Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division:	Division of Medical Imaging and Hematology Products
NDA:	22-161
Applicant:	CV Therapeutics, Inc.
Assigned Date:	May 14, 2007
Stamp date:	May 14, 2007
PDUFA Date:	March 14, 2008
Proposed Trade Name:	LEXISCAN™ (Regadenoson Injection) solution 0.4 mg/5 ml (0.08 mg/ml)
Established Name:	Regadenoson
Laboratory Codes:	CVT-3146
Dosage Form:	Injection, solution
Route of Administration:	Intravenous
Indication:	Pharmacologic stress agent for radionuclide myocardial perfusion imaging
Initial Quality Assessment by:	Jila H. Boal, Ph.D.
Date Assessment Completed:	August 20, 2007
Chemical class:	Type 1 (NME)
NDA filing category:	505 (b) (1)

	YES	
ONDQA Fileability:	√	
Draft Comments for 74-Day Letter:	√	On the last page of this document

Jila H. Boal

_____ _____

CMC Reviewer Date

_____Ravi Harapanhalli_____ _____

Branch Chief, Branch V Date

Summary, Critical Issues and Comments

Background:

The NDA is in eCTDQ format and can be accessed through the edr. The application is being submitted under section 505(b) (1) of the federal Food, Drug and Cosmetic Act. The format and content is in accordance with the 21 CFR 314.50. This has been confirmed by Dr. Harapanhalli who assessed the NDA for filing.

Introduction:

LEXISCAN™ (Regadenoson Injection) is a pharmacologic stress agent. It is for use in conjunction with radionuclide agents in radionuclide myocardial perfusion imaging (MPI) [redacted]

LEXISCAN™ (Regadenoson Injection) will be marketed as an injection solution with dose strength of 0.4 mg / 5ml (0.08 mg/ml). It will be supplied in two configurations:

- A 5 mL glass vial
- A 5 ml prefilled plastic Ansyr® syringe

Both are intended for single dose parenteral administration. The dose of 400 microgram regadenoson as a rapid (< 10 seconds) intravenous injection was used in the clinical studies and according to the applicant, it has been shown to provide consistent short duration of increased Coronary Blood Flow (CBF) needed for investigation of myocardial perfusion defects using radionuclide imaging in the clinic.

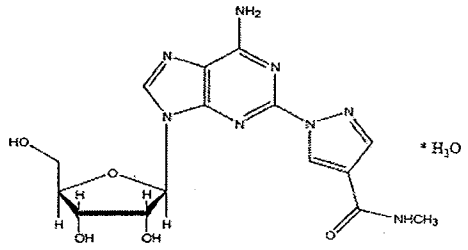
The clinical studies were initiated through the IND 62,862 submitted in June 2001. Key meetings during the development are listed. The CMC related comments from these meetings were referenced by this reviewer and where appropriate, are incorporated in this document.

Table 1 Key Meetings During Development

Type of Discussion	Description	Date
Chemistry – Pharmacology/Toxicology		
End of Phase 2 Meeting	Discussion on commercial manufacture and controls for drug substance and product and advice on drug substance impurity levels; agreement on toxicology plan	18 May 2004
Teleconference Follow-up to End of Phase 2 Meeting	Agreement on tentative specification limit for [redacted] impurity in drug substance	05 Aug 2004
Response to Sponsor Regarding Pre-NDA Chemistry-Pharm/Tox Meeting	Agreement on plan for commercial manufacture and controls for drug substance and drug product	25 Jul 2006 & 27 Jul 2006 (correction)
Response to Sponsor Request for Advice	Agency advice on qualification of drug substance impurities [redacted]	29 Aug 2006

(A). Drug Substance: Regadenoson is a white to off-white solid and is also known as adenosine, 2-[4-[(methylamino) carbonyl]-1*H*-pyrazol-1-yl]-, monohydrate. It is a new molecular entity with the structure presented below.

Figure 2.2.1:1 Structure of Regadenoson



- Regadenoson is practically insoluble in water. This is one of the reasons to formulate regadenoson with 15% w/w propylene glycol (PG).
- Regadenoson is soluble in dimethylacetamide.
- Regadenoson is slightly soluble in methanol and ethanol.

[redacted]

The pKa of ~1.2 is estimated from the pH solubility profile (Section 3.2.S.3.1.2.4). The log P (partition coefficient) between octanol and pH 7.4 buffer was determined to be -0.46.

[redacted]

[redacted] Since regadenoson is formulated as a solution, the possible polymorphic changes of the solid regadenoson are not of concern. Additionally, no precipitate was observed in the freeze/thaw study with this product.
The particle size distribution for regadenoson has not been determined because dissolution rate is not a critical parameter in the formulation process for the drug product solution.

Note: Regadenoson particle size distribution might be critical and might need be controlled from the point of manufacturability. The drug product manufacturing process requires [redacted] regadenoson in [redacted]

Drug Substance Manufacturing Sites:
Three sites were used to manufacture the drug substance supply for the NDA clinical studies. Only [redacted] will be the commercial drug substance manufacturer[redacted] will use a different process from the processes used by [redacted] The design of experiment (DOE) approach has been used to optimize the manufacturing process parameters and controls where the focus has been on process improvements relating to reduction of the genotox and process related impurities.

Note: Please check whether the critical quality attributes responsible for product performance are equivalent in regadenoson batches from the three different manufacture sites.

Description of the Drug Substance Manufacturing Process:
The drug substance manufacturing is described in the NDA i.e., no Type II DMF is cross referenced. Synthesis of regadenoson as shown in the flow chart of Figure 3.2.S.2.2.1 involves [redacted] steps.
All materials are commercially available. Control of the starting materials and reagents were based on the qualification of their suppliers by CV Therapeutics, Inc. The selection of the starting materials has been discussed and agreed upon with the agency in a Pre-NDA meeting dated July 25, 2006.

The major difference between the development and proposed commercial route is reduction in the level [redacted] as a carry over impurity in the intermediates of steps [redacted] regadenoson. This is outlined further down where the impurity profile of regadenoson is discussed. Batch size ranged from [redacted] in the phase 3 clinical studies. The batch size for the registration stability studies was [redacted]

Note: The commercial batch size is not known, this may be asked from the applicant. No executed batch record or master batch record is provided for the drug substance manufacturing. This need be asked from the applicant.

DOE Approaches:

Note that the commercial process is yet to be executed in real time. The manufacturing steps are modified based on DOE where factorial design calculation has been used. The critical process parameters (CPPs) for each step are tabulated with their associated numerical values. No explanation is given as to whether real experiments were performed and as to what approach or calculation has been used to determine these acceptable ranges as determined through the factorial DOE studies. And as to how they were determined to be optimal for commercial production. Since the manufacturing of the commercial scale process has never been tested, it might become necessary to actually see and evaluate the detail of the DOE and as to how these ranges for the CCP were deduced through the factorial calculations. What is the basis for their differences from their corresponding values in the registration stability batches? This will be asked from the applicant.

Comments to the Applicant:

1. The particle size of regadenoson may likley affect its [redacted] containing 15% propylene glycol. Provide your rational for not controlling regadenoson particle size distribution.
2. What is the anticipated batch size in the commercial production of the drug substance?
3. The commercial process is yet to be executed in real time or practice. Therefore, in order to accept the CPPs that you plan implementing in your commercial production of the drug substance, provide the raw calculations and the details of the factorial modeling approach you have used in the DOEs to deduce the final ranges for the CPPs to be used in the manufacture of the commercial batches.
4. Provide an executed batch record from the drug substance registration batches.

Drug Substance Manufacturing Process Development:

[redacted]

Figure 3.2.S.2.6:1 Synthesis of Regadenoson via the Development Process

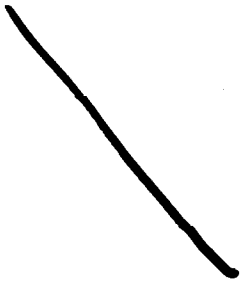
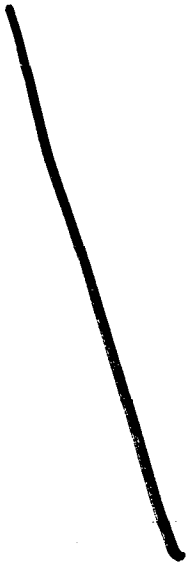


Figure 3.2.S.2.2:1 Flow Chart of the Synthesis of Regadenoson



In addition to process optimization through DOE, a final [redacted] proposed commercial process to [redacted]

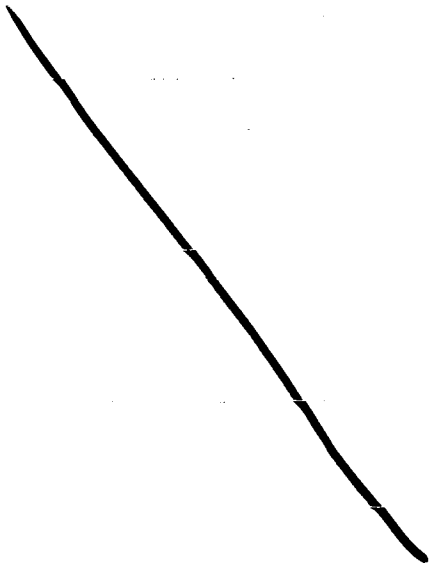
Drug Substance Proof of Structure:

The structure of regadenoson is supported by its synthetic route and has been confirmed by structural characterization using, Infrared (IR), Ultraviolet (UV), 1H-nuclear magnetic resonance (NMR) and 13C-NMR, Product ion mass spectra, and Elemental analysis on the reference standard batch 17PA03.NJ00002.

Specifications for the Drug Substance:
These are listed:

Table 3.2.S.4.1:1 Specification for Regadenoson

Attribute	Method	Acceptance Criteria



Data from drug substance batches (manufactured by manufactured by manufactured by) were considered in setting these specifications.

Assay

Note: Considering that the assay is performed by HPLC, and that the drug substance is not hydroscopic the assay should be tighter and rather set at

The acceptance Criteria for impurities in the drug substance:
Note: A single 400 µg intravenous bolus dose is proposed in clinical studies. The ICH Q3A qualification threshold for a product administered at a total daily dose of ≤ 2 g applies here. The qualification threshold for regadenoson impurities is thus NMT

- , have proposed limits of NMT w/w and are above the qualification threshold. Several toxicology studies were conducted with

regadenoson containing the [redacted] impurities. These studies were conducted to provide justification for a limit of NMT [redacted] w/w for these [redacted] impurities. This approach for qualification of the impurities in the DS was agreed by the FDA (Division of Cardiovascular and Renal Products; letter dated 29 August 2006).

- The acceptance criteria for [redacted] is NMT [redacted] and is within the ICH Q3A qualification threshold.
- The acceptance criteria of NMT 10ppm for [redacted] translates to a maximum daily exposure or Total Daily Intake (TDI) of [redacted] for a 400 microgram bolus dose of regadenoson drug product. Therefore, the TDI of [redacted] is much lower than the Safety Concerned Threshold (SCT) of 0.15 microgram per day set for a genotox impurity.
- The acceptance criteria for [redacted] impurity is set at NMT [redacted] **and is acceptable** eventhough [redacted] has not been detected above the reporting threshold of [redacted] in batches of regadenoson tested. Exposure Limits based on OSHA general Industry and OSHA construction industry PEL is 10 ppm. The acceptance criterion for [redacted] of NMT [redacted] w/w is the same as the limit for an individual unspecified impurity abd based on the proposed maximum dose, the total daily intake will be [redacted]

Inorganic Impurities:

- A general test for the presence of heavy metals is included although there are no specific sources for these impurities in the synthetic process.
- A further general test, residue on ignition, is included for quantification of general inorganic impurities.

Residual Solvents Levels in the Drug Substance (ICH Q3C):

√ [redacted] with an acceptance criteria of NMT [redacted] is acceptable. The PDE for [redacted] is [redacted]

√ [redacted] with an acceptance criteria of NMT [redacted] is acceptable. The PDE for [redacted] is [redacted]

The rest of the attributes and their acceptance criteria are acceptable.

Reviewer's Comment:

5. Assay value of [redacted] for the drug substance is not justified. The assay should be tighter, rather set at [redacted]
6. Please check with the Pharm-Tox discipline whether the design of the tox studies were adequate and address the qualification of [redacted] impurities at NMT [redacted] level.

The Drug Substance stability under basic, acidic, oxidative, heat and humidity conditions:

Results of stress testing performed on DS indicate that regadenoson is a stable compound in the solid form.

The bulk DS is packaged in [redacted]

Drug Substance Expiration Dating:

The proposed expiration dating [redacted] stability registration batches were manufactured at [redacted] the proposed commercial manufacturing site.

Supplemental stability data at 36 months for two batches and 18 months for a [redacted] batch manufactured at [redacted] which was the site that manufactured the DS for use in Phase 3 clinical studies are provided. The stability results were within specification for up to12 months for the stability registration batches and 36 months for supplemental stability batches stored at long-term storage condition of (25°C/60% RH) and up to 6 months at accelerated storage condition of (40°C/75% RH).

No significant change in any attribute was observed at either the accelerated or long-term storage condition for the DS packaged in the proposed commercial packaging or the [redacted] ; that were used for the Phase 3 studies.

Note: Based on an evaluation of the available stability data, a retest period [redacted] could be justified for the DS stored in the proposed commercial packaging at 25°C with excursions from 15°C to 30°C. Update on the stability data to confirm and further support the proposed [redacted] shelf life may be provided later.

Comment to the Applicant:

7. Provide timely stability updates on the three drug substance registration batches in SAS transport format. Also, provide statistical analysis of all stability-indicating quality attributes.

(B). Drug Product:

Drug Product Description:

Regadenoson Injection, contains 0.08 mg/mL regadenoson in a clear, colorless, sterile, non-pyrogenic, preservative-free solution for single-dose use intravenous (iv) injection.
The recommended iv dose is 5 mL (0.4 mg regadenoson) administered as a rapid bolus in 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.

Drug Product Component / Composition:

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 (0.1% w/w)
- 100 mM sodium phosphate composed of 10.9 mg/mL dibasic sodium phosphate dehydrate (or 8.7 mg/mL dibasic sodium phosphate anhydrous)
- 5.4 mg/mL monobasic sodium phosphate monohydrate, with pH between 6.3 and 7.7.

These excipients have been used before in intravenous drug formulations. All excipients comply with the requirements of the current USP.
Regadenoson degrades under extreme pH conditions. [redacted] hydrolysis occurs under basic conditions. Therefore, it is desirable to formulate regadenoson in a neutral pH.
The poor aqueous solubility of regadenoson was the main factor influencing the selection of 15% w/v PG in the formulation in order to effectively [redacted] while maintaining biocompatibility.
Propylene glycol or propane-1,2-diol is a tasteless, odorless, and colorless clear oily liquid that is hygroscopic and miscible with water, acetone, and chloroform. The formulation containing 15% PG was exposed to three freeze-thaw cycles and did not show any precipitation.
The proposed commercial formulation is the same composition used in the Phase 3 studies and late Phase 1 and 2 studies.

Drug product Manufacturing Process:

[redacted]

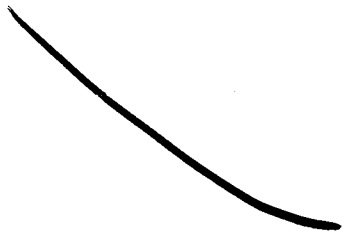
5 Page(s) Withheld

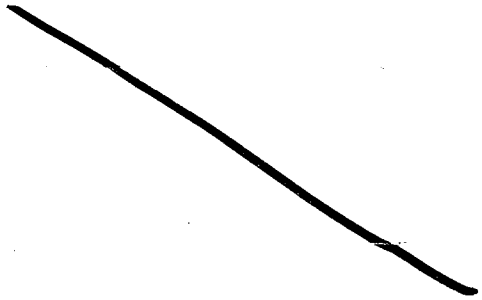
✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 3





All sites are ready for inspection.

Contact person Name: Carol D. Karp (Senior Vice President Regulatory Affairs, Quality and Drug Safety), CV Therapeutics, Inc.

Microbial Testing of the Drug Product:
Consult for review of the drug product sterilization and validation was sent to James McVey (Team Leader) in the OPS, Microbiology on June 27, 2007. This was done through the project manager of this NDA.

CDRH:
Not Applicable.

Environmental Assessment:
Based on a 5 year peak sales calculation it is estimated that the concentration of regadenoson at the point of entry into the aquatic environment will be below 1 ppb. Categorical exclusion from the requirement to submit an Environmental Assessment can be granted.

Consult to Pharm-Tox:
Drug Substance: The adequacy of the qualification studies on the drug substance related impurities that are genotoxic i.e., [redacted] and those impurities that exceeds the ICH Q3A qualification threshold should be consulted with the Pharm-Tox discipline.

Drug Product: Because of [redacted] degradation products are arising in the drug product. As discussed above these were identified and Pharm-Tox studies have been performed.
[redacted] has been identifies arising from the ANSYR Syringe system peak [redacted]
The adequacy of Tox-studies on peaks at [redacted] should be discussed with the Pharm-Tox reviewer.

Consult to ODS and DDMAC for the Proposed Proprietary Name and the Labeling:
Request for Consult to ODS for safety evaluation of labeling, and labels were submitted on May 21, 2007 through the project manager.
Request for Consult for tradename review to DMETS was submitted on May 21, 2007.
Request for Consult to Division of Study Endpoints and Label Development Team (SEALD) was submitted on May 22, 2007.

Methods Validation:
The HPLC-MS-MS method for determination of [redacted] in regadenosone API may need be validated by the FDA St. Louise Laboratory. The rest of the analytical methods may not meet any of the seven criteria for requesting method validation.

Biopharm/ClinPharm:
To be determined during the Review.

NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		

	Parameter	Yes	No	Comment
6	Has an environmental assessment report or categorical exclusion been provided?	X		Exclusion request per 21 CFR 25.31(b) is included.
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre- NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		The lab performing microbial test is entered in the EER. Review of the drug product microbial limits / tests etc is consulted to the microbiology discipline.
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA chemist or PM)	Yes		**Pharm/Tox, pending an initiation by the review chemist.**
		No need		Biopharm
		No need		**Statistics (stability)**
		Pending		**LNC**
		Medical Imaging PM has initiated the consult		DMETS/ODS
		yes		**EER, Requested on August 2007.**

II. Draft Comments for 74-Day Letter:

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7. [redacted]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jila Boal
9/21/2007 05:27:37 PM
CHEMIST

Ravi Harapanhalli
9/21/2007 06:32:21 PM
CHEMIST