U.S. Department of Homeland Security
Washington, DC 20528

APR 1 2 2007

POLICY PAPER

Federal Emergency Management Agency's Radiological Emergency Preparedness Program Guidance To States and Local Governments For Shelf Life Extension of Potassium Iodide (KI)

Statement: The purpose of this policy paper is to provide guidance to State and local governments on shelf life extension of Potassium Iodide (KI).

Purpose: Provide guidance to State and local governments to extend the shelf life of Potassium Iodide (KI).

Policy: **OPTION ONE (1);** Potassium Iodide (KI) 130mg and 65mg tablets shelf life can be extended by two (2) year increments beyond the manufacturer's original published expiration date, provided the storage was conducted in accordance with published guidelines and product packaging was not comprised but remained intact as received by the manufacturer (ref A).

OPTION TWO (2); Conduct laboratory testing in accordance with FDA Guidance (ref A).

States and Local governments would be required to develop and maintain records of tablet potassium Iodide (KI) shelf life extensions by (ref B):

Indicating manufacturer
Tablet size
Quantity of tablets by size
Lot number
Original expiration date
New expiration date

This information will be posted in the Annual Letter of Certification (ALC) paragraph 2 Emergency Facilities and Equipment.

Exception: Liquid Potassium Iodide (KI) shelf life cannot be extended beyond the manufacturer's original published expiration date.

References (Attached)

A. U.S. Department of Health & Health Services – Food and Drug Administration letter dated February 15, 2007; Ref: OGD-#07- 0163.
Paragraph one
Paragraph two – lines 5 thru 9
Paragraph three – lines 5 thru 11
Paragraph four

B. U.S. Department of Health and Human Services – Food and Drug Administration, Center for Drug Evaluation and Research, "Guidance for Federal Agencies and State and Local Governments Potassium Iodide Tablets, Shelf Life Extension", Dated March 2004

Vanessa E. Quinn
Acting Director
Technological Hazards Branch
National Preparedness Directorate

4/12/07
Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Roy Zimmerman, Director
Office of Nuclear Security and Incident Response
US NRC MS T-4D22A
Washington, D.C. 20555

FEB 15 2007

Reference Number: OGD #07-0163

Dear Mr. Zimmerman:

This is in response to a February 5, 2007 e-mail request and other e-mail exchanges from Patricia Milligan, Senior Advisor for Emergency Preparedness, US Nuclear Regulatory Commission. The communications were regarding the appropriateness of the States that had obtained Iosat® Tablets (Potassium Iodide Tablets, USP) extending the expiration dating period of these stockpiled lots to 7 years.

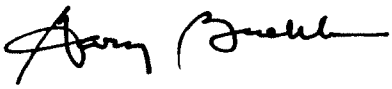
We understand that certain state governments have received from the Nuclear Regulatory Commission (NRC) Iosat® Tablets (Potassium Iodide Tablets USP) manufactured by Anbex, Inc. for stockpiling in the event of a radiation emergency. This drug product is manufactured under the approved Abbreviated New Drug Application (ANDA) 18-664. We understand that the stockpiled lots bear a 5 year expiration dating period. As it is known to the NRC that Anbex, Inc. has received approval from the Office of Generic Drugs (OGD) to apply a 7 year expiration dating period to this drug product, NRC requests advice from FDA as to whether it would be appropriate for the stockpiled lots that have a 5 year expiration date to have the expiration extended another 2 years.

When the expiration dating period of a drug product that is subject to an ANDA is extended by the manufacturer either due to FDA approval or under a protocol that had been approved by FDA, the extended expiration dating period is considered to apply to new lots manufactured after the extended expiration dating period has been implemented. The FDA does not have any regulation or policy regarding the application of an extended expiration dating period to lots that were manufactured prior to the implementation of the extended expiration dating period. However, FDA does not object to such a practice as long as adequate records are kept and doing so is scientifically sound. It would be considered to be scientifically sound if the lots having the expiration date extended had no significant difference in formulation, manufacturing process or packaging materials from current lots. The letter to Patricia Milligan at NRC from counsel to Anbex, Inc. dated January 23, 2007 indicates that this is the case.

Given the above information, it is our opinion that it would be scientifically valid and, therefore, appropriate for the stockpiled lots of Iosat® Tablets to have their expiration date extended by an additional 2 years. The States should ensure that the lots have been properly stored as recommended on the drug product label and also maintain an adequate record of the expiration date extension. This opinion is based strictly on scientific considerations. Any issues related to contractual agreements between the parties are outside the scope of these comments.

If you have any additional questions, please contact Mr. Michael Smela at 301-827-5775.

Sincerely,



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Guidance for Federal Agencies and State and Local Governments

Potassium Iodide Tablets Shelf Life Extension

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2004
Procedural

Guidance for Federal Agencies and State and Local Governments

Potassium Iodide Tablets Shelf Life Extension

Additional copies are available from:

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U.S. Department of Health and Human Services
Food and Drug Administration
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Contains Nonbinding Recommendations

Guidance for Federal Agencies and State and Local Governments[1]

Potassium Iodide Tablets Shelf Life Extension

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if that approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document is intended to provide guidance to Federal agencies and to state and local governments on testing to extend the shelf life of stockpiled potassium iodide (KI) tablets. The Agency has developed this document in response to several state inquiries on this topic. This guidance discusses FDA recommendations on testing for such shelf life extensions, the qualifications of laboratories suitable to conduct the tests, and issues regarding notification of holders of stockpiled KI tablets as well as end users[2] about changes to batch shelf life once testing has been successfully conducted.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Regulatory Framework

[1] This guidance has been prepared by the Office of Pharmaceutical Science (OPS) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For purposes of this guidance, *end users* are consumers who have purchased KI, or intermediate holders of KI, such as fire departments, health departments, hospitals, or other entities who store KI for use in emergencies.

FDA has approved two new drug applications (NDAs) for Potassium Iodide Tablets, USP.[3] Both applications[4] were approved prior to 1985 and currently provide for marketing of 130-mg KI tablets over the counter (OTC) (i.e., without a prescription). Potassium iodide tablets manufactured by one or both holders of these NDAs have been stockpiled under controlled conditions for use in a radiation emergency.

An abbreviated new drug application (ANDA)[5] for Potassium Iodide Tablets, USP (65 mg), was approved on September 10, 2002.[6]

B. HHS Role in Radiological Planning and Preparedness Activities

Under 44 CFR 351, the Federal Emergency Management Agency (FEMA) has established roles and responsibilities for Federal agencies in assisting state and local governments in their radiological emergency planning and preparedness activities. The Federal agencies, including the Department of Health and Human Services (HHS), are to carry out these roles and responsibilities as members of the Federal Radiological Preparedness Coordinating Committee (FRPCC). Under § 351.23(f), HHS is directed to provide guidance to state and local governments on the use of radioprotective substances and the prophylactic use of drugs (e.g., KI tablets) to reduce the radiation dose to specific organs, including dosage and projected radiation exposures at which such drugs should be used. As a part of HHS, FDA has been providing relevant guidance to other agencies and the public on KI.

C. FDA Guidance on Safe and Effective Use of KI as a Radioprotective Agent

In November 2001, FDA provided guidance on the safe and effective use of KI tablets as an adjunct to other public health protective measures in the event that radioactive iodine is released into the environment. The guidance *Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies* updated FDA's 1982 recommendations for the use of KI tablets to reduce the risk of thyroid cancer in radiation emergencies involving the release of radioactive iodine. The recommendations in that guidance addressed KI dosage and the projected radiation exposure at which the drug should be used. In April 2002, FDA issued another document, *Frequently Asked Questions on Potassium Iodide (KI)*. Additional information was provided for emergency pediatric dosing in *Home Preparation Procedure for Emergency Administration of Potassium Iodide Tablets to Infants and Small Children* (Home Procedures document), updated on July 3, 2002.[7]

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[3] United States Pharmacopeia.

[4] NDAs 18-307 and 18-664.

[5] Application ANDA 76-350.

[6] For an up-to-date listing of all approved KI products, consult the online version of FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (Electronic Orange Book) at http://www.fda.gov/cder/ob/default.htm.

[7] These guidances can be found at http:www.fda.gov/cder/guidance/index.htm; http://www.fda.gov/cder/drugprepare/KI_Q&A.htm; and http://www.fda.gov/cder/drugprepare/kiprep.htm, respectively.

D. Shelf Life Extension of KI Tablets

A number of state and local governments maintain stockpiles of KI tablets for use in the event of a radiation emergency involving the release of radioactive iodine. Several states have asked FDA what would be necessary to provide confidence that stockpiled KI tablets have retained their original quality (i.e., purity and potency) after passing the expiration date.

Previously, two approaches have been used to extend the shelf life of expired drug products: (1) the ordinary approach taken by drug manufacturers, and (2) the Department of Defense (DOD) Sponsored Shelf Life Extension Program.

1. Ordinary Shelf Life Extension

In the preferred method of shelf life extension for drug manufacturers, the manufacturer of an approved drug product may propose an extension of the expiration dating period for that product based on acceptable data from full, long-term stability studies on at least three production batches in accordance with a protocol approved in the application. The data can be reported and FDA can be notified of the extension of the expiration dating period in an annual report submitted to the NDA or ANDA if, after obtaining and analyzing the data in accordance with the protocol, the criteria set forth in the approved stability protocol are met. [8]

2. DOD-Sponsored Shelf Life Extension Program

Certain drug products have been qualified for shelf life extension through the Shelf Life Extension Program (SLEP), which is sponsored by the DOD and performed by FDA. The SLEP is sponsored by the DOD because of the substantial savings to the government from extending the shelf life of certain antibiotics and other drug products of strategic importance that are stored in Federal stockpiles in large quantities under controlled conditions.

It is unlikely that any manufacturer of KI tablets would be willing to conduct testing of all of the lots of KI tablets that have already been distributed, and it would be infeasible for FDA to include KI tablets in a DOD-sponsored program. Because several states have inquired about possibly testing stockpiled KI for shelf life extension, the Agency is providing this guidance on testing for such shelf life extensions of KI that is being stockpiled under controlled conditions. The Agency is also providing guidance on how to identify laboratories suitable to conduct the tests, how to notify holders of stockpiled KI tablets and end users about changes in shelf life,[9] and how to distinguish stockpiled batches with different shelf lives.

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[8] In June 1998, the Agency issued a draft guidance on stability testing, *Stability Testing of Drug Substances and Drug Products*. Once finalized, this guidance will represent the Agency's current thinking on this topic.

[9] The shelf life extension testing described in this guidance can provide confidence only that KI that has been stored in accordance with the conditions described in the labeling will retain its potency and quality for an extended period of time.

III. DISCUSSION

Studies conducted during the SLEP program on a variety of drug products have shown that shelf lives of most drug products can be extended well beyond their expiration dates, but the additional stability period for a given drug can be highly variable. It was concluded that, due to lot-to-lot variability, the stability and quality of drug products with extended expiration dates could only be assured by continual testing and systematic evaluation of each lot.[10]

A. Observations About KI Tablet Stability Based on Historical Data

Potassium Iodide Tablets, USP, is a compendial drug product that is manufactured to meet the recommended tests and specifications listed in the USP monograph. Assay and dissolution are the two specifications with potential relevance to stability, assuming identification and content uniformity testing were performed at release.[11] Stability studies over many years have confirmed that none of the components of KI tablets, including the active ingredient, has any significant potential for chemical degradation or interaction with other components or with components of the container closure system when stored according to labeled directions.

To date, the only observed changes during stability testing have been the failure of some batches of KI tablets to meet the USP S_1 dissolution specification, Q=75 percent in 15 minutes. Some tablets tested required slightly longer than the specified time to achieve dissolution, but even in the case of a failure of this sort, the product would remain usable. In such cases, instructions can be provided to crush the tablets and mix them with a juice or other liquid prior to administration as suggested for emergency pediatric dosing (see Home Preparation Procedures document cited above). In any long-term stability evaluation, appearance should be monitored as a matter of course. In the specific case of KI tablets, a yellowish discoloration would be indicative of stability problems. Since pure KI is known to be very stable (as long as it is protected from moist air),[12] ongoing evaluation and testing of each batch is probably unnecessary as long as the market package remains intact and continues to be stored under controlled conditions as described in the labeling.

B. Recommended Protocol for Shelf Life Extension of KI Tablets

An example of a protocol for shelf life extension of KI tablets from a given manufacturer (manufacturer A) of stockpiled KI tablets is illustrated in the table later in this section.

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[10] "Stability Profiles of Drug Products Extended Beyond Labeled Expiration Dates," AAPS Poster Session, November 2001, Center for Drug Evaluation and Research, Office of Pharmaceutical Sciences, Division of Product Quality Research.

[11] The quality control division of the manufacturer performs identification and content uniformity testing before the product can be released for sale.

[12] "Slightly deliquescent in moist air; on long exposure to air becomes yellow due to liberation of iodine, and small quantities of iodate may be formed; light and moisture accelerate the decomposition," *The Merck Index, 12th edition, 7809, Potassium Iodide.*

We recommend that samples of three batches of KI tablets from each manufacturer be selected and stored under controlled conditions of temperature and humidity and that the samples be tested periodically for compliance with the USP assay and dissolution specifications. Each sample should consist of at least 25 tablets per test, but it would be prudent to select larger samples so that sequential testing and extensions can be performed indefinitely. Accelerated stability testing storage conditions are 40°C/75% relative humidity (R.H.). These conditions stress the product and are thought to be conservatively predictive of future stability for a period of time under room temperature conditions. Accelerated data are commonly used to establish initial expiration dates for pharmaceuticals. The expiration dates are confirmed with real time stability data. For KI tablets, results of these tests could support shelf life extensions as follows:

- If the testing results are acceptable after 3 months of storage under accelerated storage conditions, all batches of KI tablets from that manufacturer can be considered to be tentatively qualified for an additional 2 years.
- We recommend that additional samples of the three batches, stored at room temperature in a warehouse or other facility, be tested at the end of 2 years from the date of initial sampling to confirm the shelf life extension tentatively qualified by the accelerated studies.
- After this confirmation, additional shelf life extensions in increments of 2 years can be qualified in the same fashion (i.e., 3 months storage at accelerated conditions followed by confirmatory data from samples stored at room temperature for 2 years).

We recommend that adequate records of the testing be kept even when a batch fails stability testing.

As already mentioned, in any long-term stability evaluation, we recommend that appearance be monitored. Discoloration of the tablets would provide an early indication of stability problems.

Table: Example of a Protocol for Shelf Life Extension

Batch Identification	Conditions	Start date	Finish date	Tests/Specifications* per USP: Assay: 60.1-69.9 mg	Diss.: 75% in 60 min.	Appearance	Stations Monitored	Shelf life	Expiry
Manufacturer A	90 days accelerated.	10/1/02	12/31/02	√	√	√	0, 1, 2, 3 months	5 years (tentative)	10/04 (tentative)
"	24 months long term confirmatory	10/02	ongoing	√	√	√	0, 3, 6, 9, 12, 18, 24 months	5 years (confirmed)	10/04 (confirmed)
"	90 days accelerated	10/1/04	12/31/04	√	√	√	0, 1, 2, 3 months	7 years (tentative)	10/06 (tentative)
"	24 months long term confirmatory	10/02	ongoing	√	√	√	0, 3, 6, 9, 12, 18, 24 months	7 years (confirmed)	10/06 (confirmed)

Test	***USP Specification***
Potassium Iodide (USP method – titration)	60.1– 69.9 mg (92.5% - 107.5%) **(65 mg tablet)**
Dissolution	NLT 75% (Q) of labeled amount in 15 minutes
Appearance (visual) (Not USP)	No appreciable discoloration

C. Identifying a Suitable Laboratory

If the decision is made to contract to have shelf life testing performed, we recommend that a suitable laboratory be identified. The testing suggested in this guidance is uncomplicated, and most laboratories should be capable of performing the tests. General laboratory GMPs are discussed in detail in *Guide to Inspections of Dosage Form Drug Manufacturer's CGMPRs*.[13] The recommended assay test is a titration. Dissolution testing and the requisite apparatus are adequately described in the USP. Because these are compendial tests, the validation of methodology is straightforward (i.e., typical parameters are listed in USP <1225>). Potassium iodide is a very soluble drug substance and will be dissolved in the specified medium upon tablet disintegration, confirmed by measurement of the UV (ultraviolet) absorbance at the specified wavelength using a UV spectrophotometer.

D. Identification of Batches Qualified for Extension and Notification of Expired Batches

Once KI tablets from a given manufacturer have been qualified for shelf life extension by the program described above, we recommend that some provision be made to notify holders of stockpiled KI and end users as to which drug product has been qualified and what the new expiration date should be. The identification and notification procedures should be amenable to additional extensions. Potassium iodide tablets that are centrally stored can be shrink wrapped and marked with the qualified shelf life extension dates to distinguish them from other KI tablets that have different expiry dates. Each individual container need not be relabeled. End users can be notified of the extension of the expiration date using the batch identification number on each bottle.

Due to the inherent stability of KI tablets, stockpiled or distributed batches will probably not need to be replaced frequently. As noted previously, even if a batch fails the dissolution test, instructions for crushing the tablets can be provided with distributed batches.

[13] This document is available at http://www.fda.gov/ora/inspect_ref/igs/dose.html.