that oseltamivir retains potency defined by United States Pharmacopeia acceptance criteria beyond the labeled expiration date.

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BACKGROUND

Infection with the influenza virus can lead to devastating complications, including mortality.¹ The influenza pandemic in 1918 and the Asian H5N1 outbreak in 2005 taught our nation a valuable lesson about the importance of creating a national preparedness plan to combat the spread of infection. Because health care workers are at high risk for exposure, with attack rates as high as 59% in outbreaks,² preparedness plans for individual health care institutions are also essential.

Influenza vaccination alone is not sufficient to control transmission of the virus because production of a vaccine against an identified strain would take an estimated minimum of 6 months.³ Furthermore, infection control practices such as instituting droplet precautions are not expected to eliminate the risk of infection and transmission amongst health care workers.² Chemoprophylaxis and treatment of high-risk individuals with antiviral agents can help to control infection rates.^{4,5} Thus, stockpiling of effective neuraminidase inhibitors, such as oseltamivir, is an accepted method of influenza pandemic management endorsed by the World Health Organization.⁶

In 2005, our 930-bed tertiary care hospital implemented a strategy to stockpile enough oseltamivir to treat between 1,500 and 3,500

hospital employees because up to 35% are expected to become ill even with the institution of optimal infection control practices during an influenza pandemic.⁷ Although imperative, this strategy created a significant financial burden on our institution: A 5-day treatment course of oseltamivir is considerably expensive (\$120/box of 10 75-mg capsules, University of Michigan Health System, unpublished data). Because oseltamivir has a shelf-life of 5 years as determined by the manufacturer, a substantial cost would be incurred every 5 years to maintain an adequate stockpile.⁸ Strategies to defer this replacement cost were examined nationally. The Food and Drug Administration (FDA) first explored shelf-life extension of oseltamivir and after stability testing declared an expiry extension to 7 years in 2010 and later to 10 years in 2013 for particular lots following the 2009 H1N1 outbreak and 2013 oseltamivir shortage, respectively.⁹ Given the results of this stability analysis, it is possible that oseltamivir retains potency for a significant time beyond the labeled expiration date.

In an attempt to optimize the use of our existing oseltamivir stockpile, we conducted a potency analysis to determine whether lots that have exceeded their labeled expiration date should be discarded or whether they should be retained for potential use in the event of a pandemic.

METHODS

According to United States Pharmacopeia (USP) acceptance criteria, oseltamivir phosphate capsules contain oseltamivir phosphate equivalent to no less than 90.0% and no more than 110.0% of the

* Address correspondence to James G. Stevenson, PharmD, Pharmacy Services, University of Michigan Health System, Ann Arbor, MI.

E-mail address: jimsteve@med.umich.edu (J.G. Stevenson).

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Table 1

Summary of the percentage of the labeled amount of oseltamivir (75 mg) in the capsules from different lot numbers during July 2014

Lot No.	Labeled expiration date	Trial 1 (%)	Trial 2 (%)	Trial 3 (%)	Mean (%)	Standard deviation
B1119	4/2010	106.5	110.0	97.9	104.8	6.2
B1120	4/2010	103.8	98.9	92.9	98.5	5.5
B1183	1/2011	97.6	96.4	98.4	97.4	1.0
U2004	8/2010	95.5	100.9	99.8	98.7	2.9
U2007	8/2010	100.2	99.3	98.1	99.2	1.0
U2096-01	10/2011	98.4	93.4	92.0	94.6	3.3
U2110	11/2011	91.9	91.9	91.9	91.9	0.0
U4071	9/2012	90.6	87.8	94.8	91.0	3.5
Unexpired		88	86.8	95.8	90.2	4.9

labeled amount of oseltamivir. A potency analysis was conducted in late July 2014 to determine the percentage of the labeled amount (75 mg) of oseltamivir in the different lots of our institutional stockpile using an analytical instrument, high-performance liquid chromatography and ultraviolet detection.

Our stockpile included lots with labeled expiration dates ranging from 2010-2012. Twenty capsules from each lot were used to create a sample solution that was compared with the USP standard. The samples preparation and analysis were performed as described in the USP chapter for oseltamivir phosphate capsules assay.¹⁰ The peak areas of oseltamivir from the samples were collected for the calculation. Based on the USP criteria, the percentage of the labeled amount of oseltamivir in the samples tested was calculated using the following equation, $\text{result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$ where r_U = peak response from the sample solution, r_S = peak response from the standard solution, C_S = concentration of USP oseltamivir phosphate RS in the standard solution (milligrams/milliliter), C_U = nominal concentration of oseltamivir in the sample solution (milligrams/milliliter), M_{r1} = molecular weight of oseltamivir (312.40), and M_{r2} = molecular weight of oseltamivir phosphate (410.40).

RESULTS

Eight lots that had exceeded their labeled expiration and 1 unexpired lot were tested in this analysis. This potency analysis confirmed that all lots were within the USP acceptance criteria of 90%-110% labeled oseltamivir. Results are described in Table 1.

DISCUSSION

Maintaining a stockpile of oseltamivir is considered an appropriate strategy for pandemic preparation by national and international organizations. In fact, the US government has added oseltamivir to its strategic national stockpile.¹¹ However, national and state stockpiles are not expected to provide individual health care centers with enough antiviral medications for treatment and chemoprophylaxis of high-risk health care providers. Thus, institutions should maintain adequate drug stockpiles.

Stockpiling oseltamivir represents a significant financial burden especially for an institution of our size. If the labeled shelf-life of 5 years was used, a cost of nearly \$350,000 would be incurred (treatment of up to 3,500 employees with 75 mg twice daily for 5 days at \$120/course). To defer the high replacement costs, the government formed the Shelf Life Extension Program to evaluate the stability and potency of expired drugs. Through this program the shelf-life of oseltamivir was expanded from 5-10 years.⁹ The lots in our stockpile have exceeded this expiry extension. Thus, an evaluation to determine whether the existing lots of oseltamivir could

still be used in event of a serious pandemic or whether they should be discarded was necessary.

Whereas federal law requires that drug products bear an "expiration date determined by appropriate stability testing," it does not state that a product is adulterated or misbranded if dispensed after that date.¹² In fact, the FDA recognizes that many drugs remain safe and effective long after the initial expiration date has passed and in 1986 created the Shelf Life Extension Program to extend the life of these products to facilitate efforts to establish a strategic national stockpile of stable medications to respond to large-scale public health emergencies.¹³ In addition, the FDA provides at least 3 other exemptions to allow emergency use of medications that remain stable despite being past the initial expiration date. The FDA can provide an Emergency Use Authorization (Section 564), or use their explicit authority to extend expiry under the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 or by choosing not to take enforcement action.¹³

The results of our analysis demonstrate that the lots of oseltamivir in our stockpile are still within the USP potency standard of 90%-110% labeled drug. This suggests that it is unnecessary to replace the entire cache at this time. Instead, we propose a strategy to create a rotating inventory so that the cost of replacement is distributed over several years and the life of the existing lots is extended. This strategy will allow our institution to retain a relatively large cache of antiviral product on hand in the event of a true influenza pandemic, while avoiding a large expenditure in 1 year to replace the entire cache, which has exceeded its labeled expiration date.

Limitations to uniformly implementing this strategy exist, including lack of availability of high-performance liquid chromatography and ultraviolet detection technology to assay product. Federal law exempts dispensers of prescription medications from many of the labeling requirements for manufacturers, including the necessity of placing an expiration date on the label of the package dispensed to a patient.¹⁴ Some states have labeling and other requirements based on expiration dating. Therefore, practitioners who intend to stockpile and use viable product in a pandemic situation after the initial expiration date should research applicable state law. Thus, when formulating a program to be able to use stable but technically expired medications, entities should plan to draft patient consent forms disclosing that the product is technically outdated and interface with relevant governing bodies at both the state and federal levels to obtain waivers and/or approvals to ensure legal compliance.

If an influenza pandemic occurred, infection would undeniably threaten the lives of countless patients and health care workers. Although antiviral medications would be available through national and state stockpiles, it is imperative for institutions to also stockpile antivirals to ensure an adequate supply.

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