

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-161

CHEMISTRY REVIEW(S)

Branch Chief Memorandum

NDA #: 22-161
Drug Name: Lexiscan™ (Regadenoson) Injection 0.4 mg/5 ml (0.08 mg/ml)
IQA: Jila Boal, Ph.D. (Review in DFS dated 9/21/2007)
CMC Reviewers: Jila Boal, Ph.D. and Sharmista Chatterjee, Ph.D.
(Review in DFS dated 3/14/2008)
Peer review talk: February 27, 2008 (No critical issues raised)
Recommendation: Approval
Post-marketing agreements/commitments: None

Introduction:

The detailed CMC review by Dr. Jila Boal and Dr. Sharmista Chatterjee is placed in DFS. Reviews of all pertinent DMFs are also signed off in the DARRTS. This NDA contained detailed QbD elements pertaining to DoEs for the drug substance manufacturing process development but the firm did not seek any flexible regulatory approaches. All CMC-related consults were received and were deemed acceptable. Since all CMC approvability issues were resulted at the time of completion of the primary review, we recommended approval of the NDA and indicated that the only pending issues to be captured in the subsequent memo are the following.

- (i) Ensure lower casing of the trade name in the container and closure labels.
- (ii) Review the SPL DLDE elements for compliance with the Agency's recommendations.

This review serves to capture these two pending issues and to reiterate that the two CMC comments listed below (which were also captured in the primary review) be included in the action letter.

Background:

Regadenoson (also known as CVT-3146) is a new molecular entity, an adenosine analog with the chemical name adenosine, 2-[4-[(methylamino)carbonyl]-1H-pyrazol-1-yl]-, monohydrate. Regadenoson is a low-affinity, selective A_{2A} adenosine receptor (A_{2A}-AdoR) agonist and a potent coronary vasodilator. It is mentioned that activation of the A_{2A}-AdoR by regadenoson causes coronary vasodilation and increases coronary blood flow (CBF). The duration of effect of regadenoson to increase CBF is short and consistent with that needed for investigation of myocardial perfusion defects using radionuclide imaging in the clinic. The proposed indication for LEXISCAN™ (Regadenoson) Injection is for use as a pharmacologic stress agent, in conjunction with radionuclide, for myocardial perfusion imaging (MPI).

The drug product (DP), Regadenoson Injection, contains 0.08 mg/mL regadenoson in a 5 mL clear, colorless, sterile, non-pyrogenic, preservative-free solution intended for intravenous (iv) injection. The DP will be supplied in two configurations intended for single dose parenteral administration.

- A 5 mL [REDACTED] vial closed with a [REDACTED] rubber stopper and flip off overseal. The stopper is [REDACTED]
- A 5 mL ANSYR [REDACTED] syringe closed with [REDACTED] stopper and luer tip [REDACTED]

Both presentations will be packaged in paperboard individual (unit) cartons. Regadenoson Injection is not light sensitive. Therefore, the carton is a non-functional secondary package component.

Review of SPL Elements: Acceptable

The final SPL and the DLDE label elements were submitted on March 26, 2008. The product information table containing the DLDE elements is copied here.

Lexiscan (regadenoson)

PRODUCT INFO

Product Code	0469-6501	Dosage Form	INJECTION, SOLUTION
Route Of Administration	INTRAVENOUS	DEA Schedule	

INGREDIENTS

Name (Active Moiety)	Type	Strength
regadenoson (regadenoson)	Active	0.08 MILLIGRAM In 1 MILLILITER
 dibasic sodium phosphate dihydrate	Inactive	10.9 MILLIGRAM In 1 MILLILITER
 dibasic sodium phosphate anhydrous	Inactive	8.7 MILLIGRAM In 1 MILLILITER
 monobasic sodium phosphate monohydrate	Inactive	5.4 MILLIGRAM In 1 MILLILITER
 propylene glycol	Inactive	150 MILLIGRAM In 1 MILLILITER
 edetate disodium dihydrate	Inactive	1 MILLIGRAM In 1 MILLILITER
 Water	Inactive	

IMPRINT INFORMATION

Characteristic Appearance	Characteristic	Appearance
Color	Score	
Shape	Symbol	
Imprint Code	Coating	
Size		

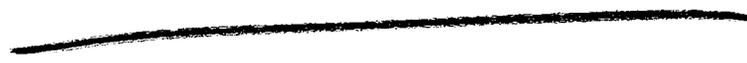
PACKAGING

# NDC	Package Description	Multilevel Packaging
1 0469-6501-05	5 MILLILITER In 1 VIAL, GLASS	None
2 0469-6501-89	5 MILLILITER In 1 SYRINGE, PLASTIC	None

Revised: 03/2008 Astellas Pharma US, Inc.

All the elements conform to the Agency recommendations and are acceptable. Also, the highlighted section of the label (the beginning part) conforms to the standardized terminology recommended in the SPL labeling format.

Review of updated Container and Carton labels: Acceptable



3 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Chemistry- 1

CMC Comments to be included in the action letter:

These are also listed in the primary review.

1. An expiry period of 30 months is granted for Regadenoson Injection in 5 mL vial and in 5 ml ANSYR Syringe, when stored at controlled room temperature (25°C with excursions to 15°C to 30°C permitted). You may extend the expiration dating period based on the satisfactory accrual of real time data and report it in an annual report.
2. Under section S.2.5, it is stated that process validation and/or evaluation is not applicable to regadenoson drug substance because it is not sterilized and is not intended to be a sterile drug substance. Please note that the drug substance and the drug product manufacturing processes are expected to be evaluated by manufacturing appropriate batches to demonstrate the validity of the processes at the time of commercialization. You may refer to ICH Q7A and FDAA, Sec. 490,100, Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08), March, 2004 for details.

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/s/

Ravi Harapanhalli
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CHEMIST

NDA 22-161

**Lexiscan™ (Regadenoson) Injection
0.4 mg/5 ml (0.08 mg/ml)**

**Jila H. Boal, Ph. D.
Sharmista Chatterjee, Ph. D.**

**Division of Pre-marketing Assessment III and
Manufacturing Science, ONDQA**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	10
I. Recommendations	10
A. Recommendation and Conclusion on Approvability	10
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	10
II. Summary of Chemistry Assessments	10
A. Description of the Drug Product(s) and Drug Substance(s)	11
B. Description of How the Drug Product is Intended to be Used	17
C. Basis for Approvability or Not-Approval Recommendation	17
III. Administrative	17
A. Reviewer's Signature	17
B. Endorsement Block	17
C. CC Block	18
Chemistry Assessment.....	18
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	18
S DRUG SUBSTANCE [Name, Manufacturer]	18
P DRUG PRODUCT [Name, Dosage form]	84
A APPENDICES	172
R REGIONAL INFORMATION	173
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	
A. Labeling & Package Insert	173
B. Environmental Assessment Or Claim Of Categorical Exclusion	175
III. List Of Deficiencies To Be Communicated.....	177

Chemistry Review Data Sheet

1. NDA # 22-161
2. REVIEW #: 1
3. REVIEW DATE: January 24, 2008
4. REVIEWER: Jila H. Boal, Ph. D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
IND 62,862 (Original Submission)	July 2, 2001
End of Phase 2 Meeting (CMC and Toxicology)	May 18, 2004
Teleconference Follow-up to End of Phase 2 Meeting Impurity level was reduced to 10ppm)	August 5, 2004
Pre-NDA (Chemistry-Pharm/Tox Meeting)	July 25, 2006
Memorandum (Correction to Preliminary Response)	July 27, 2006
Information Request, Advice, & General Correspondence Letter (The agencies agreement on sponsor's Tox studies to support lack of toxicity of the impurities in question)	August 29, 2006
NDA 22-161(N-000)	May 14, 2007
Amendment 0001 (Draft labeling which included the revisions that were requested by the clinical Division in the filing letter dated July 27, 2007)	September 14, 2007
Amendment 0002 (Response to CMC IR letter 1)	October 19, 2007
Amendment 0003 (Response to CMC IR letter 2)	November 26, 2007



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Amendment 0004 (Modification to drug substance assay method, revised carton label for ANSYR syringe and updates on the drug substance and the drug product stability data).	November 30, 2007
Amendment 0009 (Response to CMC IR letter 3, detail of the factorial design calculations for the drug substance manufacturing CPPs)	December 18, 2007
Amendment 0011 (Response to CMC IR letter of January 4, 2008 for validation of the drug product sterilization process, requested by the microbiology reviewer)	January 7, 2008
Amendment 0013 (Response to CMC IR e-mail of February 26, 2008) to perform the volume in container test for the vial and syringe configurations on stability and the ANSYR syringe functionality test on stability.	February 27, 2008
Amendment 0014 (Response to CMC IR e-mail of March 10, 2008) in reference to CMC and DMETS recommended package insert, vial, syringe, and carton labeling and label changes.	March 11, 2008

7. NAME & ADDRESS OF APPLICANT:

Name: CV Therapeutics, Inc.
Address: 3172 Porter Drive
Palo Alto, CA 94304
Representative: Carol D. Karp
Senior Vice President, Regulatory Affairs,
Quality and Drug Safety
Telephone: 650-384-8875
Fax: 650-494-8769

8. DRUG PRODUCT NAME/CODE/TYPE:

- a. **Proprietary Name:** Lexiscan
- b. **Non-Proprietary Name (USAN):** Regadenoson
- c. **Code Name/# (ONDQA only):** CVT-3146
- d. **Chem. Type/Submission Priority (ONDQA only):** 1 S
- e. **Chem. Type: Standard Review, substantially equivalent**
 - a. **Submission Priority:** Standard

9. **LEGAL BASIS FOR SUBMISSION:** This NDA is submitted pursuant to section 505 (b) (1) of the FDA Act. Regadenoson is an NME.



Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: Pharmacologic stress agent for radionuclide myocardial perfusion imaging

11. DOSAGE FORM: Injection, solution

12. STRENGTH/POTENCY: 0.4 mg/5 ml (0.08 mg/ml)

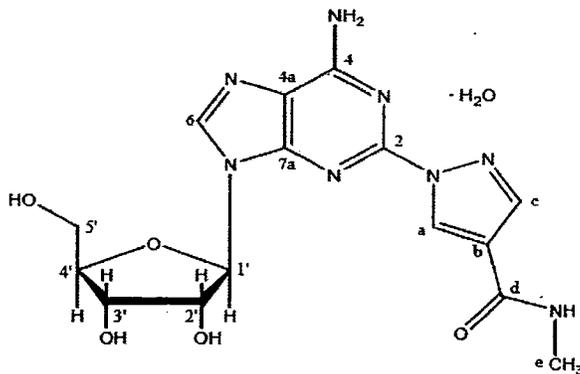
13. ROUTE OF ADMINISTRATION: Intravenous, bolus injection

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not Needed.

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structural Formula:



Chemical Name (s): Adenosine, 2-[4-[(methylamino)carbonyl]-1H-pyrazol-1-yl]-monohydrate

1-(6-amino-9-β-D-ribofuranosyl-9H-purin-2-yl)-N-methyl-1H-pyrazole-4-carboxamide, monohydrate

(1-{9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide, monohydrate

2-[N-1-(4-N-methylcarboxamidopyrazolyl)] adenosine, monohydrate

(CAS) Registry Number: 875148-45-1



CHEMISTRY REVIEW



Chemistry Review Data Sheet

MW: 408.37

Molecular Formula: $C_{15}H_{18}N_8O_5 \cdot H_2O$

17. RELATED/SUPPORTING DOCUMENTS: None

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	V			7 (reviewed by the Microbiology discipline)	Adequate	January 10, 2008	See the microbiology review by Bryan S. Riley, Ph.D.
	III			1	Adequate.	December 13, 2007.	See review # 1 of the DMF by Jila. H. Boal, Ph.D.
	III			3	Adequate.	September 27, 2007.	Reviewed by Jane L. Chang, Ph.D.
	III			1	Adequate.	December 20, 2007.	See review # 1 of the DMF by Jila. H. Boal, Ph.D.
	III			3	Adequate.	Reviewed by Stuart Zimmerman, Ph.D. Reviews dated February 1, 2000, and September 18, 2001. [REDACTED] [REDACTED] [REDACTED] reviewed for Adenocard drug product.	The DMF update of December 7, 2007 was reviewed by this reviewer to see if there are any changes to the raw materials since the last review of the DMF for the formulation of the [REDACTED]. The update contained the same formulation. The only difference observed was one compound's code number but it is the same chemical entity. The [REDACTED] with [REDACTED].



CHEMISTRY REVIEW



Chemistry Review Data Sheet

							<p>_____ is the same chemical entity with _____ that was reported previously in the past two reviews.</p>
1	III	_____	_____	1	Adequate	December 14, 2007.	See review # 1 of the DMF by Jila H. Boal, Ph.D.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62,862	
ANDA	75-151	Hospira, Inc. 50% magnesium sulfate injection in 5 mL ANSYR® Syringe.
Patent	6,403,567	
Patent	6,642,210	
Patent	7,144,872	
Patent	7,183,264	

18. STATUS:

ONDQA:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Consulted for review and	November 30,	Roswitha Kelly,



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	evaluation of the statistical SAS stability data submitted for extrapolation of 30 months shelf-life for the drug substance and the drug product and were deemed adequate.	2007	M.S., OTS/OB/DB6
EES	Overall recommendation is acceptable.	December 20, 2007	Ferguson (HFD-322)
Pharm/Tox	Confirmed the adequacy of the qualification studies on the drug substance related impurity that is genotoxic. Confirmed the adequacy of the toxicity studies, on the identified impurities in the drug substance that their acceptance criteria exceed the qualification threshold recommended by the ICH Q3A.	October 29, 2007	Siham Biade, Ph.D.
Biopharm	Not Needed.		
LNC	N/A (Conventional dosage form).		
Methods Validation	Not needed before approval. The HPLC-MS-MS method for determination of at 10 ppm threshold in the regadenoson drug substance should be validated by FDA method validation Laboratory. Under the ONDQA Method Validation Program Procedures, the rest of the analytical methods do not meet the criteria for requesting method validation.	January 24, 2008.	Jila H. Boal, Ph.D.
OPDRA / DDMAC	Reviewer for the Proposed Product Labeling	January 15, 2008	Sean Bradley, DDMAC
OSE/DMETs	For Proprietary Name, Label, and Labeling Review. Please see the review in DFS. There were several comments these are listed at the end of this	March 5, 2008	Denise V. Baugh, PharmD, BCPS, Safety Evaluator



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	review and were resolved see the final conclusion summary at the end of this review.		
EA	Categorical exclusion from the requirement to submit an Environmental Assessment is granted.	January 24, 2008.	Jila H. Boal, Ph.D.
Microbiology	For review and evaluation of the drug product sterilization process and its validation. It was recommended for approval.	January 10, 2008.	Bryan S. Riley, Ph.D.

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The Chemistry Review for NDA # 22-161

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

All CMC deficiencies have been resolved satisfactorily. The product quality microbiology discipline recommended approval of the NDA. The Office of Compliance deemed the facilities acceptable for cGMP compliance. All CMC-related consults have provided acceptable recommendations. The revised container and carton labels submitted on March 11, 2008 addressed all of the CMC and DMETs comments except that the firm did not _____

The firm has agreed to do so. The firm also indicated that the SPL data elements will be submitted once the package insert is finalized. From CMC perspective, the NDA is recommended for approval. The SPL data elements will be reviewed upon submission of this data.

The following two statements on expiration dating period and on process validations should be included in the action letter.

1. An expiry period of 30 months is granted for Regadenoson Injection in 5 mL vial and in 5 ml ANSYR Syringe, when stored at controlled room temperature (25°C with excursions to 15°C to 30°C permitted). You may extend the expiration dating period based on the satisfactory accrual of real time data and report it in an annual report.
2. Under section S.2.5, it is stated that process validation and/or evaluation is not applicable to regadenoson drug substance because it is not sterilized and is not intended to be a sterile drug substance. Please note that the drug substance and the drug product manufacturing processes are expected to be evaluated by manufacturing appropriate batches to demonstrate the validity of the processes at the time of commercialization. You may refer to ICH Q7A and FDAA, Sec. 490,100, Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (CPG 7132c.08), March, 2004 for details.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable – N/A

II. Summary of Chemistry Assessments

Introduction:

Executive Summary Section

The proposed indication for LEXISCAN™ (Regadenoson) Injection is for use as a pharmacologic stress agent, in conjunction with radionuclide, for myocardial perfusion imaging (MPI).

Regadenoson is a low-affinity, selective A_{2A} adenosine receptor (A_{2A}-AdoR) agonist and a potent coronary vasodilator. It is mentioned that activation of the A_{2A}-AdoR by regadenoson causes coronary vasodilation and increases coronary blood flow (CBF). The duration of effect of regadenoson to increase CBF is short and consistent with that needed for investigation of myocardial perfusion defects using radionuclide imaging in the clinic.

A. Description of the Drug Product(s) and Drug Substance(s)**Drug Product:**

The drug product (DP), Regadenoson Injection, contains 0.08 mg/mL regadenoson in a 5 mL clear, colorless, sterile, non-pyrogenic, preservative-free solution intended for intravenous (iv) injection. The DP will be supplied in two configurations intended for single dose parenteral administration:

- 1) A 5 mL _____ glass / _____ vial closed with a _____ rubber stopper and flip off overseal. The stopper is _____
- 2) A 5 mL ANSYR _____ syringe closed with _____ stopper and luer tip (_____)

Both presentations will be packaged in paperboard individual (unit) cartons. Regadenoson Injection is not light sensitive. Therefore, the carton is a non-functional secondary package component.

To support an expiration dating period a total of _____ primary registration batches, i.e. _____ stability registration batches in vial manufactured in March 2006 and additional _____ separate stability registration batches in syringe configuration manufactured in January and February 2006 were placed on stability program. The drug product and drug substance stabilities were conducted according to ICH Q1A. Based on an evaluation of the stability data from these batches, an expiry period of 30 months is proposed for Regadenoson Injection in 5 mL vial and in 5 ml ANSYR Syringe stored at controlled room temperature (25°C with excursions to 15°C to 30°C permitted). No trends indicative of product instability were observed during the 18 months of DP stability studies. Per ICH guideline Q1E, the applicant submitted least squares regression analysis of the stability indicating attributes, at the long-term storage condition, to extrapolate the proposed 30 months expiration dating period. The statistical review team concurred with the applicant's SAS analysis data confirming the 30 months expiration dating period. Please find their review in DFS. The applicant is committed to monitor stability of these registration batches up to 48 months.

Executive Summary Section

The composition of Regadenoson Injection is as follows: 0.08 mg/mL regadenoson (anhydrous basis), 150 mg/mL propylene glycol (PG) (15% w/w), 1 mg/mL edetate disodium dihydrate (EDTA) (0.1% w/w), 100 mM sodium phosphate composed of 10.9 mg/mL dibasic sodium phosphate dihydrate (or 8.7 mg/mL dibasic sodium phosphate anhydrous) and 5.4 mg/mL monobasic sodium phosphate monohydrate, with pH between 6.3 and 7.7. These excipients are compendial-grade pharmaceutical ingredients commonly used in intravenous drug products. Rational for selection of each of these excipients and their critical role in maintaining stability of regadenoson in an injection solution that is formulated for parenteral administration are described in detail in the pharmaceutical development section. Briefly summarizing here; the pre-formulation studies were mainly focused on overcoming the low solubility of regadenoson in aqueous media. Based upon the dosing requirements, two formulation systems were developed:

1) _____

2) A system containing propylene glycol formulated _____ used in clinical and registration stability studies.

The PG formulation showed a better stability profile i.e., the ability to withstand _____ and superior buffering capacity in a semi-permeable container, such as a plastic syringe, and was therefore selected as a viable commercial formulation. The concentration of PG at 15% was selected to ensure that regadenoson will remain in solution when exposed to low temperatures during transportation or external handling. At this PG concentration, the concentration of regadenoson in the drug product is about 50% below its saturation solubility. In addition the formulation containing 15% PG exposed to three freeze-thaw cycles did not show any precipitation. To support the commercial production process and the composition of the formulation, _____ stability registration batches for vial presentation and _____ stability registration batches for ANSYR syringe presentation were manufactured at pilot scale. _____ In addition, in the clinical study CVT 5131 the proposed commercial formulation containing _____ regadenoson was used and in the study CVT 5132 the commercial formulation that contained 0.08 mg/mL of regadenoson was used. The remainder of the Phase 1 and 2 clinical studies, including CVT 5112, CVT 5123, CVT 5124, CVT 5125 and CVT 5126 were done with the proposed commercial formulation that contained 0.08 mg/ mL of regadenoson.

Two separate sites will be manufacturing, and performing QC testing (product release and stability testing) for the vial and the ANSYR syringe presentations for commercial distribution. The _____ processes for the two presentations are comparable with some minor process differences in the _____ processes. These differences are required to accommodate the different packaging presentations. Baxter Pharmaceutical Solutions LLC (DMF 10304) manufactures vials and Hospira, Inc. (DMF 20430) manufactures syringes. Baxter and Hospira both have described the manufacturing process in their respective DMFs. However, sufficient documentation was provided in the NDA describing the manufacturing process and in-process controls and were deemed adequate. For example, adequate compatibility

Executive Summary Section

studies of the interaction of formulation with the [REDACTED] used in the manufacturing process were provided. Compatibility of the formulation with the [REDACTED] were examined under a [REDACTED] for a microbial retention challenge study. The commercial production scale is [REDACTED]. The manufacture scale for the clinical and stability registration batches was [REDACTED]. Commercial production will be transferred to [REDACTED]. The drug product solution is [REDACTED].

[REDACTED] The formulation and [REDACTED] equipment used for the registration stability batches will be identical to those for commercial production. The most significant changes associated with the switch to [REDACTED] and filling process parameters (speed) and equipment, with similar product contact surfaces [REDACTED] and in-process controls.

For the NDA clinical studies the drug product supply was packaged solely in vial presentation [REDACTED] proposed for commercial manufacture of both glass vial and plastic ANSYR Syringe configurations. The feasibility of the [REDACTED] process was evaluated. One clinical batch of DP in vials (803604), subjected to different [REDACTED] conditions and placed on stability (referred to as batch PDR-227-03), was evaluated for the feasibility of the [REDACTED] process. One batch in vials and two batches in syringes were manufactured to further confirm the feasibility of the [REDACTED] process for vials and syringes. [REDACTED] minor impurity peaks were observed in these samples when analyzed by HPLC. The chemical structure of these peaks were identified and were determined to be due to degradation of regadenoson, but all were present in very small amounts i.e., well below the reporting threshold recommended in the ICH Q3B. Thus [REDACTED] studies on all of these batches demonstrated the feasibility of the [REDACTED] process. The feasibility studies further demonstrated that Regadenoson Injection prepared using a [REDACTED] process shows acceptable stability over 36 months at room temperature. Based on the results from the [REDACTED] [REDACTED] will be used for the commercial process in vial presentation. [REDACTED] for the ANSYR Syringe was selected. The validation of the [REDACTED] cycles were reviewed through a consult to the microbiology review team and were deemed acceptable. Please see the microbiology review of this NDA in DFS.

The bulk solutions of the formulation prepared and stored in [REDACTED] containers under ambient condition showed no significant change in stability profile of the regadenoson over a hold time of 72 hours. The hold time study including bioburden testing will be repeated on a full scale commercial batch during process validation.

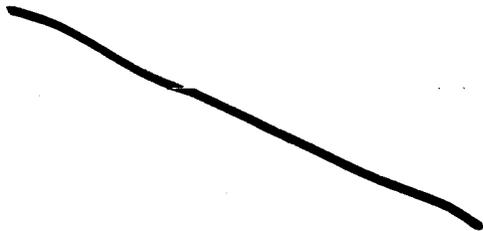
Compatibility of the container closure systems with Regadenoson Injection was confirmed.



Executive Summary Section

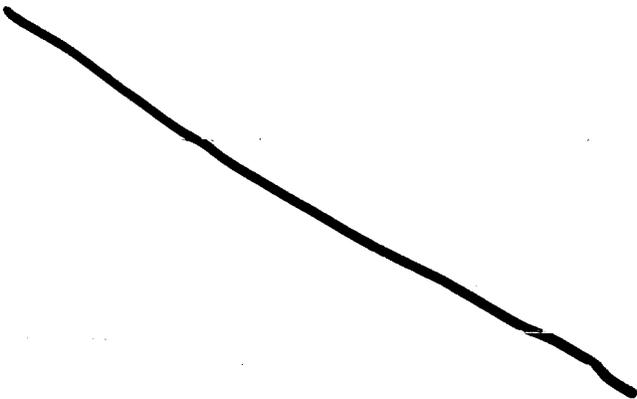
Two types of studies were performed to demonstrate the suitability of the vial container closure system for its intended use.

- A container closure integrity test (using a Microbial Ingress Challenge) with respect to prevention of microbial contamination was evaluated. The results of the Microbial Ingress Challenge study demonstrated that the 5 mL/ [REDACTED] container closure system is capable of maintaining the sterility of Regadenoson Injection when capped and sealed using [REDACTED]
- An extractables study under exaggerated conditions was carried on the vial stopper that is in contact with DP. [REDACTED]



Except for the plunger rod, all other parts in the ANSYR Syringe presentation are considered primary container closure components, because they have direct product contact. Compatibility of the syringe components with the DP included the following.

- Feasibility studies were conducted where filled syringes were [REDACTED]



[REDACTED] The stability data indicated that Regadenoson Injection is stable as manufactured, processed and packaged with a 5 mL fill in the 5 mL ANSYR Syringe.



Executive Summary Section

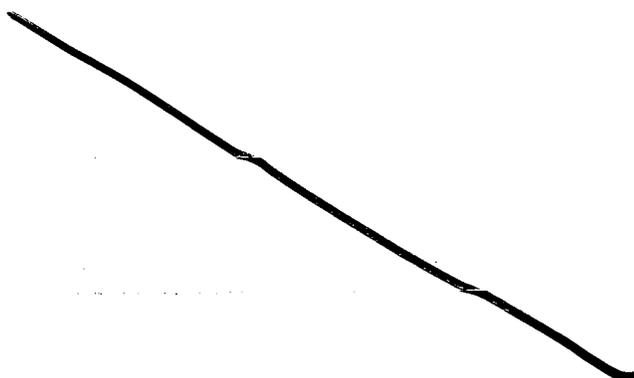
- Compatibility of the ANSYR syringe components with the DP also included container closure extractables analysis. Trace levels of extractables have been detected in Regadenoson Injection.

These were,

- a. Class III solvents: The potential patient doses (PPD) of the Class III solvents are at least 50-fold lower than the permitted daily exposure (PDE) per the ICH Guidelines.
- b. Extractable compounds not listed in ICH:



- Based on the toxicity assessment performed on extractables from the ANSYR syringe container closure system the potential patient doses (PPD) of the extractable compounds were determined to be in a range that is at least 10 to 2600-fold lower than the estimated Permitted Daily Exposure (PDE) for these extractables.
- Elastomeric Commodity Material Safety Evaluation on the rubber stopper and luer tip cover of the ANSYR Syringe entailed qualification of the rubber material based on the USP biological and physicochemical testing.
- Results of the integrity test of the syringe container closure system is provided in Hospira's Type III DMF "ANSYR® Syringe Drug Product".



The drug product release specifications and acceptance criteria are based on the ICH Q6A as recommended for an injection solution. The proposed acceptance criteria were based on the collection of data from ~~one~~ drug product batches that were used in clinical studies and were the registration stability batches. The specifications for the impurities and degradation products in the drug product were according to the ICH Q 3B recommendations.

Drug Substance:

Executive Summary Section

The drug substance (DS) in Regadenoson Injection, is a novel compound. Regadenoson (also known as CVT-3146) is an adenosine analog with the chemical name adenosine, 2-[4-[(methylamino)carbonyl]-1H-pyrazol-1-yl]-, monohydrate. Among the physico-chemical properties of this drug the most important one is its low solubility in aqueous media leading to a formulation of the DS containing 15% PG.

Regadenoson is manufactured by _____ . The synthetic route used to prepare regadenoson involves _____

The DS manufacturing process was optimized at laboratory scale using the DoE approach. The optimization effort was conducted following production of registration stability batches to define the commercial manufacturing process. The optimization effort consisted of an EOF PAR study (Edge Of Failure, Proven Acceptable Range), OP PAR study (Operability Proven Acceptable Range) followed by a demo batch at commercial scale. The EOF PAR and OP PAR studies were conducted for each step of the DS synthesis. The objective of the EOF PAR study was to identify the CPPs (Critical Process Parameter) and to estimate the optimal CPP range that would be evaluated in the OP PAR study. The EOF PAR studies were designed as fractional factorial screening studies to evaluate simultaneously as many factors as possible over extreme possible ranges, and to identify if possible an optimal range. Since interaction effects are masked for fractional designs, the values of the NCPP (Non Critical Process Parameters) were maintained at target for the OP PAR studies as well as for the demo batch. The EOF PAR study was followed by the OP PAR study that was carried out to identify optimal operating ranges for the CPP's at commercial scale. These studies were designed as full factorial studies using only the CPP's, that allowed evaluation of all interaction effects. The EOF PAR and OP PAR studies culminated in defining an optimized commercial process at laboratory scale. The process parameters were then verified using a GMP, pre-validation, commercial scale Demo batch (regadenoson batch 17PA03.NJ00006). The Demo batch succeeded in producing material that met all intermediate and final product acceptance criteria.

Since multivariate DoE's were used to map out ranges for the CPPs, the sponsor could have proposed the region defined by these ranges, as a design space for the DS CPP's. However, it was not done so in this application. It is to be noted that the full description of the optimization approach was not provided in the original submission, but was garnered by the reviewers via multiple IR letters. The commercial scale is the same as the scale used to manufacture the DS for clinical studies.



Executive Summary Section

The specifications for regadenoson are [REDACTED]

The specifications for impurities and degradation products in the DS are according to the ICH Q3A recommendations. Analytical procedures are standard USP methods except the HPLC method for assay, impurities and degradation products and the HPLC-MS method for determination of [REDACTED] for which method validation reports were submitted.

To support the proposed 30 months expiration shelf-life, stability data for up to 18 months for [REDACTED] DS registration batches were submitted. Extrapolation of the DS shelf-life from the SAS analysis of the stability data were consulted to the statistical review team and were deemed adequate. The review of the SAS stability data and analysis can be found in DFS. Expiration dating of 30 months could be extrapolated per ICH Q1E and is granted. Thus the shelf life for the drug substance is 30 months when drug substance is stored [REDACTED]

[REDACTED] at 25°C with excursions of 15°C to 30°C permitted. The drug substance is not light sensitive.

B. Description of How the Drug Product is Intended to be Used

For DP administration use aseptic techniques.

The recommended iv dose is 5 mL (0.4 mg regadenoson), administered as a rapid bolus (approximately 10 seconds). The injection is to be followed immediately by a 5 mL saline flush, and the radiopharmaceutical agent is to be administered 10–20 seconds after the saline flush.

C. Basis for Approvability or Not-Approval Recommendation

All CMC deficiencies have been resolved adequately. The application is recommended for approval from CMC perspective including product quality microbiology. This drug is well designed, well characterized and well controlled in terms of product quality as related to product stability and performance.

The associated DMFs were found adequate and their review were completed, please see the DMF table for detail. The manufacturing and testing sites were reported as being acceptable for cGMP compliance through the EES.

III. Administrative

A. Reviewer's Signature: (electronic)

B. Endorsement Block

Chemist Name/Date: JBoal and SChatterjee/
CMC Branch Chief Name/Date: RHarapanhali, BC /
Project Manager Name/Date: TBrown /

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/s/

Jila Boal
3/14/2008 11:43:49 AM
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Sharmista Chatterjee
3/14/2008 01:43:10 PM
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Ravi Harapanhalli
3/14/2008 05:00:27 PM
CHEMIST
BC Memo to follow