NRC FORM 7 (8-2010) 10 CFR 110 — U.S. NUCLEAR REGULATORY COMMISSION

APPLICATION FOR NRC EXPORT OR IMPORT LICENSE, AMENDMENT, OR RENEWAL

(See Instructions on Pages 4 and 5)

APPROVED BY OMB: NO. 3150-0027 — EXPIRES: 08/31/2012

Recd

PART A. FOR NRC USE ONLY	☑ PUBLIC OR ☐ NON-PUBLIC	DATE RECEIVED: DEC 07 2010 JC
LICENSE NUMBER: XMAT 414	DOCKET NUMBER: 11005905	ADAMS ACCESSION NUMBER:

PART B. TO BE COMPLETED FOR ALL LICENSES, AMENDMENTS, OR RENEWALS

(If more space is needed to complete any of the items, use Pages 3-4 first, and then attach additional sheets, if necessary.)

1. NAME AND ADDRESS OF APPLICANT/LICENSEE	1a. NAME OF APPLICANT'S CONTACT	1b. APPLICANT'S REFERENCE NUMBER
CONCERT PHARMACEUTICALS, INC. 99 LEXINGTON AVENUE, SUITE 500 LEXINGTON, MA 02421	ANDREA E. DORIGO	N/A
	1c. PHONE NUMBER: (781) 674-5286	1d. FAX NUMBER: (781) 674-5386
	1e. E-MAIL ADDRESS: adorigo@concertpharma.com	

2. TYPE OF ACTION REQUESTED *(Check One)*

☑ EXPORT (Parts B, C, E) ☐ IMPORT (Parts B, D, E) ☐ AMENDMENT/RENEWAL Existing License Number: _____

3. CONTRACT NUMBER(S)	4. FIRST SHIPMENT DATE	5. LAST SHIPMENT DATE	6. PROPOSED EXPIRATION DATE
N/A	12/01/2010	12/01/2015	

PART C. TO BE COMPLETED FOR EXPORT LICENSES, AMENDMENTS, OR RENEWALS

(If more space is needed to complete any of the items, use Pages 3-4 first, and then attach additional sheets, if necessary.)

7. NAME(S) / ADDRESS(ES) OF SUPPLIERS AND/OR OTHER PARTIES TO THE EXPORT	8. NAME(S) / ADDRESS(ES) OF INTERMEDIATE FOREIGN CONSIGNEE(S)	9. NAME(S) / ADDRESS(ES) OF ULTIMATE FOREIGN CONSIGNEE(S)
CAMBRIDGE ISOTOPE LABORATORIES, INC. 50 Frontage Road Andover, MA 01810-5413		Asymchem Life Science (Tianjin) Co., Ltd. No.71, 7th Street TEDA, Tianjin, 300457 PR China
7a. FUNCTION(S) PERFORMED/SERVICE(S) PROVIDED: Supplier	8a. INTERMEDIATE USE(S):	9a. ULTIMATE END USE(S): Use D2O in API manufacture

10. DESCRIPTION OF RADIOACTIVE MATERIALS, SEALED SOURCES, NUCLEAR FACILITIES, EQUIPMENT, OR COMPONENTS; FOR NUCLEAR EQUIPMENT INCLUDE TOTAL DOLLAR VALUE OF EQUIPMENT FOR EXPORT	10a. MAX TOTAL VOLUME / ELEMENT WGT (KG), OR TOTAL ACTIVITY (TBq)	10b. MAX ENRICHMENT OR WGT %	10c. MAX ISOTOPE WGT (KG)
Heavy water (D2O)	~ 20,000 kgs (liters) of D2O over license life	> 99% enrichment relative to water (H2O)	N/A (D2O is not radioactive waste)

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11. FOREIGN OBLIGATIONS (BY COUNTRY AND BY PERCENTAGE OF MAXIMUM TOTAL VOLUME)

DEC 07 2010 JC

NRC FORM 7
(8-2010)
10 CFR 110

U.S. NUCLEAR REGULATORY COMMISSION

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LICENSE NUMBER	DOCKET NUMBER	ADAMS ACCESSION NUMBER	
XMAT414	11005905		☑ PUBLIC OR ☐ NON-PUBLIC

PART D. TO BE COMPLETED FOR IMPORT LICENSES, AMENDMENTS, OR RENEWALS

(If more space is needed to complete any of the items, use Pages 3-4 first, and then attach additional sheets, if necessary.)

12. NAME(S) / ADDRESS(ES) OF FOREIGN SUPPLIERS AND/OR OTHER PARTIES TO IMPORT	13. NAME(S) / ADDRESS(ES) OF INTERMEDIATE CONSIGNEE(S)	14. NAME(S) / ADDRESS(ES) OF ULTIMATE U. S. CONSIGNEE(S)

12a. NRC EXPORT LICENSE NUMBER(S) *(if applicable)*	13a. LICENSE NUMBER(S) / EXPIRATION DATE(S)	14a. LICENSE NUMBER(S) / EXPIRATION DATE(S)
	13b. INTERMEDIATE USE(S)	14b. ULTIMATE END USE(S)

15. DESCRIPTION OF RADIOACTIVE MATERIALS, SEALED SOURCES, NUCLEAR FACILITIES	15a. MAX TOTAL VOLUME / ELEMENT WGT (KG), OR TOTAL ACTIVITY (TBq)	15b. MAX ENRICHMENT OR WGT %	15c. MAX ISOTOPE WGT (KG)

16. FOREIGN OBLIGATIONS (BY COUNTRY AND BY PERCENTAGE OF MAXIMUM TOTAL VOLUME)

PART E. TO BE COMPLETED FOR ALL LICENSES, AMENDMENTS, OR RENEWALS

17. ADDITIONAL INFORMATION PROVIDED ON PAGES 3, 4, AND/OR ON SEPARATE SHEETS?	17a. COPIES OF RECIPIENTS' AUTHORIZATIONS PROVIDED?
☑ YES ☐ NO	☐ YES ☑ NO

18. CERTIFICATION: I, the applicant's authorized official, hereby certify that this application is prepared in conformity with Title10, Code of Federal Regulations, and that all information provided is correct to the best of my knowledge.

18a. PRINT NAME AND TITLE OF AUTHORIZED OFFICIAL	18b. SIGNATURE -- AUTHORIZED OFFICIAL	18c. DATE
Robert Zelle, Ph. D. Vice President, Drug Development	Robert Zelle	30-Nov-2010

DEC 07 2010

NRC FORM 7
(8-2010)
10 CFR 110

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ADDITIONAL INFORMATION *(Reference applicable block numbers from page 1 and/or page 2 for each entry)*

Block 17:

Applicant (see Block 1) plans to have produced the active pharmaceutical ingredient (API) known as CTP-499, which incorporates deuterium. The manufacturing process in its first step uses > 99% isotopically enriched heavy water (D2O) (see Blocks 10 and 10b) as the source of deuterium to achieve a hydrogen-deuterium exchange, as shown in Scheme 1 (Attachment A). Applicant plans to have Asymchem Laboratories, Inc. (Foreign Consignee - see Block 9) perform the manufacturing process in its plant in Tianjin, People's Republic of China. Applicant and Foreign Consignee have already signed an agreement directed to the cGMP manufacture of Applicant's APIs. Applicant further plans to request Cambridge Isotope Laboratories, Inc. (Other Party - see Block 7) to export, on behalf of Applicant, the D2O required for the manufacturing process to Foreign Consignee.

Applicant expects that current demand for D2O for the above API manufacture will be in excess of the 1000kg/annum export limit specified in 10 CFR 110.24 and is likely to increase year-on-year, reaching an expected demand of about 10 tonnes (10,000 kgs) of D2O in 2015, the last year of the license. The total amount of D2O exported on behalf of Applicant is expected to be about 20 tonnes (20,000 kgs or liters) over the life of the license.

Applicant plans to return (import) to the U.S. any D2O that remains unutilized at the completion of the reaction of Attachment A, and to recycle the re-imported D2O to obtain D2O that is > 99% isotopically enriched. Then the > 99% isotopically enriched D2O would then be exported (back) to China for use in the process of Attachment A to obtain a new batch of CTP-499.

Applicants also plan to reutilize the D2O at each step of a batch run in the process as described in Attachment B, which schematically shows how the unutilized D2O from a hydrogen/deuterium exchange in a given batch run (which typically involves three successive exchanges, as shown in Attachment B) is reutilized in an earlier hydrogen/deuterium exchange in a subsequent batch run.

The above approach to the recycling and reutilization of D2O is environmentally advantageous relative to one where the unutilized D2O is discarded at the end of every batch run (or at the end of every exchange in a three-exchange batch run), and is therefore advantageous from the point of view of public health and safety, since it reduces the amount of > 99% isotopically enriched D2O that has to be made from other sources. A mass balance is provided in Attachment C, which shows (i) the amount of D2O that is exported to the Foreign Consignee, (ii) the amount of D2O that is returned to the US, and (iii) the difference in the two amounts.

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DEC 07 2010
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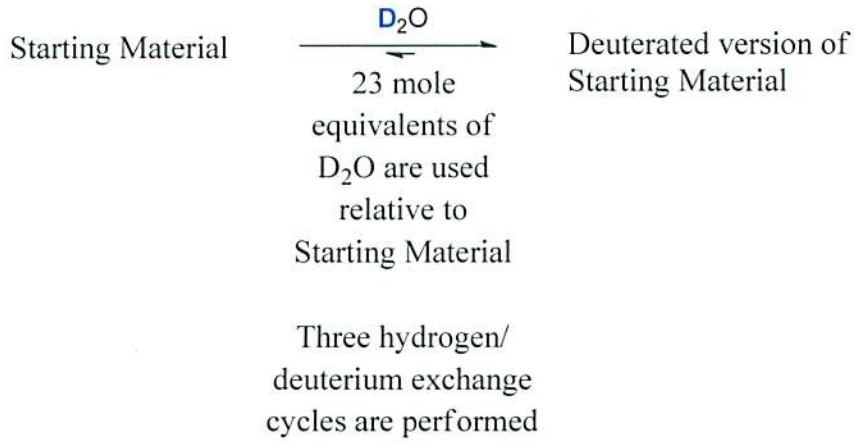
Attachment A:

Scheme 1. Exchange of Hydrogen with Deuterium in Step 1 of CTP-499 manufacturing process



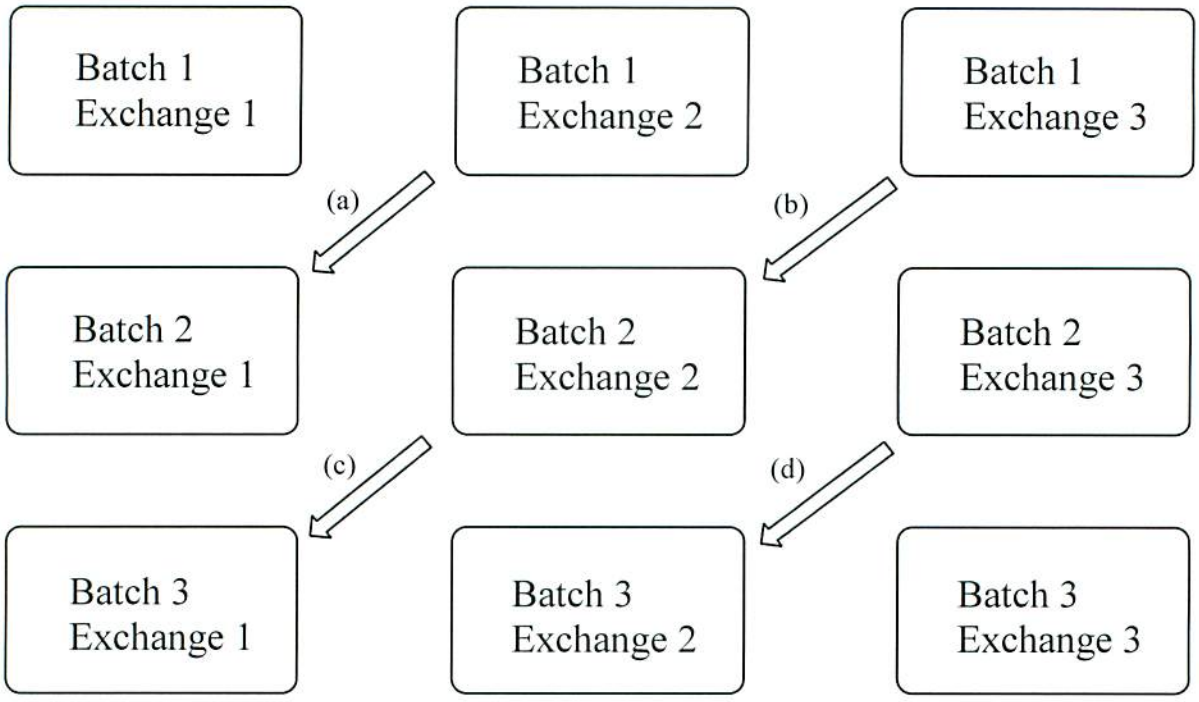
The Scheme shows how D_2O (deuterated water) is used to make a deuterated version of the Starting Material in the CTP-499 manufacturing process Step 1, which involves an exchange of hydrogen in the Starting Material with deuterium. The exchange may be repeated, so that for a given batch of CTP-499 three exchanges are typically used, as shown in more detail in Attachment B. The deuterium content purity is enhanced at successive exchanges. The unutilized D_2O from a hydrogen/deuterium exchange in a given batch run is reutilized in an earlier hydrogen/deuterium exchange in a subsequent batch run. For example, referring to Attachment B, the unutilized D_2O from Exchange 2 of the first batch is reutilized in Exchange 1 for the second batch.

XMAT414

Rec'd
DEC 07 2010
JC

Attachment B:

Scheme 2. Recycling of D_2O in Step 1 of Manufacture of CTP-499 shown for three batch runs each involving three successive hydrogen/deuterium exchanges (a hydrogen/deuterium exchange is shown in Attachment A). The unutilized D_2O from an exchange in a batch run is reutilized in an earlier exchange in a subsequent run



(a) unutilized D_2O from Exchange 2 of first batch is reutilized in Exchange 1 for second batch

(b) unutilized D_2O from Exchange 3 of first batch is reutilized in Exchange 2 for second batch

(c) unutilized D_2O from exchange 2 of second batch is reutilized in Exchange 1 for third batch

(d) unutilized D_2O from Exchange 3 of second batch is reutilized in Exchange 2 for third batch

All D_2O that remains unutilized in the above process is combined and returned (imported) to the U.S.

XMAT414

Rec'd

DEC 07 2010

JC

Attachment C:

Mass balance for D_2O in Step 1 of the CTP-499 manufacturing process.

This mass balance assumes that Step 1 is conducted on **50 kg** of the Starting Material of Attachment A.

(i) **Amount of D_2O that is exported to the Foreign Consignee:**
247.5kg

(ii) **Amount of D_2O that is re-imported:**
246 kg

(iii) **Difference between the amount of D_2O exported and amount re-imported,** which is the **net amount of D_2O consumed by Applicant's approach:**
247.5 kg – 246 kg, or **1.5 kg**.

This mass balance shows that only **1.5 kg** of the D_2O that is exported is not re-imported back to the United States. Of this amount, 0.89 kg is the amount that is theoretically required to introduce deuterium in the Starting Material shown in Attachment A. The remaining 0.61 kg of D_2O (i.e., 1.5 – 0.89), which is a very tiny fraction of the exported amount, represent an amount that is ordinarily not recovered in processes of this type, mainly due to evaporation of D_2O or its dissolution in the organic solvents used to extract the deuterated product of the reaction of Attachment A.

XMAT 414

Rec'd

DEC 07 2010

JC